“I feel happy to see this photo. These children didn’t refuse when I asked if I could take a picture of them. It made me laugh, which does me good.”

About the Artist

Cecilia lives with her grandmother and older brother; their parents died of AIDS when Cecilia was very young. Her brother, Serge, runs a small business, providing the family with some income. Contributions from Reencontro, a local NGO, also help make ends meet.

Cecilia loves school. She walks 30 minutes each way to school every day and hopes to be a director of a school when she grows up. Many of her concerns are with her family and home because the roof of the house leaks when it rains and she worries about her grandmother’s health.
from the ground up
BUILDING COMPREHENSIVE HIV/AIDS CARE PROGRAMS IN RESOURCE-LIMITED SETTINGS
VOLUME I:
LAYING A STRONG FOUNDATION

VOLUME II:
ESTABLISHING A FRAMEWORK FOR SUCCESS

VOLUME III:
DEVELOPING PATHWAYS AND PARTNERSHIPS
FROM THE GROUND UP:
Building Comprehensive HIV/AIDS Care Programs in Resource-Limited Settings

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These three volumes are dedicated to the health care workers, individuals, families, and communities on the front lines of the AIDS pandemic. Through their strength and perseverance in this prolonged time of crisis, solutions are now beginning to take hold . . .

from the ground up.
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HE END OF AIDS IS STILL NOWHERE IN SIGHT. Every day, almost three times as many people become newly infected with HIV as those who start taking antiretroviral treatment. Now that we are well into the new millennium, the HIV/AIDS response must also enter a new phase, a phase that combines continuing crisis management with a long-term, sustainable response.

One of the main lessons we have learned through the experience in recent years of providing antiretroviral therapy to millions of people is that we should not wait until systems are fixed before acting. Getting three million people on antiretroviral therapy is an achievement that would have been unthinkable back in 1999. Yet if we had continued to wait, if we had listened to those who said it couldn’t be done, the majority of these three million people would no longer be with us.

Our efforts thus far, while far from perfect, are proof that great progress can be made when dedicated people in all parts of the world join together to do the best they possibly can despite limited financial and human resources. The chapters contained in the three volumes of *From the Ground Up*, while representing only a small fraction of these efforts, are a testament to this unyielding will, and the immense amount of experience that has been accumulated in this relatively new field.

Yet great progress cannot be achieved in isolation. We in the AIDS movement must forge more concrete linkages with those working to improve health systems generally, so that we can achieve maximum benefits all around. We will need to work across sectors to achieve the massive scale-up of efforts that is required—that is why this text covers not only the direct provision of prevention, care, and treatment services, but a myriad of related issues that must be considered if the care that we do deliver is to be of the highest quality. By the same token, the AIDS response cannot be disconnected from overall development efforts, or from other health activities, such as TB and reproductive, maternal, and child health.

Getting the “how” as well as the “what” of implementation right is critical to reaching our collective goal of stopping this pandemic. *From the Ground Up* is part of a rapidly growing movement to collect and disseminate the best practices and lessons learned from our monumental efforts over the last quarter century. We must continue to find new and better ways of harnessing this critical information to quicken the pace of progress and avoid duplication of efforts. We are at the point where we must start to think—and implement—in new ways. But one thing will not change: the only way we will ever succeed is by working together.

Peter Piot

*Peter Piot, M.D., Ph.D. served as executive director of the Joint United Nations Programme on HIV/AIDS (UNAIDS) from the agency’s creation in 1995 until the end of 2008. He currently serves as a professor and director of the Global Health Institute at Imperial College London and is a senior fellow at the Bill & Melinda Gates Foundation (2009) and scholar in residence at the Ford Foundation (2009).*
Preface

The title of this publication, From the Ground Up, reflects our desire to establish a new paradigm for sharing the enormous wealth of information stemming from over 20 years of HIV/AIDS program implementation experience. By reversing the typical “top-down” flow of information, the voices of hundreds of talented professionals on the front lines of the HIV/AIDS response can now be heard by all those who stand to benefit, regardless of their geographic location or position within the vast network of institutions and individuals that comprise the global HIV/AIDS community. While the Elizabeth Glaser Pediatric AIDS Foundation has served as the publisher of this text, the methods by which the content was developed are characterized by a remarkable level of collaboration involving hundreds of individuals and their affiliated institutions. A total of over 320 individuals contributed to these three volumes, generously volunteering their time to document an array of efforts in all aspects of HIV care, treatment, and prevention, as well as a host of related issues that constitute a truly comprehensive response to HIV and AIDS.

Comprehensive HIV/AIDS care is defined here as all approaches that hold the potential to enhance the health and well-being of people living with and affected by HIV and AIDS. Yet it must be recognized that it would be impossible for any single publication, no matter how large, to contain an exhaustive review of all efforts constituting an effective HIV/AIDS response. In fact, despite the large quantity of information gathered within these pages, they contain a mere snapshot of the multitude of impressive efforts underway in sub-Saharan Africa and elsewhere. We hope that this text, despite its limitations, will serve as a significant milestone along the multiple, simultaneous but often distinctive paths that are leading us out of the current crisis and toward a new era of long-term, strategic, and informed approaches to HIV/AIDS program implementation in resource-limited settings. We can learn a great deal from one another, and the information gathered here brings us a small step closer to achieving the level of knowledge sharing required to further the pace of progress in every aspect of our work.

Readers will quickly notice that the Foundation’s programs are not the focus of this text; rather, the Foundation’s work is profiled alongside that of more than 140 respected public health institutions around the world. This is in recognition of the fact that the global response comprises a multitude of individual efforts and experiences and is greatly enriched by a diverse array of practical and philosophical approaches. We have also made a concerted effort to reflect the Foundation’s specific focus on women and children throughout this publication. In accordance with the Foundation’s mission “to prevent pediatric HIV infection and to eradicate pediatric AIDS through research, advocacy, and prevention and treatment programs,” several chapters have been devoted to the care of women and children living with and affected by HIV and AIDS. In addition, each author has been asked to consider the special care needs of women and children in the context of their chosen topic in an effort to urge us all to be as inclusive and strategic as possible in addressing the needs of these particularly vulnerable groups.

The three volumes of From the Ground Up are named and organized according to the key stages of comprehensive HIV/AIDS program implementation. Each volume opens with an introduction by a recognized leader in the HIV/AIDS field, framing the chapters that follow in the context of the author’s
own vast professional experience. Bookending the regular chapters of each volume, readers will find full-color profiles of remarkable individuals on the front lines of the HIV/AIDS response. These true heroes embody the unyielding devotion to their work and tireless spirit that characterize so many in our field, and we are proud to be able to highlight their remarkable contributions within these pages to inspire and uplift us all.

The chapters contained in the first of these three volumes, “Laying a Strong Foundation,” emphasize the importance of ensuring that a range of critical program components, from workforce capacity to human rights, are in place before embarking on service provision. Such considerations are critical to the success of any comprehensive program, and as such should always be made at the outset of program planning and implementation. The chapters contained in the second volume, “Establishing a Framework for Success,” remind us that the creation of a strong foundation, while critically important, is only the first step. We must then establish a framework of proven strategies, based on the best available scientific evidence, which will guide us in every aspect of our work. The chapters in the third and final volume, “Building Pathways and Partnerships,” show us that once programs are established, the human networks that provide access to and enhancement of the services provided are critical to their ultimate success. Only by ensuring that programs are appropriately linked with the populations they serve and are working in concert with complementary community-based efforts, can we be confident that services will reach those who need them most.

Finally, we wish to point out that this text is not meant to serve as a definitive guide to program implementation. As we are all aware, there is no magic formula that, if followed to the letter, will yield a perfect HIV/AIDS program. Rather, From the Ground Up contains a number of different viewpoints for the benefit and enrichment of the reader, some of which may reflect differing perspectives on a given issue, and some of which may not be applicable in a given setting. As such, we encourage readers to apply the knowledge and experience documented within these pages at their discretion, just as we encourage all those in this dynamic field to never cease building and improving upon their own work and that of their colleagues. As implementers, we all are in the process of “learning by doing,” but we must not forget that it is equally, if not more important, to “learn by listening” to our venerable colleagues and the communities we serve around the globe.

Richard G. Marlink
Sara J. Teitelman
Introduction

SINCE THE FIRST CASES OF INFECTION with what became known as HIV were reported in 1981, the AIDS pandemic has grown into one of the most devastating public health threats of our time. The Elizabeth Glaser Pediatric AIDS Foundation is proud of its efforts over the last two decades, growing from a small domestic organization to a worldwide leader in the fight against pediatric HIV and AIDS. And while our work and the work of our colleagues is far from over, it is important to reflect on what has been accomplished to date and the challenges that lie ahead as we move toward creating a generation free of HIV. In this spirit, the Foundation is proud to have led the creation of From the Ground Up, a landmark effort to compile valuable insights and experiences from a wide array of HIV/AIDS professionals working in resource-limited settings.

Many remarkable achievements have been made in the HIV/AIDS field since the virus was first discovered, from scientific advances to the breaking down of political and social barriers. Of particular importance, the wider availability of more effective, less costly treatments has begun to convert HIV infection from a death sentence into a chronic, manageable disease. These developments have led to the roll-out of antiretroviral therapy programs in even the most resource-limited settings, which are now delivering life-saving treatments and essential care and prevention services to millions of people. Such rapid progress has been made possible in part by historic increases in funding for international HIV/AIDS care, treatment, and prevention programs.

We have come a long way, but much more remains to be done. In the hardest hit regions of the world, where both financial and human resources for health are in short supply, HIV and AIDS remain formidable threats to the health and well-being of millions of people. In 2007, an estimated 33 million people were living with HIV, up from 29 million in 2001. At the end of that year, some 2.7 million people, 370,000 of whom were children, had been newly infected with the virus, and an estimated 2 million people had died of AIDS-related illnesses. Sub-Saharan Africa remains the most affected region in the world, and is home to more than two-thirds of all people living with HIV, the majority of whom are women. In response, the Foundation is working hard to address the health needs of affected women and their families in the 18 countries where we work.

As we enter a new era characterized by the wider availability of antiretroviral therapy, we must remember that treatment and prevention go hand in hand. We will only be doing half of what is required to bring the epidemic under control unless we can stem the tide of new infections. Promising steps are being taken in this regard: By the end of 2007, 34% of HIV-positive pregnant women globally received the medicines they needed to prevent transmission of HIV to their babies, up from 14% in 2005. Much of that increase came from the expansion of services in low- and middle-income countries. The Foundation is doing its part to ensure expanded access to both prevention and treatment services. As of December 2008, we have provided more than 6.6 million women with services to prevent the mother-to-child transmission of HIV and have enrolled more than 620,000 people, including more than 50,000 children, in HIV care and treatment services. But there is still much to be done. At the end of 2007, just 31% of the 9.7 million people in need of antiretroviral treatment worldwide were receiving it.
Given the urgency and complexity of our work, we rarely have an opportunity to stop and consider what lessons can be culled from our own experiences, let alone those of others. Yet learning from one another is precisely what is needed to quicken the pace of progress and ensure that the experiences of the past serve to strengthen future efforts. *From the Ground Up* is a testament to the importance of working together, highlighting how greater collaboration and communication can enable those working on the front lines to mount new and more effective responses to the HIV/AIDS crisis.

*From the Ground Up* is not a “how-to” manual. Rather, it is a collection of many different viewpoints and experiences, each as unique as its authors. The Foundation spearheaded this important project not only to broaden our own base of knowledge about the current state of HIV/AIDS program implementation, but also to encourage the application of these lessons by others in our field. As you begin to explore these three volumes, you will find that the chapters have been written by a group of more than 320 HIV/AIDS professionals working in a variety of resource-limited settings and representing a multitude of institutions—ranging from large international consortiums and national governments to community-based organizations. These diverse professionals have shared their experience and expertise on a wide variety of topics, from workforce capacity and human rights to HIV medicine and community-based care. Each informative and thought-provoking chapter forms part of a rich and colorful mosaic of the wide variety of efforts currently underway around the globe.

We hope you enjoy reading and using this text as much as we have enjoyed assembling it. While the road ahead is sure to be challenging, learning from the experiences of our colleagues can help us to end the AIDS pandemic—and create a generation free of HIV.

Pamela W. Barnes

*President and CEO*
*Elizabeth Glaser Pediatric AIDS Foundation*
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MARA BANDA WITH MIRACLE, THE BOY THAT SHE SAVED FROM BEING KILLED BY HIS FAMILY AFTER BOTH HIS PARENTS DIED FROM AIDS
Mara Banda

Director of Paradiso Community Health Project, Malawi

MARA KUMBWEZA BANDA’S life had always been full of turmoil. When she was a girl, her father was suddenly fired from his job as a minister in the Malawian government, and the family lost their house and all the belongings inside. As a young mother of four boys, her husband died in a traffic accident. And then in 2000, Banda learned she was HIV-positive.

In those days in the Ngwenya Township southwest of Lilongwe, she remembers, people all around her were dying from AIDS. “We used to have six funerals a day. People died as couples. The wife would die in the morning and the husband would die in the evening,” she said.

It was one such tragedy that changed Banda’s life. One day in 2002, a woman in her community died giving birth. Her baby boy survived. But a week later, the father died as well, and the family decided quietly that they were going to kill the boy, believing he was a witch.

Banda, knowing AIDS had killed the couple, stepped in. “I said, ‘You can’t kill him, he’s innocent. Let’s keep the baby. We’ll help.’”
People brought clothes and food, and Banda found women to nurse the baby. The baby lived.

That started her on a project to look after the sick and the children in her community. She founded Paradiso House and Home-Based Care in a building donated by community leaders. It sits on the side of a stone mountain, where local people slowly chip away at the rocks, crushing rock piles into stone, and sell their labors for $1 a day to construction companies.

In just a few years, her project has taken off. Twenty volunteer home-based workers check in on a total of 300 people in their homes a few times a week. She has registered 264 orphans, feeding them twice a week and supporting 70 with school fees. And in 2007 she did it on just $13,000—by far her biggest budget yet. The donations come from Americans, Scots, Norwegians, and many Malawians.

The advent of free antiretroviral treatment and the greater acceptance of people getting tested for HIV has dramatically changed the work around AIDS, she said. But the community also has greatly benefited from Banda’s vision.

“She didn’t want to just help herself,” said Georgina Msito, 24, Banda’s niece, who now volunteers at Paradiso. “She has got a heart for others.”

So for Banda, 48, a life’s worth of turmoil has abated, for the time being. She has her health. She has the support of her four boys. She dances and sings with her volunteers nearly every week outside her building, their feet raising dust and their voices rising above the sounds of makeshift hammers striking stones in the hill above.

And she has that boy whom she helped save one night not so long ago. Sitting in a meeting room at Paradiso, she asked her youngest son to go find him. He returned a few moments later with a boy who had round checks and a dazzling smile.

“This is that boy—that boy we saved,” Banda said, as the boy climbed onto her lap and nestled in her arms. “We call him Miracle.”
Q: When was the moment that you felt you were committed to this work?
“When we got the building in 2003. I cried. I still cry when I think about it. [She starts to weep.] It’s so emotional. It was exciting. People had acknowledged my work. My work would grow. I would have a place of my own. I cried the whole night, the whole next day. I came in that morning to sweep. Everybody was so excited. Everybody was crying.”

Q: When did you realize that working on AIDS would be so consuming?
“When the community started catching on to the work we were doing, it dawned on me that maybe I will have to do this work my entire life. It is so much better today than it was just a few years ago, when people were knocking on my door at all hours, people were dying every day. But I still have to put all my effort into this. I am starting to look at the future of the program. If God keeps me alive into my 80s, maybe—maybe—I won’t be able to do all this work then” [laughs].

Q: How will you sustain Paradiso?
“We are doing a lot of outreach to the youth. It’s the old way of elders handing down information. It isn’t anything written down. It is young people watching elders do things. And we in turn are observing and encouraging the youth so they can fully develop. This youth team will bring this disease down. The youth have gotten really frightened about HIV and AIDS. They say they are not going to make any silly mistakes. They are going in for testing and counseling. And we have very few HIV-positive youth here.”

Q: What will be the biggest challenges in the years ahead?
“There’s a very weak link between the health sector and the donors with the community-based organizations. A lot of big umbrella organizations get funding from the Global Fund or PEPFAR [President’s Emergency Plan for AIDS Relief]. But the funding often stays in those organizations, the big institutions. It’s very difficult for groups like ours to access funding.

“The other big challenge is that we need to start income-generating activities. Paradiso is drifting into a donor-dependency situation. We’re not doing something to sustain us. This should be our main focus ahead—to start a project that will sustain us without outside funds. We need to have a good capital base.”
Introduction to Volume I: Laying a Strong Foundation

As HIV/AIDS professionals, we go to work every day with a sense of great urgency. The services we provide can literally mean the difference between life and death for millions of individuals. Yet while there will always be a temptation to rush into service provision given the overwhelming demand that exists, HIV/AIDS services must be built upon a strong foundation, consisting of a capable workforce, sound laboratory and pharmacy infrastructure, appropriate monitoring and evaluation strategies, and a commitment to upholding human rights principles in all that we do.

In 1998, the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) issued guidelines concerning the “minimum requirements” for the provision of safe and effective antiretroviral therapy. These included: laboratory facilities to monitor adverse reactions, appropriate training for clinicians and nurses in the correct usage of antiretroviral drugs, social support networks, and reliable drug supplies. The sections contained in this first of the three volumes of From the Ground Up closely mirror these original key requirements, which remain the cornerstones of quality HIV care and treatment today. In addition, and reflective of the social support requirement mentioned by WHO and UNAIDS at that time, the final section of this volume emphasizes that programs must operate in accordance with basic human rights principles, and that we as HIV/AIDS professionals must work to respect and uphold the basic human rights of the individuals and groups we serve.

Without these basic building blocks, programs risk failure and in some cases, may end up doing more harm than good. But while these building blocks are all essential ingredients, there are a variety of different viewpoints and approaches to fulfilling these requirements, a portion of which are reflected in the chapters contained in the following sections. In the “Workforce Capacity” section, we will learn how to estimate workforce needs, while other chapters will guide us in how to retain and strengthen this workforce once it has been assembled. In the “Laboratory and Pharmacy Services” section, we will learn of some of the key challenges facing programs given the increased availability of antiretroviral therapy and other services, and how lack of laboratory capacity can serve as a debilitating bottleneck if not properly managed in concert with other scale-up activities. We will also see how innovative approaches to lower-cost laboratory monitoring, as well as expanded roles for pharmacy staff, can help overcome some of these significant challenges.

In the “Monitoring, Evaluation, and Quality Management” section, the authors provide us with a “big picture” of the key principles of monitoring and evaluation, as well as how these are being put into practice in novel and interesting ways that reflect the additional technological tools we have at our disposal in the 21st century. We will also learn how to ensure the quality of our programs through quality management, a powerful tool for enhancing patient care, maximizing resources, and improving workforce morale. And finally, in the “Human Rights and HIV Care” section, we learn how several national HIV/AIDS programs are performing in terms of their stated commitment to human rights, as well as some the key challenges in reaching the most vulnerable groups, such as women and men who have sex with men.
While the international HIV/AIDS response is an ever-changing mosaic of initiatives, affected populations, and social issues, many things remain constant. Among these constants are the cornerstones of good service provision mentioned earlier. Another constant is the opportunity we all have to use our work in HIV/AIDS as an avenue for addressing the broader iniquities and stigma that afflict so many modern societies. As you read through the chapters that follow, I urge you to take a moment to imagine a future in which all health programs, whether for HIV/AIDS or other grave public health threats, are built upon these cornerstones of quality service provision, and how such a reality could bring us closer to reaching the ambitious yet imperative goals we have set for ourselves to transform societies for the benefit of all, and especially for historically underserved populations.

Shelia Tlou

Shelia Tlou, MSN, Ph.D., is the former Minister of Health for Botswana (2004 to 2008) and a professor of nursing. Dr. Tlou has also served as the AIDS coordinator for the University of Botswana since the inception of the position. Her work continues to focus on raising public awareness of issues related to HIV/AIDS, women’s health, gender, and human development.
Daniel Onayi in front of one of his rock paintings that states “say no to AIDS”
LARGE, MAJESTIC BOULDERS line either side of the rutted dirt road that passes through the village of Ibwona in western Kenya. Villagers often climb to the top of those easily scalable rocks to see the world from a different height. But Daniel Ongayi saw the boulders serving another purpose—as his own personal canvas.

A canvas of rock to fight AIDS.

In white paint, he wrote messages on the boulders lining over a mile of road: “Stress is a Killer,” “AIDS has entered into the beds like bedbugs,” “Give HIV-Positive Person an Opportunity, not Sympathy,” and “Girls: Avoid Vitamin M”—M standing for the money older men give girls for sexual favors.

He drew animals as well: hippos, giraffes, crocodiles, and birds. On several of the boulders, he signed his work, boldly and with a hint of humor:
“I panicked. I felt my whole family would die. I built a
to my self, my wife, and our five children.”

“By Dan-HIV Man.”

Then, to make sure people would have no trou-
ble finding him, he painted his cell phone number
on boulder after boulder.

“I did it because people should be aware that
AIDS is all around them,” Ongayi said on one recent
afternoon by his boulders. “I did it so that people
wouldn’t be afraid to tell others about their status.”

He stood among the boulders at a local gathering
spot. More than a dozen villagers sat on the huge
rocks, waiting for taxi vans. One by one, people
walked by on a path that leads to one section of the
village and on into a forested area. A few walked over
to him to say hello. Some said he had affected the
lives of everyone in the village, which has an estimated
population of 20,000. In the AIDS world, the village
has become a rare place where most people not only
know their status but are not afraid to talk about it.

“At first, people looked at him like he was not
normal,” said Haddah Otwoma, 26, a university
student majoring in information science. “But we
found out that he’s OK. Because of him, people are
coming out and talking about their status. It’s a very
good thing.”

Ongayi walked over to show the drawings of ani-
mals on the rocks. Each, he said, has a meaning.

The hippo: “It’s a huge animal that stays under-
water, in mud, during the day. It walks out only at
night, the better to hide itself—just like a person
with AIDS who hides their status.”

The giraffe: “It is tall and brave. When you use
ARVs [antiretroviral medicine], you slowly stand
on your feet again. ARVs make you stand tall like
a giraffe.”

The skull of a crocodile: “It means if you play
with AIDS, it will not spare you. Just like if you go
into the water, the crocodile will eat you.”

Ongayi, 47, the father of five children, first
tested positive for HIV in 1994. He hasn’t limited
his AIDS work to boulder art. He also helped form
the ANDEKA Association, a support group for men
infected with the virus.

Two of his friends hopped out of a taxi van. “This
one is positive living,” Ongayi said. “And that one
with the white cap, he is positive living, too.”

Harrison Omuka, 52, the man in the white cap,
greeted him. “We are free,” he said. “It is not a big
deal to say you’re positive—not in this village. By
coming out, it’s a kind of medicine of its own. You
don’t have to hide.”
Q: Was it always so easy for you to talk about your HIV status?
What happened after you learned you had HIV?
“I was a driver. You know how drivers act. I had a girlfriend in another place. My girlfriend, it turns out, was positive. So I caught the disease. When I told my wife, she wanted to leave me. But she just prayed to God and found peace. I was very fortunate. She decided not to leave me.”

Q: How did the rest of your family react?
“I remember that my mother cooked some tea for me. I told her and the rest of my family. And after I finished the tea, my brother took the cup I was using and threw it into the pit latrine. I started feeling I could die at any moment. I panicked. I felt my whole family would die. I built a huge grave by the side of my house—big enough for myself, my wife, and our five children. I also decided they shouldn’t spend money on my coffin, that I should build my own. I did that. I built it and I put it under the bed.”

Q: You slept over your coffin?
“For six years.”

Q: Then what happened?
“I started on ARVs. It was 2002. My CD4 count was 140. I improved almost immediately, and I destroyed the coffin.”

Q: How did people react to you initially when you starting writing and drawing on the boulders?
“Most of the people here said that I was using witchcraft. That I was a witch. But I told them, ‘No, we are trying to disseminate practical information about AIDS.’ I told them that if I could do this writing on stones, I would be trying to call people together. I would be using common sense—let people know about the disease, tell everyone that it’s OK to say you have it.”

Q: What will be the biggest challenges for people living with HIV in the years ahead?
“The medicine is there for us now. But more and more people will need basic things—food, shelter, access to water, money for transport. Right now, I myself cannot send two of my children to secondary school because I do not have the money for school fees. Sometimes I get really depressed—not because of my HIV status, but because it’s so hard to earn a living.”
WORKFORCE CAPACITY
HEALTH-CARE FACILITIES IN RESOURCE-limited settings have long faced chronic shortages of appropriately trained staff. The World Health Organization (WHO) estimates that there are currently more than 39 million health service providers worldwide. Yet sub-Saharan Africa, home to nearly one-quarter of the world’s disease burden, retains only 3% of the global health workforce. Despite the significant unmet workforce need in many countries in the region, 25% of physicians and 20% of nurses trained in Africa currently work in high-income, Organization for Economic Co-operation and Development (OECD) countries. Although this phenomenon is not new and has been widely reported, the HIV epidemic and the recent focus on expanding HIV clinical care programs only serve to heighten awareness of and concern for this issue. The complex nature of implementing and sustaining quality HIV care—in particular, providing antiretroviral therapy (ART)—requires a team of well-trained clinical staff, auxiliary health personnel, and nonclinical staff. Health-care systems in resource-limited countries are overburdened and understaffed and face competing demands for the same staff. In light of this situation, the public-health system, especially HIV treatment programs, is finding that one of the greatest obstacles to rapid expansion of ART programs is the shortage of human resources. Unless immediate attention is paid to this critical need, we may find ourselves in a situation referred to as “medicines without doctors.”

GENERAL FACTORS THAT INFLUENCE WORKFORCE DEPLOYMENT

A number of often interrelated factors impact the ability of facilities, programs, and national health authorities to adequately address the staffing needs of HIV clinical care programs. Some influences are common across the health-care system, while others are specific to HIV. Some internal and external factors include the following:

- **Emigration.** Given the relatively low salary levels in most resource-limited countries, physicians and nurses opt to leave their homes for more lucrative opportunities in countries that have higher compensation levels.

- **Decline in life expectancy.** The health sector keenly feels the economic impact of HIV. With lower life expectancy in many of the
countries most heavily affected by HIV, countries must address a shrinking workforce due to mortality.3

- **HIV-related absenteeism.** In many countries that are severely affected by HIV, there is significant lost work productivity due to individuals who are absent from work in order to tend to their own HIV clinical care needs or illnesses, to care for a family member living with HIV, to attend to the needs of orphans and vulnerable children who have joined the family, or to participate in funerals. This often unplanned time away from work complicates routine provision of clinical and support services.

- **Migration to the private sector.** In many countries, there is an increased migration of qualified clinical personnel from the public to the private sector. The reasons for this internal migration are numerous, but include relatively better salary and compensation levels in the private sector, better working conditions, better access to necessary equipment and supplies, and less likelihood of transfer to or posting in rural sections of the country.

- **Recruitment by international organizations.** With increased international support for HIV treatment, international nongovernmental organizations (NGOs) and governments have become important employers of national staff. Increasingly, host country clinicians and program experts are being hired to run internationally funded program operations, effectively taking them out of the pool of health-care providers.

- **Donor reluctance to directly fund staffing.** Many countries have limited budgets to support continuous costs, including personnel, related to the design, implementation, and management of health-care systems. Donors, both bilateral and multilateral, have been reluctant to directly support human resource needs through salary and compensation benefits; this reluctance is largely due to concerns about sustainability. Only in rare cases, such as Malawi, has the donor community committed large-scale resources to address these challenges.4 Without adequate financial resources, it is unlikely that human resource needs, including ART initiatives, can be met for the public-health system.

- **Armed conflict and political instability.** A number of countries that embarked on ambitious ART roll-out campaigns have seen efforts slowed by internal armed conflict and political instability. Civil strife in Côte d’Ivoire, for example, has led to significant reductions in staffing at public and private service providers, as well as stock-outs of antiretrovirals (ARVs).5

- **Training needs.** HIV treatment, and in particular ART management, requires specific initial and continuing education through a combination of short courses and in-service training. Even the relatively minimal time required for training places a burden on health facilities, as they often have to arrange to cover those in training.

- **Vertical programs and competing demands.** HIV is not the only public-health priority in most countries implementing ART scale-up. Ministries of health and clinical facilities must address competing demands with insufficient human resources. The approach to program development and implementation has often been to establish vertical programs with limited or no overlap in service delivery or staffing. This often leads to inefficient or suboptimal utilization of critical staff, including physicians and nurses.

- **Shift from episodic or preventive medicine to chronic disease management.** Traditionally, public-health systems in resource-limited countries were developed to provide preventive (e.g., immunization) or episodic (e.g., prenatal, family planning) care services. The scale-up of HIV
treatment has required a shift to a chronic disease management model for both service delivery and staffing.

- **Provider stigma.** Provider stigma around caring for people living with HIV often complicates staff recruitment and retention. Directly related to this are provider concerns about occupational exposure to HIV, given the generally poor implementation of infection control programs and the limited access to postexposure prophylaxis (PEP).

- **Task assignment restrictions.** Professional associations and government regulatory authorities often have restrictive rules in place regarding the authority and responsibility for carrying out essential clinical care activities, including patient contact, counseling, and prescribing and dispensing pharmaceuticals. These restricted assignments limit a facility’s or program’s flexibility in adapting approaches according to local context and situations and often result in less-efficient and less-effective uses of already scarce resources. Barriers to implementing task shifting include system and organizational issues, such as the rules and regulations of national governments and professional organizations or facilities, as well as individual challenges, such as already overburdened staff and volunteers. Additional challenges include the need to develop and implement staff training and to revise supervision systems in order to monitor task assignment changes and to provide constructive, on-the-job assistance.

There has been increased recognition in the literature and at public conferences of the challenges regarding the human resource needs for ART scale-up. However, for program managers at the facility, district, regional, and national levels, there has been limited practical guidance in assessing human resource needs, developing approaches based on these assessments, and monitoring and making changes based on program evaluation.\(^2,3,6-11\) This chapter presents information and approaches for estimating human resource needs and identifies approaches and innovations to take into consideration as ART programs are developed, implemented, and monitored.

**METHODS FOR ESTIMATING HUMAN RESOURCE NEEDS**

The first step in determining the staffing needs for an ART program is to consider the basis for making these estimations. A number of approaches are commonly used for determining health-care human resource needs.

- **Population-based ratios.** Using the number of providers by cadre and the total population to be served, human resource need estimates can be made. As an example, a district hospital that provides a full complement of clinical services through a variety of programs could make estimates based on the number of specific cadres of staff who can provide services for the entire catchment area. So, in this instance, for every 5,000 people, there would be two nurses and one physician. The benefit of a population-based ratio is that it takes into consideration the broad community’s health needs and sets staffing levels according to the total number of health-care staff required. However, it does not take into consideration the complexity of different types of programs and whether proposed staff are appropriately trained and efficiently deployed.

- **Community health.** In this approach, ratios are determined using information about a community’s health and disease burden. Although more exact than general population-based ratios, this approach tends to look at health needs vertically, rather than examining opportunities for
collaboration and synergy across the system. For example, a health center may have identified five priority health issues—maternal and child health, child immunization, general surgery, HIV, and malaria—for which staff must be hired and trained. This health center would then fill the human resource needs for each vertical program, without examining opportunities for cross-training and for task assignment across program areas.

- **Target setting.** Increasingly, ART programs are being designed with explicit service delivery targets. In such settings and circumstances, these targets can be used as a basis for determining human resource needs. For example, if in one year, 1,000 people are to be newly started on treatment and 1,500 patients are to be maintained, what staffing levels are needed? This approach tends to focus vertically on specific HIV clinical care program initiatives and typically does not take into consideration the specific tasks necessary for achieving and maintaining quality services.

- **Task related.** In this approach, staffing levels are determined by examining the discrete tasks and steps necessary for completing a patient interaction. Each task required to ensure quality patient management is identified, irrespective of job title. Staffing needs are determined by the number and type of tasks, identifying appropriate people based on their skills rather than on their titles. This approach allows programs the flexibility of shifting assignments based on need rather than job title.

These approaches are not mutually exclusive. In many settings, the best approach may be one that merges a number of different approaches. For example, given the focus on targets in many programs, the ideal approach may be to examine targets alongside tasks and then make human resource estimates accordingly.

**FACTORS TO CONSIDER WHEN ESTIMATING HUMAN RESOURCE NEEDS FOR ART PROGRAMS**

Estimating staff needs for ART programs is a continuous process that must take into consideration numerous variables, many of which change over time. HIV prevalence and incidence, site experience, program stage (e.g., implementation, scale-up, and maintenance), and patient clinical status change over time and require reassessment of human resource needs and reallocation of staff. Therefore, program managers must continuously review staffing needs by revisiting different program parameters and making adjustments accordingly. The following are program factors that should be taken into consideration when determining staffing needs for ART programs.

**Service Model**

Clinical services offered to people living with HIV range from free-standing ART treatment centers to fully integrated efforts that combine HIV care with other primary health-care or infectious disease programs. Program placement decisions greatly influence and impact staffing levels. For example, although stand-alone ART treatment centers allow for higher patient-to-staff ratios, they also require a significant commitment of human resources to care for a relatively limited number of people, even in high-prevalence settings. The service model approach may also incorporate task shifting, which can maximize the use of specialized staff.

An increasingly common approach in high-prevalence settings is the integration of HIV treatment into primary health care. Yet this approach can result in providers specifically trained in HIV clinical management spending significant amounts of time tending non-HIV-related illnesses. From the health-system perspective, this is likely to be advantageous, as more patients can be seen in a more timely fashion and human resources can be
used to maximum efficiency. For people living with HIV, however, this situation may present challenges, as waiting times will likely be longer and actual time with the provider will be suboptimal from the patient’s perspective, though it may reduce separate referrals for non-HIV services. This integrated approach may reduce staff migration to well-financed HIV treatment programs. Like the HIV primary health clinic, this approach requires that significant attention be paid to task assignment.

**Existing Staffing Patterns, Responsibilities, and Available Resources**

Most ART programs are implemented within the context of ongoing HIV treatment efforts or primary health-care initiatives. For this reason, it is crucial to consider the current human resource needs for existing programs when determining additional changes in task requirements. To maximize staff efficiency and to utilize training and resources most effectively, staffing decisions should be made based on expected task assignments rather than on positions. For example, the number of people needed to conduct clinical follow-up assessments for patients on ARVs needs to be determined, with the understanding that the people conducting the actual assessment could be physicians, clinical officers, or nurses. Essential to this assessment is the determination of nonclinical needs, such as adherence counseling and referral for nonclinical services. In many settings, nurses undertake these functions; however, in some settings, these tasks are being shifted to lay counselors or appropriately trained and supervised peers. Continuing adherence support and outreach for missed clinical visits and pharmacy pickups are other critical tasks that should be reflected in task assignments and human resource determinations. Even if volunteers are used for these functions, appropriate staffing levels need to be calculated and supervision of volunteers must be taken into consideration.

**Schedule of Visits**

Expected frequency of clinical visits and pharmacy pickups will influence staffing needs. Directly related to these needs is the balance between enrolling new patients and maintaining patients already in care or on treatment. Increasingly, programs are implementing clinical visit schedules that differentiate between patients newly on ARVs and stable patients on treatment. For patients already on ARVs, the schedule typically evolves over time, with a more intense schedule of clinic visits in the first three to six months of treatment and then decreasing depending on stability. For patients not on ARVs, the typical follow-up schedule is two clinical visits per year. Regardless of the number and frequency of clinic visits, however, patients are typically expected to return to the pharmacy monthly for ARV pickup. The number and complexity of tasks to be completed during the pharmacy pickup (e.g., adherence measurement and support, dispensing) will help determine appropriate staffing levels. For both clinical visits and pharmacy pickups, protocols related to follow-up of missed visits will also influence human resource needs. If there is a system of active engagement for clients who have missed either type of visit, appropriate resources need to be allocated.

**Site and Program Factors**

No two sites or programs are exactly the same. Each has a unique set of circumstances and infrastructure that may support and enhance the ability to expand services or that may serve as a barrier to rapid, efficient, sustainable growth. Of particular importance in estimating human resource needs are (1) location (i.e., urban vs. rural), (2) physical space, (3) type of site (i.e., public, NGO, private, commercial, workplace), and (4) level of service and program integration. All factors are interrelated, and each directly impacts the ability of individual systems and programs to address short- and
ratios. Experience in many settings has shown that during the initial stages of implementing HIV treatment service delivery, enrollment in general and the number of patients placed on ART are low. These numbers increase as the staff gains greater confidence in patient management. In addition, as more patients are put on ART, there will be a shift from focusing primarily on initiating treatment to a situation in which starting treatment is part of a complex sequence of patient follow-up. This sequence may include long-term management of stable patients, more intense care for patients who have experienced treatment failure, and routine follow-up of all patients, with each task requiring a different mix of staff capabilities.

Staff training, attitudes, and characteristics

The success of any HIV treatment program depends in large part on the staff assigned to provide care to people living with HIV. A broad range of issues will directly impact human resource estimations. Some of these issues, such as training and prior experience, are tangible criteria that can be measured and assessed directly. Others, such as personal beliefs

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<td>Rural clinics often face challenges in recruiting and retaining trained clinical staff. In addition, the need for outreach workers to reach patients who missed visits may be higher. In urban settings, populations are often more likely to relocate, either within an urban setting or to another setting. Staff assignments to follow up with clients need to reflect these challenges.</td>
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<td>Physical space may limit the actual number of providers who can work within a prescribed setting.</td>
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<td>Public-sector programs often have explicit rules and regulations regarding task assignments and how positions are developed, recruited, and compensated. Commercial, NGO, and workplace programs tend to have greater flexibility in hiring decisions and in task assignment.</td>
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<td>Although integration may increase the number of available staff to provide HIV clinical and nonclinical support, it will also require training and supervising a greater number of people who have broad health-care responsibilities.</td>
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long-term human resource needs. Box 1 presents issues raised by these factors.

Current Resources and HIV Clinical Service Experience

It has been well documented that most resource-constrained settings face significant staffing shortages in the health sector. In most countries, HIV treatment roll-out and expansion are only adding to this crisis. Where HIV care is being integrated into ongoing outpatient care services, the outstanding human resource needs must be taken into consideration. In many settings, this will require training larger numbers of providers to be multiservice providers. In instances where HIV clinical care is a stand-alone service, staffing to support active and efficient referral networks must be addressed. Regardless of the model of care, particular attention must be paid to nonclinical services and requirements, including drug dispensing, maintenance of medical record systems, and data collection and reporting requirements.

In addition to existing gaps in human resource needs, prior experience in providing HIV clinical care will impact staff needs and patient-provider ratios. Experience in many settings has shown that during the initial stages of implementing HIV treatment service delivery, enrollment in general and the number of patients placed on ART are low.
about behaviors related to HIV acquisition and people living with the disease, stigmatization, and fatigue, are often harder to identify and may serve as barriers to providing the highest-quality client-centered care. Provider characteristics, both tangible and intangible, will affect the time required by providers to care for individual patients and the ability of sites and programs to implement and scale services up and out. For example, if motivated staff are identified but have minimal or no training in general HIV care or ART management, significant resources and time will be required as the program is implemented. For more mature programs, issues of staff fatigue and burnout need to be considered, with appropriate shifts in tasks and patient load per provider being made as necessary.

Although many acknowledge that HIV prevalence in the health-care workforce is an issue, this prevalence is rarely directly addressed in human resource estimations. In general-population high-prevalence settings, some proportion of the staff is likely living with HIV. Providing clinical care for health-care staff living with HIV is important for supporting a stable workforce. In addition, anecdotal reports suggest that providing HIV care has lessened health-care worker stigma toward people living with HIV. Although HIV prevalence among the health-care workforce is an important issue, testing of any health-care workers should be voluntary, and confidentiality regarding individual HIV status must be protected at all times.

HIV Prevalence and Patient Profile

Prevalence of HIV in the community will greatly impact human resource needs, particularly for long-term staff planning. In the immediate future, as treatment programs are initiated either as integrated or stand-alone efforts, decisions about target populations will influence staffing needs. New HIV clinical services often focus on providing care to those in greatest clinical need. These patients tend to require more significant provider management, because they tend to have more clinically advanced HIV or have comorbid conditions, such as tuberculosis, that complicate care. Likewise, programs that identify pregnant women as a target population will likely have more complex human resource needs.

Although the initial patient burden often addresses those in greatest clinical need, it is expected that individual patient profiles, and therefore the overall population profile, will change over time. As access to and utilization of counseling and testing services increase and as there is more widespread implementation of opt-out testing programs, it should be anticipated that more people at an earlier stage of the disease will be identified. These largely asymptomatic patients will require less-intensive clinical management and will therefore require fewer human resources.

It is important to remember that none of these factors is static. Each factor will change repeatedly, evolving in response to factors directly and indirectly related to the HIV epidemic in a particular setting. The challenge for public-health professionals and health planners is to constantly review human resource needs, scanning the environment at the community and national level to identify shifts and to make appropriate changes. When possible, data should be used to guide changes in human resource need estimates.

Establishing Staff Plans and Strategies to Address Workforce Shortages

Establishing program- and site-specific staffing plans and strategies is not an exact science. It requires knowledgeable health-care workers and public-health planners who have an understanding of health-care service delivery in the country, as well as particular expertise and experience in the setting in which HIV clinical care services will be provided.
Of the approaches to human resource estimation presented earlier, two approaches are likely to best suit HIV treatment scale-up efforts. The preferable method is to take a team approach, which bases estimates on the need to complete specific and discrete patient care tasks. This approach allows for better utilization of often scarce resources, such as physicians, and gives sites and programs the flexibility to shift tasks in response to program and patient profile changes and staffing demands. However, as discussed earlier, this approach is not feasible in many situations due to regulatory or other reasons, and thus provider estimates are required. Although this approach often makes it simpler to calculate the estimates (e.g., for every 200 patients on ART, one physician is needed), it constrains the ability of sites and programs to respond quickly to shifting patient dynamics.

The following are issues to consider when estimating human resource needs for specific cadres of health-care workers, including program management. Together these issues represent the staff composition necessary to provide comprehensive, quality HIV care services.

Clinical Staff
Physicians, clinical and medical officers, and nurses form the front line of HIV care. Specific functions performed by members of each cadre vary widely according to site, program, and national guidelines. Across settings, these staff are collectively responsible for initial assessment and screening, determining ART eligibility, prescribing medications, providing follow-up care (including refills for existing prescriptions), authorizing regimen switches, referring for other clinical care, and, in many settings, providing general HIV counseling and adherence support. Some tasks may be allocated downstream in order to relieve the burden on the scarcest resources, typically physicians. This allows other adequately trained and supervised staff to manage routine care so that the greatest number of patients can be seen while providing maximum-quality care. For example, a clinical or medical officer is responsible for initial screening and eligibility determination, while nurses are responsible for follow-up of clinically stable patients with no comorbidities. This setup allows sites and programs to strategically use the expertise of trained physicians to address the needs of more complex cases, including regimen switches. It also requires shifting to other trained staff tasks typically performed by nurses, such as general and adherence counseling and tracking patients who have missed clinical visits.

Auxiliary Staff
Treatment and adherence support providers, as well as general counselors, are increasingly seen to be a critical part of a successful HIV treatment initiative. Many programs rely on trained, nonclinical staff to provide routine and ongoing support to patients regarding treatment adherence, nutritional support, prevention for positives, outreach for missed visits, and home-based care. The work required of this level of staff is intensive and often leads to provider fatigue and burnout. In estimating realistic human resource needs, nontraditional factors should be addressed, including distances that need to be traveled to follow up with clients who miss their clinical visits. The limited data available for estimating levels of staffing for this cadre of staff range between 10 and 20 patients per provider. Although shifting crucial nonclinical tasks to this group of providers may significantly relieve burdens at higher levels of the health system, supervision and ongoing education needs must be taken into consideration and assigned to appropriate staff.
BOTSWANA STARTED PROVIDING antiretroviral (ARV) medicines at public sector health facilities to the citizens in 2002. The ARV services started at four sites, where each site consisted of one hospital and four satellite clinics. Initially, the ARVs were prescribed by specialists and dispensed by pharmacists at the hospitals, while the clinics were limited to screening and pre-antiretroviral treatment investigations.

As more patients enrolled in the program, the challenges began to emerge, including patients traveling long distances to hospitals, congestion at the health facilities, and long queues and waiting hours, especially at the hospital pharmacies.

To mitigate some of the challenges, strategies to increase access to ARVs were developed. These included accelerating roll-out to the remaining hospitals and outsourcing the ARV services to private practitioners through the medical aid administrators’ public-private partnership. This resulted in temporary relief of the congestion, but following the approval of a routine HIV testing policy, more patients were identified as eligible, resulting in further long waiting times at all facilities.

Some of the patients started defaulting and cited travel logistics, such as lack of transport and financial constraints, as some of the reasons for not adhering to therapy.

The policy to roll out the ARV services to lower-level facilities (i.e., to allow the clinics to prescribe and dispense ARVs) was put in place. Major constraints included limited infrastructure for ARV storage, consultation and dispensing, as well as personnel shortages (especially pharmaceutical officers). Development partners offered to support the government by providing infrastructure and, where possible, providing personnel as project posts. However, recruitment of pharmaceutical officers lagged behind and remained a major bottleneck to the program. The policy to authorize nurses to prescribe and dispense ARVs was approved in 2006.

In Botswana, nurses are the pillars of the primary health-care system, as they form the bulk of the health-care delivery system. They are already involved in the prescribing, dispensing, and inventory management of medicines, even though they have not received formal training on pharmaceutical activities.

In 2007, the Botswana Harvard Partnership (BHP)-PEPFAR Master Trainer Program was mandated to equip nurses with the knowledge and skills to adequately manage and dispense ARV medicines to deserving patients. A four-day training program was developed to cover pharmacotherapy of ARVs, dispensing techniques, ARV medication adherence counseling, and appropriate ARV inventory.
management. This included quantification, the ordering process (procurement), receiving, and the appropriate documentation. The training consists of formal lectures, group discussions, role plays, and actual practical training at facilities. There is also a pre- and posttest.

After the training, the participants are mentored and monitored by the pharmaceutical officers at the hospitals or dispensing satellite clinics. A monitoring tool, consisting of the dispensing log for the participant and the performance log for the supervisor, is one of the tools used for evaluating the officer.

Training nurses in ARV drug management and dispensing has facilitated roll-out to the clinics. Services may be rendered on-site or as an outreach service. Eighty-five nurses have been successfully trained, and 25 clinics in the country are served by the trained nurses. In some facilities, the nurses dispense ARV drugs on their own, while in others, they dispense with pharmaceutical officers on a rotational basis.

The experience in Botswana has shown that with adequate training, nurses may play a pivotal role in ARV dispensing, especially where there is a shortage of pharmaceutical officers.

Technical Support Staff
Pharmacists and laboratory technicians are critical team members who are often underrepresented in HIV workforce estimations. In most resource-constrained settings, there is already a critical shortage of both laboratory technicians and pharmacists. Often, pharmacy and laboratory staff serve an entire facility and not a particular program. Therefore, existing workload burden and staffing gaps must be taken into consideration when adding HIV care. For pharmacists in many HIV clinical care programs, there is an expectation that they provide adherence counseling in addition to their dispensing and record-keeping responsibilities. In making determinations about pharmacist staffing needs, decisions need to be made regarding their role, if any, in adherence counseling, and estimates are needed for the time of patient-provider interaction. For example, a study in Zambia determined that for every 1,000 patients on treatment, 1.5 pharmacists were needed, with an average patient-provider interaction time of 8 minutes.10 Similar determinations need to be made at the site and program level. Likewise, for laboratory technicians, considerations regarding the scope of services and tests to be performed must also be considered when determining staffing needs.

Program Management
As clinical care programs become more complex and as program, administrative and financial management, and reporting requirements increase, there will be a growing need for qualified staff to fulfill these functions. In some settings, clinical staff assume some or all of these responsibilities. As human resource estimates are being made, discussions should include the appropriateness of this approach and should consider identification of staff responsible solely for program administration, including data collection, analysis, and reporting. As discussed previously, identifying the tasks that must be completed on a per-patient or monthly basis, while also taking into consideration patient volume, will likely result in the most appropriate staffing levels.

No one-size-fits-all calculation allows a facility or program to enter the current or projected
number of people enrolled in HIV care and to receive in return a staffing figure and pattern. Human resource needs must be adjusted to address the current situation, building on assets and taking into consideration existing constraints. It is also critical to remember that staffing needs are not static. Staffing levels need to be routinely reevaluated, using patient load and staff efficiency data to make adjustments in task assignments. Existing staff should be trained to take on new or different responsibilities, and appropriate staff should be hired to address critical gaps, if necessary.

CONCLUSION
The past five years have seen tremendous success in expanding access to and utilization of HIV clinical care. National and international resources have been mobilized to meet demand, and today people living with HIV are living longer because of these efforts. However, during this time of rapid expansion of service delivery, we have learned that a critical need is additional human resources to meet current and projected staffing needs. Sites, programs, and national governments are demonstrating flexibility in task assignment and in the use of nontraditional staff. In the coming years, continued attention must be paid to human resource needs to ensure that eligible patients are enrolled in HIV clinical care and that those already enrolled continue to receive the highest-quality care possible. This will require a commitment at all levels of local, national, and international health systems to continuously monitor human resource needs and provide the necessary resources.
REFERENCE LIST


A comprehensive response to human-resources-for-health (HRH) challenges requires both macro- and micro-level interventions. Macro-level interventions are well suited for international- and national-level action. At the service delivery level, however, institutional and micro-level interventions are required to attract, train, and retain health workers in sufficient numbers. These workers must then be equitably deployed and consistently motivated to provide high-quality services. The second High-Level Forum on Health Millennium Development Goals (MDGs), held in Abuja, Nigeria, in December 2004, acknowledged that unless action is urgently taken to address the HRH crisis, many countries will fail to reach the MDGs. It was acknowledged at that time that this failure would represent not merely a missed deadline but a real calamity for the impoverished citizens of the affected countries.¹

The HRH crisis is being experienced by fragile health-care systems in many developing countries and is the result of several macroeconomic factors as well as poor governance. This crisis, while longstanding, is compounded by the magnitude of the HIV pandemic, which has led to excessive workloads and burnout, high worker attrition rates, and limited entry of young professionals into the workforce. Any solutions to this crisis must therefore address broader macroeconomic factors as well as the local conditions influencing the availability of human resources on the ground. The World Health Organization (WHO) 2006 World Health Report included global, regional, and country-level profiles of workers in the health sector and provided new data on health worker demographics. It also provided recommendations for the future development of HRH from the WHO-led task-shifting consortium.³

According to the Global Health Workforce Alliance, in 2006, sub-Saharan Africa, home to about 11% of the world’s population, bore more than 24% of the global disease burden; yet it was home to just 3% of the global health workforce and spent less than 1% of the world’s financial resources on health. In most developing countries, the health workforce is concentrated in major towns and cities, while rural areas, on average, contain only 23% of the country’s doctors and 38% of its nurses.⁴ Imbalances exist not only in the total numbers and geographical distribution of health workers, but also in the skills mix of available health workers. WHO estimates that 57 countries worldwide (36 of
which are in sub-Saharan Africa) have such a critical shortage of health workers that the countries would need to increase their health workforce by about 140% to achieve enough coverage for essential health interventions in order to make a positive difference in the health and life expectancy of their populations.⁵

**REASONS FOR THE HUMAN RESOURCES CRISIS**

The major challenges to building an effective health-care workforce in developing countries include

- low absolute numbers of trained health workers;
- difficulties in recruiting, retaining, and managing health workers;
- the impact of HIV on the health workforce; and
- poor health-worker performance.

**Low Absolute Numbers of Trained Health Workers**

In many developing countries, the capacity for training health workers is limited. For example, Ethiopia, with a population of 75 million, trains about 200 doctors a year, whereas the United Kingdom, with a population of 60 million, trains more than 6,000 doctors a year.⁶ Two-thirds of the countries in sub-Saharan Africa have only one medical school, and some countries have none.⁷ In addition to the low capacity for training, there is a growing sense that in sub-Saharan Africa, the medical profession—and the clinical disciplines in particular—have become less attractive to new entrants due to low salaries in the public sector, low morale among existing health-service providers, dilapidated health systems, and fear of HIV infection. These factors need to be researched further to understand the role they play in attracting and retaining a high-quality health-care workforce.

**Difficulties with Recruitment and Retention**

Many facilities face difficulties in recruiting and retaining health staff. An important reason for this challenge is that health workers often migrate to find better opportunities. This migration includes international migration, internal rural-to-urban migration, migration from clinical to administrative jobs, migration from the public to the private or nongovernmental organization (NGO) sectors, or migration out of the health-care sector entirely.

Both push and pull factors are associated with migration. Push factors are those negative factors that lead to dissatisfaction with where the health worker currently works. Low wages, lack of additional training opportunities, poor working and living conditions, and lack of social and retirement benefits are commonly cited push factors.⁸ Pull factors are those factors that make other potential jobs or areas more attractive, including higher salaries, better working conditions, better benefit packages, training opportunities, and recognition of good performance.⁹

In a 2004 analysis of staff loss rates in Zambia, Huddart et al.¹⁰ showed an annual rate of loss of 20% for clinical officers and 36% for midwives, with loss rates for doctors and nurses falling somewhere in between. In Malawi, death and resignation were the main causes of health-care worker attrition (Figure 1).¹¹ Deaths often result in posts being left vacant because no additional staff are available to replace those who have passed away.

**Impact of HIV Infection on the Health Workforce**

In the study by Gonani et al.¹¹ death contributed 48% of health-worker attrition—with 73% of these deaths attributed to HIV—making HIV a significant threat to HRH. The Joint Learning Initiative has identified three ways in which HIV poses a great threat to the health workforce.¹² First, HIV
is associated with increased workloads and skill demands; second, health workers frequently fall ill and die from HIV infection; and third, health workers must cope with the psychosocial stress of caring for increasing numbers of dying patients, in addition to caring for their own sick family members. In addition, fear, stigma, and discrimination affect worker motivation and performance.

A major concern among clinical service providers and other support staff in developing countries is the risk of contracting an infection such as HIV in the course of performing their regular duties. In studies conducted in Kenya and Malawi, 9 out of 10 health managers perceived the risk of HIV infection to be high or very high. Reasons for this perception included lack of skills in infection prevention, delays in investigation of patients (e.g., those with signs or symptoms of TB), and lack of protective materials due to stock-outs and staff negligence. These fears led providers to avoid performing certain tasks or to leave clinical service altogether.

A study in South Africa found that 11.5% of health workers in two public hospitals were HIV positive. The proportions were highest among nurses, student nurses, and younger staff. Of those living with HIV, 19% had CD4 counts below 200 cells/mm³ and were therefore eligible to receive antiretroviral therapy (ART). In addition to directly affecting the lives of health workers, the HIV epidemic has led to widespread fear of infection, increased workload, and burnout. Research in Swaziland has suggested that these factors can lead to significant decreases in the quality of health-care services.
There is also fear that the rapid scale-up of ART, because it is so labor intensive, will negatively affect other non-HIV-related health programs. However, early evidence suggests that the number of health worker lives saved by ART may offset the additional human resources needed to implement HIV treatment programs.17

**Poor Health Worker Performance**
In addition to problems created by the lack of absolute numbers and the inequitable distribution of health workers, there is also the problem that health workers do not always provide an acceptable level of care. In a 2005 review of this issue published in *The Lancet*,18 it was found that determinants of health workers’ performance included their knowledge, skills, motivation, and experience, and attitudes toward their job, workplace, and patients. The review also listed nonhealth-worker factors, such as the quality of the guidelines workers are expected to follow and the health facility environment (e.g., workload, availability of equipment, attitudes of co-workers and supervisors, and the degree of control workers have over the work environment), as well as external factors, such as the socioeconomic and political environments of the country or region in which the workers are practicing.

A study by Manongi et al.19 explored the experiences of health workers in the primary health-care facilities of the Kilimanjaro region of Tanzania. The study looked at workers’ motivation, satisfaction, and frustration and attempted to identify areas in which sustainable improvements to services could be achieved. It was discovered that the primary factors influencing worker motivation were the complexities of multitasking in the context of staff shortages, a desire for more structured and supportive supervision from managers, and improved transparency in career development opportunities.

**STRATEGIES TO ADDRESS HRH CHALLENGES**

**Increase the Number of Trained Health Workers**
Efforts to train existing health workers in developing countries are growing as wealthier nations increase aid to these countries and recognize the futility of providing lifesaving medicines in the absence of properly educated medical personnel. National governments of developing countries are also beginning to increase investments in training more health workers, but these investments have so far fallen short of what is needed.

Some innovative approaches to increasing the number of trained health workers and for developing training programs to address some of the maldistribution problems have been attempted in various countries. For example, some countries offer free medical training to students from developing countries. Cuba graduated nearly 4,000 international students from its medical schools between 1966 and 2004.20 Medical schools within developing countries have also been founded or expanded using funds from international donors, including governments, nongovernmental development agencies, or medical schools in wealthier countries.21 Increasing the number of medical trainees will not necessarily solve all aspects of the workforce crisis. Egypt, for example, trains more physicians than it needs, but because of the low remuneration for working in rural areas, doctors often prefer to leave the country or leave the profession rather than move to rural areas.22

**Recruitment and Retention**

*Decrease the Barriers to Hiring New Staff*
The Capacity Project, an initiative supported by the United States Agency for International Development (USAID), has worked with health sector leaders to develop the Emergency Hiring
Plan (EHP), a rapid-response staffing and training model designed to increase the number of qualified health professionals available to work in public health facilities. The EHP is helping the Kenyan Ministry of Health expand access to treatment and care through rapid hiring, training, and deployment of 830 health workers. This aid has shortened the recruitment process from more than a year to three and a half months. The new hires are given three-year contracts; afterward, the Ministry of Health absorbs them into the regular workforce. EHP hires also receive a two-week training session prior to starting work to update their HIV-related clinical skills. Once these workers are absorbed into the permanent service of the Ministry of Health, they receive routine in-service training alongside other regular staff.

Reduce Internal Migration

Whereas most workers identify salary level as an important push or pull factor, it is not the only factor in worker retention. Good accommodations, the quality of health-care facilities, and the welfare of the worker’s entire family are all important in the professional development of health workers. Attention to these factors has been shown to improve retention in high-income countries. A common strategy for increasing the number of health workers in rural areas is to provide training for students who come from rural areas. A wealth of evidence from developed countries indicates that students from rural areas are more likely to practice their profession in rural areas. This finding also holds true in South Africa and Thailand, where medical students from rural areas are more likely to return to those areas after graduation. Even if students do not originate

Decrease Rural/Urban Health-Care Inequities

The unequal distribution of health staff is a significant challenge for rural facilities. For example, in Nairobi, Kenya, there is one doctor per 500 people, whereas the remote Turkana district of Kenya has one doctor per 160,000 people. Countries have used a variety of strategies to reduce geographical disparities, including increasing training opportunities for students from rural areas, providing a rural experience during pre- or postgraduate training, increasing the number of nonspecialist trained staff, and providing financial and nonfinancial incentives for health workers in rural areas. A common strategy for increasing the number of health workers in rural areas is to provide training for students who come from rural areas. A wealth of evidence from developed countries indicates that students from rural areas are more likely to practice their profession in rural areas. This finding also holds true in South Africa and Thailand, where medical students from rural areas are more likely to return to those areas after graduation. Even if students do not originate
from rural areas, providing rural experiences during pre- or postgraduate training can increase the chances of their practicing in rural areas. Again, although much of these data are from developed countries, evidence also exists from Ghana and Thailand that providing rural training experiences will increase the chance of trainees accepting a rural position. Another strategy is to increase the number of general physicians trained. Brazil and Canada have attempted this strategy based on the assumption that generalists are more likely to move to rural areas.

In addition to making changes in the education of medical professionals, governments have provided incentives to recruit and retain staff in rural areas. South Africa, for instance, has introduced an 8% to 22% salary bonus for staff working in rural areas, depending on the cadre of staff and the rural designation of the placement. A survey conducted soon after this program was implemented found that 28% to 35% of staff in rural areas had decided to stay for the next year because of the rural allowance. According to another South African study, rural doctors stated that higher salaries would have the most effect on retention in rural areas but that nonfinancial incentives were also important. The three most important nonfinancial factors identified in this study were suitable accommodation, a good hospital environment and working conditions, and increased career opportunities. At least one of the doctors interviewed also listed access to continuing medical education, recognition and appreciation, and good staff relationships as important factors in retention.

Decrease Staff Turnover
Most of the data on reducing staff turnover come from fields outside of health care or from health-care systems in high-income countries. In the following sections, we will review the general principles from these fields and then discuss examples of how these principles have been practiced in developing countries.

Husselid examined the association between human resource (HR) management practices of 968 American companies in various fields and their turnover rates, productivity, and financial performance. He grouped HR management considerations into two categories: (1) employee skills and organizational structures and (2) employee motivation (see Box 1).

The average annual turnover across all the companies in Husselid’s study was 18%. Companies that received higher ratings for employee skills and organizational structures had lower turnover rates. The factors relating to employee motivation were not associated with turnover. The author felt that although paying attention to motivation would help decrease turnover, performance appraisal and linking compensation to performance could increase turnover by causing weak staff members to leave. The same study found that staff productivity and company financial performance are both positively associated with good employee skills, good organizational structures, and employee motivation.

Within the health-care field in developed countries, a number of studies have examined the characteristics of hospitals with low turnover rates and the reasons staff members choose to leave a given facility. The NEXT Study Group compared the opinions of 1,175 nurses from hospitals with low and high turnover rates. Nurses from the low-turnover hospitals perceived fewer job opportunities in their local area, but they also expressed more positive feelings about the hospital where they worked. For instance, those nurses had a shorter commute, recognized lower exposure to hazards in the workplace, had more control over their work schedule, were happier with their roles and the latitude to make decisions in their jobs, and had a better effort-reward ratio. They also recognized better relationships with management.
Africa (Angola, Botswana, Republic of Congo, Kenya, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, South Africa, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe), health workers receive a variety of nonfinancial incentives, including training and career path incentives, housing, transportation, child care, improvements to facilities, and security. Of the 16 countries assessed, 15 had also developed HR information systems.

Reduce the Effects of HIV
The first step in reducing the direct effects of HIV, as well as the stress related to the fear of infection, should be the introduction of good infection control procedures to protect health workers from nosocomial HIV infections. The use of postexposure prophylaxis to be taken in the event of a needle

<table>
<thead>
<tr>
<th>Box 1. Human Resources Management Considerations Associated with Turnover Rates</th>
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<tbody>
<tr>
<td><strong>Employee skills and organizational structures</strong></td>
</tr>
<tr>
<td>- What proportion of the workforce is included in a formal information-sharing program (e.g., a newsletter)?</td>
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<tr>
<td>- What proportion of the workforce has been subjected to a formal job analysis?</td>
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<tr>
<td>- What proportion of the workforce participates in attitude surveys on a regular basis?</td>
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<tr>
<td>- What proportion of non–entry level jobs have been filled internally in recent years?</td>
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<tr>
<td>- What proportion of the workforce participates in quality-of-work/life programs, quality circles, and/or labor-management participation teams?</td>
</tr>
<tr>
<td>- What proportion of the workforce has access to company incentive plans, profit-sharing plans, and/or gain-sharing plans?</td>
</tr>
<tr>
<td>- What was the average number of hours of training received by a typical employee over the past 12 months?</td>
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<tr>
<td>- What proportion of the workforce has access to a formal grievance procedure and/or complaint resolution system?</td>
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<tr>
<td>- What proportion of the workforce is subjected to an employment test prior to hiring?</td>
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<tr>
<td><strong>Employee motivation</strong></td>
</tr>
<tr>
<td>- For what proportion of the workforce are performance appraisals used to determine compensation?</td>
</tr>
<tr>
<td>- What proportion of the workforce receives formal performance appraisals?</td>
</tr>
<tr>
<td>- Which of the following promotion decision rules are used most often: (1) merit or performance rating alone, (2) seniority only if merit is equal, (3) seniority among employees who meet a minimum merit requirement, or (4) seniority alone?</td>
</tr>
<tr>
<td>- For the five positions that the firm hires most frequently, how many qualified applicants are there per position (on average)?</td>
</tr>
</tbody>
</table>

Source: Adapted from Husselid.
management and support approaches that lead to higher levels of performance and improved outcomes. For example, in a study to gather examples of how different service delivery organizations in Guatemala try to manage and improve the performance of their staff, it was found that availability of resources is a key factor in influencing staff performance. Providing resources to carry out fieldwork and offering salaries that are competitive within the national labor market appeared to have the greatest influence on staff performance. Additional important influences for ensuring improved performance included supervision linked to support for the performance of clearly defined individual tasks, coaching and mentoring, measuring, and monitoring.

Quality Improvement Methods
Over the years, the Quality Assurance Project (QAP)—the predecessor of the Health Care Improvement Project implemented by University Research Co. LLC—has been involved in using quality improvement methods to help provider teams identify barriers to providing effective and efficient health care and to develop solutions to these problems. This approach has led to more motivated staff, improved service delivery systems, and improved care outcomes. Examples of programs that have utilized this approach with subsequent improvements in staff performance and outcomes are presented on the QAP Web site (http://www.qaproject.org). Some of the improvements achieved by these programs include decreased postpartum hemorrhage, improved compliance with standards of care, improved adherence to antiretroviral (ARV) medicines, better triaging of children with serious illnesses, and better outcomes of emergency care, such as reduced deaths within 24 hours of admission. Importantly, these improvements have been made by changing the process of care delivery and without increasing the number of health-care workers.
THE PERFORMANCE OF A HEALTH care system is only as good as the performance of the service managers and care providers within that system. Illustrating this point are findings of a 2003 study from Vietnam investigating factors influencing job motivation among rural health workers. According to the authors of the study report, managers and policymakers considered supervision to be an important tool in controlling the work of health workers; this supervision took place regularly, though the frequency varied for each level of staff. The authors considered supervision to be integrated to some extent, as all activities were checked during a single visit. However, according to them, the vertical programs had their own supervision system. For example, health workers perceived supervision as a means of controlling their work plan without providing feedback, and positive feedback was lacking when the health workers performed well. This point is illustrated by the following comment from a staff member of a preventive health team at the district level:

During supervision of the provincial program, such as for malaria, the supervisor comes and looks at the record books. If there is something wrong we sit together and fix it. But there is no feedback, and sometimes I don’t know if my work is acceptable or not.

Feedback is one way for managers and colleagues to show appreciation, which was found to be the most important motivating factor for health workers in the Vietnam study.

In this study, staff appraisal, including evaluation of the health facility, took place biannually, as explained by the managers interviewed. As part of this appraisal, health workers had to assess themselves in writing and assess the team during a meeting. The health workers considered the appraisal to not be very useful and saw it mainly as an administrative exercise. They had the feeling that they could write anything they wanted. As one community health center staff member remarked,

We send the appraisal report to the district health center in a certain period and in the report we write down what we have done and we give a self assessment, but we always assess ourselves positively. The result will affect the assessment of the group.

Appreciation can be shown during performance appraisal and can serve as an important entry point for staff motivation. According to managers and policymakers, an additional token of appreciation commonly used in Vietnam is the award system, which is linked to the biannual appraisal. Awards, in the form of money, certificates, or other tokens, are given to people who are assessed as excellent workers. Although its value has decreased over the years, the award system is still appreciated by health workers. Apart from the award system, however, other strategies to motivate staff are not commonly employed.
CHANGES IN HEALTH CARE SERVICE DELIVERY

Highly skilled doctors are not available in large enough numbers to provide services to the majority of clients, especially in rural areas. One solution to address this is task shifting to well-trained lower-level cadres of service providers—for example, clinical officers and nurses instead of doctors. Different countries have a variety of locally trained indigenous health professionals—clinical officers in Malawi and Zambia, surgical and medical technicians in Mozambique, assistant medical officers with surgical and obstetric skills in Tanzania, and medical assistants in Ghana. The medical licentiates and clinical officers in Tanzania are trained to diagnose, treat, and prescribe and can therefore fulfill many functions in district hospitals that the shortage of doctors would otherwise have made impossible. Likewise, nurse practitioners in Swaziland and enrolled nurses in Malawi have played immense roles in their health systems, particularly in remote areas where it is difficult to get better-qualified health professionals to practice. These cadres typically require two to three years of postsecondary training, rather than the five to six years required for medical doctors.

Data show that tasks previously performed by doctors can be performed equally well by both nonphysician clinicians and nurses. Other data support the use of lay health workers to effectively deliver malaria treatment, increase immunization uptake, and improve treatment of TB. Mounting evidence also indicates that nonphysician practitioners (primarily clinical officers and nurses) can, with adequate training, deliver ART to HIV-positive patients.

A few studies have documented the effectiveness of using nonphysician providers and lay health workers to increase capacity for HIV-related services. In 2003, a study conducted at 16 health-care sites in Zambia offering various HIV-related services (e.g., voluntary counseling and testing, prevention of mother-to-child transmission, and ART) demonstrated that it is possible to improve performance through the use of trained laypersons.

In Mozambique, an intervention involving nurses performing CD4 lymphocyte counts, when implemented correctly, was associated with a more rational use of higher-level clinical providers, which may improve overall clinic flow and efficient use of the limited HR supply. However, this particular intervention did not lead to an increase in the number of patients starting ART or a reduction in the time to ART initiation. The length of time that the program had been operating played an important role in all outcomes, suggesting that general improvements in clinic efficiency may have overshadowed the effect of the intervention. The lack of observed effect in these outcomes may also be due to additional health system bottlenecks that delay the initiation of treatment in ART-eligible patients.

More studies are needed to clarify the impact of changes to service delivery on the health workforce, particularly in light of increased global support for task shifting as a means to support the rapid scale-up of services. Although no one solution is available or feasible, the overall goal should be to get the right health workers with the right skills in the right place and doing the right things. Although each country is unique, each can and should learn from the experiences of others—best practices abound and need to be shared.
NE OF THE KEY CONSTRAINTS to the expansion of HIV services in resource-limited settings is a serious shortage of human resources for health. The shortage of well-trained health workers is global, but resource-constrained countries, particularly those in Africa, feel the crisis most acutely (see Figure 1). Put simply: there are not enough health workers to deliver on the target of universal access to HIV services.

The health workforce crisis is multifaceted and demands a comprehensive response that is aligned with broader health systems strengthening, including strategies to protect the health of the workforce and to treat those who are sick, to retain health workers in their jobs, and to train new and greater numbers of qualified professionals.1,2 There is also a need to seek innovative ways to make the best use of the available human resources for health and to quickly expand capacity. Many countries have responded pragmatically by adopting a task-shifting approach. This involves redistributing tasks rationally among health workforce teams so that specific tasks are moved, where appropriate, from highly qualified health workers to health workers with shorter training and fewer qualifications. Where further additional human resources are needed, task shifting may also involve the delegation of some clearly delineated tasks to newly created cadres of health workers who receive specific, competency-based training (see Figure 2). For example, in Malawi and Uganda, the basic care package for people living with HIV has

<table>
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<tr>
<th>Cadre</th>
<th>South Africa</th>
<th>Botswana</th>
<th>Ghana</th>
<th>Zambia</th>
<th>Tanzania</th>
<th>Malawi</th>
<th>USA</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors</td>
<td>69.2</td>
<td>28.7</td>
<td>9.0</td>
<td>6.9</td>
<td>2.3</td>
<td>1.1</td>
<td>230</td>
<td>256</td>
</tr>
<tr>
<td>Nurses</td>
<td>388.0</td>
<td>241.0</td>
<td>64.0</td>
<td>113</td>
<td>36.6</td>
<td>25.5</td>
<td>1212</td>
<td>937</td>
</tr>
</tbody>
</table>

Figure 1. The human resources crisis: health-care personnel (doctors and nurses) per 100,000 population

been designed to be delivered by nonspecialist doctors or nurses, supported by community health workers and people living with HIV. Similarly, Ethiopia has implemented a plan to train and hire community health workers to expand the current workforce delivering HIV services. This can free up the bottlenecks in service delivery and support a rapid expansion in the availability of HIV services, especially at the community level.\textsuperscript{3}

In January 2008, the World Health Organization (WHO) published a series of evidence-based recommendations and guidelines that represented the culmination of a broad-based process of consultation and evidence-gathering lasting more than two years.\textsuperscript{4} The WHO Global Recommendations and Guidelines on Task Shifting provide an authoritative framework that can help support and guide widespread implementation in countries that choose to adopt the approach as a national strategy for organizing the health workforce. This framework aims to bring clarity to the task-shifting experience and to identify and define the conditions and systems that must be in place if the approach is to prove safe, efficient, effective, equitable, and sustainable.

Note: PLHIV = people living with HIV

Figure 2. Task shifting: expanding the pool of human resources for health

The recommendations and guidelines cover the need for consultation, situation analysis and national endorsement, and the need for an enabling regulatory framework. They specify the quality assurance mechanisms, including standardized training, supportive supervision, and certification and assessment, that will be important to ensure quality of care. The guidelines also cover the elements that will need to be considered for the purpose of ensuring adequate resources for implementation and offer advice on the organization of clinical care services under a task-shifting approach.

At the International Conference on Task Shifting in Addis Ababa, Ethiopia, the WHO Recommendations and Guidelines were endorsed in the Addis Ababa Declaration, which was unanimously adopted on January 10, 2008.6

Recent interest in task shifting has been accelerated by the need to urgently respond to the HIV pandemic with a rapid expansion of treatment and care. Task shifting, however, involves rationalizing and decentralizing the way in which all health services are delivered and embodies the core principles of public health services that are accessible, equitable and of good quality. As such, task shifting also offers long-term potential for all primary health-care services and for overall health systems strengthening.

Note: The WHO Global Recommendations and Guidelines on Task Shifting can be downloaded at http://www.who.int/healthsystems/task_shifting/en/.

CONCLUSION

A major challenge to delivering quality services in developing countries is the growing shortage of trained health workers in countries already burdened with insufficient infrastructure, poor government health-care systems, and extreme poverty. Academic institutions lack the resources and faculty to produce enough qualified physicians. Doctors and nurses are leaving their home countries for better-paying jobs in developed countries or are migrating toward urban areas. Health-care professionals are also dying from the very infectious diseases they are needed to help prevent and treat. Overdependence on highly trained professionals, such as doctors, will thus limit the ability of these countries to scale up access to services.

Ultimately, in order to cope with these human resources challenges, it is essential to address both institutional and individual factors. Approaches at the institutional level include improved workforce management systems that pursue equitable distribution of health workers, staff inclusion in staffing-related decision making, clear job descriptions, improved communication between management and staff, supportive supervision, mentoring, and coaching. Approaches at the individual level include monetary and nonmonetary incentives, performance appraisal, career development, and task shifting linked to increased skills development. An effective response therefore requires a comprehensive approach that addresses institutional, facility, and individual factors in a holistic manner, while taking into consideration the needs and dynamics of the entire health-care system.
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Caring for Caregivers: Lessons Learned in Addressing the Needs of Health-Care Workers Affected by HIV/AIDS

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The NORWEGIAN NURSES Organization (NNO) is working in partnership with the Zambia Union of Nurses Organization (ZUNO) and the National Organization of Nurses and Midwives of Malawi (NONM) to assist nurses who are infected or affected by HIV/AIDS. This article shares experiences and insights gained, primarily in Zambia but also in Malawi, from the implementation of the “Caring for Caregivers” projects in both countries.

The Caring for Caregivers project has been operating in Zambia since 2003, and a similar project was initiated in Malawi in 2006, drawing on the experience gained in Zambia. We believe that what we have learned can be of value to nurses and nurses associations in similar resource-limited settings. If nurses and their nurses associations in countries such as Zambia and Malawi can be mobilized, encouraged, and empowered, then this should also be possible in other countries facing similar circumstances.

Nurses in resource-limited settings regularly face a number of challenges, including high patient loads, lack of psychosocial support, limited infrastructure, and limited opportunities for professional development and/or continuing education. Such burdens can easily lead to apathy and professional “paralysis.” Nurses in these situations may often find themselves simply attempting to get through one day at a time, hoping and praying that they, along with their patients, will survive.

PROJECT DESCRIPTION
The development of the Caring for Caregivers project was based on the results of a needs assessment survey that used both qualitative and quantitative research methods. Nurses in Zambia and Malawi were asked to articulate their needs and concerns, with the results of the survey providing an empirical basis for the project design.

The main objective of the project was to provide care and support to nurses and other healthcare workers. In Zambia, care and support activities were limited to nurses. Based on the project’s experiences in Zambia, the target population in Malawi was expanded to include other health-care workers. Desired outcomes included the provision of updated knowledge on HIV/AIDS, development and implementation of routines for infection prevention and control, and the creation of local
support groups to provide psychosocial and financial support to HIV-infected and affected health-care workers.

At first, the concept of caring for caregivers was not so easily understood or accepted, even among health-care professionals. Many asked, “Why should nurses be given preferential treatment?” or, “Can they not queue up for treatment together with their patients?” As nurses, we serve not only as professional caregivers but also as positive role models. For many nurses, the idea of publicly displaying a need for treatment is simply too embarrassing or shameful. This is especially true if the nurse suspects that he or she is HIV infected, due to the social stigma attached to this diagnosis. As a result, many choose not to seek treatment, preferring illness and a potentially early, unnecessary death over the consequences of disclosure. Other times, nurses may seek treatment far away from home so that they can remain anonymous, only to have their treatment interrupted or fail due to their inability to travel on a regular basis.

The Caring for Caregivers project was a creative response to these challenges. The mission of the project was simple and clear: nurses were getting sick and dying, and they were in need of special attention. The illness or loss of these nurses was being felt by the greater community as well, since shortages of health-care workers result in limited or diminished care. Indeed, without enough healthy nurses, how can a community remain healthy so that fields can be tended and businesses can be run? A prerequisite for a healthy community, a healthy workforce, and a healthy nation is the availability of enough health-care workers to provide quality care.

The Caring for Caregivers project consisted of four major interventions:

1. Nurses were provided with updated knowledge about HIV/AIDS. Many nurses had no formal HIV/AIDS training and had seldom if ever attended workshops or refresher courses (this was especially true among those living in rural areas).

2. A countrywide list of voluntary counseling and testing (VCT) centers was compiled and presented to workshop participants. Nurses were encouraged to be tested and were offered the option of being tested in a neighboring town if they felt that confidentiality might be compromised in their home areas.

3. In Zambia, procedures for infection prevention and control in the workplace were developed, tested, and implemented. These procedures were approved and adopted by the Zambian Ministry of Health for all health-care institutions.

4. Local support groups were established so that nurses could start income-generating activities to provide money that they could use to help each other. These support groups also served as gathering points for nurses to provide psychosocial support to each other, breaking the bonds of secrecy, silence, and stigma.

CREATING LOCAL SUPPORT GROUPS

Formation
Local nurses had to take a series of steps in order to establish a local support group. First, support group leaders had to gather 30 interested nurses. The nurses then organized themselves, electing a chairperson, secretary, and treasurer, and opened a local bank account. Leaders collected fees from the members for the support group and deposited them in the newly opened bank account. They also developed a written proposal for the support of income-generating activities that was then sent to the project coordinator and project manager for review, alteration if needed, and approval. Only
then was the group qualified to receive seed money, usually US$1,000 or US$500.

The success of these support groups was dependent on close collaboration, from the very beginning, with the administration and management of the local heath-care institutions. Their support and understanding was invaluable.

**Support Activities**

While the support groups at the beginning were quite focused on starting their income-generating activities, they were continually encouraged by the project managers (respected nurses) to reach out and help each other by providing psychosocial support. Nurses often know when a fellow nurse is ill. Instead of silently noting their colleague’s illness and absence from work and doing nothing about it, they were encouraged to actively help him or her. The saying ”No nurse should get sick and die” became a standard phrase used by project staff when speaking with nurses in the various local support groups around the country.

At the beginning, nurses often paid for food and medicine for sick colleagues from their own pockets. As the support groups began to make money, they were able to more actively support sick nurses. Support could come in the form of food and medicine purchases, paying for someone to clean the sick nurse’s home, or financial support when the nurse, as a family breadwinner, was incapacitated over a lengthy period.

Support groups also sought out the orphaned children of deceased nurses and paid their school fees as well as providing for other basic needs. This created a strong impetus for nurses to become members of their local support groups, as they realized that their children would be looked after by their colleagues in the event of their own illness or death. Money was also provided so that deceased nurses could be given proper burials.

Eventually, support group activities began to focus more on psychosocial and emotional support than on financial support. However, the ability of nurses to provide financial support to those in need added to their empowerment.

**Income-Generating Activities**

The specific types of income-generating activities undertaken were left to the imagination and decision of the local nurses. Circumstances differed from area to area, and the local nurses often knew best what types of activities might be able to generate a profit. The following are examples of activities that were successfully executed:

- “Tuck” shops (kiosks or small shops) selling low-cost items such as soft drinks, snacks, and telephone cards
- Poultry farming
- Pig farming
- Catering
- Tailoring
- Cafeteria
- Pool table rental
- Health-care checks (blood pressure and weight) for a fee

**GROWING PAINS**

The establishment of income-generating activities requires some level of business skills. Accounting, marketing, and separating capital expenses from operating costs are concepts that most nurses in the support groups were not familiar with. On discovering that greater supervision was needed, at least initially, to help familiarize the nurses with the running of a small business, the project leaders decided to increase the level of monitoring and counseling being directly provided to each local support group by project staff. This was a major undertaking, considering that the project had created over 80 support groups in Zambia, spread out across the country. It was also decided that a
three-day small-business-skills workshop would be
offered to support group representatives.

In several of the support groups, problems were
noted due to some nurses not sharing informa-
tion, not agreeing on how funds should be used,
not working well together, or not depositing
funds in the support group bank account. Most of
these “growing pains” were due to personal issues
and required some mediation from project staff
to resolve.

As expected, another challenge involved getting
nurses to commit their time and personal effort to
establishing and building the support group, since
most nurses were already terribly overburdened
and had little if any free time. Fortunately, having
at least 30 nurses in each support group usually
provided enough human resources and a dedi-
cated core of nurses who were able and willing to
put in the extra effort required. It should be noted
that the establishment of local support groups had
a strong psychological effect. We called it “the psy-
chology of hope,” the idea being that if we could
give nurses renewed hope by showing them that
they had not been forgotten, but rather were being
cared for and cherished, then they would respond
by mobilizing and playing their part. This proved
true in Zambia, time and time again, and is also
proving to be true in Malawi.

UNEXPECTED GAINS
As part of project implementation, a separate
research project was carried out by an external
researcher to evaluate the effectiveness of local
support groups. Responses from questionnaires
and focus group discussions revealed that a major
unexpected gain was the sense of unity and purpose
that had developed among the nurses. Previously,
there had been little or no contact between junior
and senior nurses, between privately employed and
public nurses, or between staff and administra-
tion. The newly established support groups often
represented a cross section of these groupings, and
by coming together during workshops and through
their local support group activities they were able
to forge a new sense of unity and purpose.

THE ROLE OF THE NATIONAL
NURSES ASSOCIATION
Local support groups will not function efficiently
over time without the support of a strong national
nurses association. Support groups require some
form of regular contact and monitoring. If this
contact is not provided, many will gradually
lose momentum and become dysfunctional. The
national nurses association benefits from its sup-
port of these groups by having a well-developed
network of nurses at the grassroots level.

FOR NURSES ONLY OR FOR ALL
HEALTH-CARE WORKERS?
One of the lessons learned during the Zambian
project was that local support groups in rural areas
often ran into a bit of trouble when other health-
care workers felt excluded from participation.
Nurses have been, and generally still are, an under-
privileged group within the health-care sector, and
many feel quite strongly that the support group
they have worked for and created is “by them and
for them.”

In Zambia, we chose to let the support groups
remain support groups for nurses, and not for-
mally expand them to include other health-care
workers. However, each support group can decide
who it wants to support, and if there are good rea-
sons for supporting a non-nursing colleague, then
the group is free to do so.

In Malawi, the main project also includes other
health-care workers. However, the activity is still
being initiated and run by nurses and should,
therefore, remain under the control of the nurses.

It should be noted that a gender issue is
involved here. Nurses are mostly female, while
other health-care workers (medical doctors, clinical officers, etc.) are mostly male. The nurses expressed concern that their male colleagues were interested in joining their support groups, reaping the benefits of the income-generating activities, and even taking control of activities, and that this might be at the expense of some of the needs of the female nurses and their families. Also, some nurses expressed indignation, saying that we, as nurses, were neglected for such a long time, and now, when we finally have something being done “by nurses, for nurses,” suddenly other health-care workers also want to share in the benefits. These are issues that need to be addressed and discussed in an open and honest manner.

We are still in the early days in Malawi in terms of the establishment of support groups, so time will tell how successful a support group structure run by nurses, but inclusive in nature, will be. We believe, however, that inclusiveness is a good thing to work toward, especially in smaller rural areas where communities are traditionally very close-knit. Our initial experiences with inclusive support groups have shown that hospital administration seems to be more inclined to approve and provide support to the establishment and running of such support groups, since it is an intervention that helps all health-care workers, not just an exclusive segment (i.e., nurses) of the workforce.

In Malawi, NONM has become the leading health-care professional agency in the country, organizing more than 2,700 nurses nationwide. From time to time, nurses will support and speak out on behalf of other health-care workers who do not have a strong association backing them. In such a setting, it is a natural to expand local support groups to include other health-care workers, while at the same time not relinquishing nursing control.

**THE WAY FORWARD**

With the experiences gained in Zambia and more recently in Malawi, NNO feels confident that it has developed a process and structure for the establishment of local support groups in resource-limited settings in which ownership and direction are developed and supported by local grassroots activity.

In Zambia, many of the local support groups have established themselves as viable organizational and financial entities. Several of them have sizable bank accounts and are continuing with their income-generating activities as a base for funding support activities. As the project draws to a close, these support groups will continue to function as part of ZUNO. A national network of local support groups within Zambia is an asset for ZUNO, both from an organizational standpoint and as a base for human resource development.

In Malawi, the project is still developing its network of support groups, but already considerable interest is being shown by a number of local groups of nurses who want to develop their own support groups. In Mzimba, in northern Malawi, a local support group has formed and already opened a cafeteria, supplying food and soft drinks to hospital employees, patients, and visiting relatives. Additional support groups are being established, and the issue of orphan support is high on the agenda.
HE PROVISION OF HIV TREATMENT and care in resource-limited settings is expanding rapidly. Health-worker training is one of many factors critical to the rapid scale-up of high-quality care.¹⁻⁶ Large numbers of health workers require HIV training, yet few countries have a comprehensive training plan to guide their training activities, a clear assessment of ongoing training needs, a plan to implement training on a large scale, or adequate funds budgeted for training. In this setting, an extensive variety of HIV-related training programs have sprung up over the past few years. Unfortunately, data measuring their effectiveness are limited, and no consensus exists about what constitutes effective training.

Underlying the looming challenge in health-worker training, most resource-limited countries face a chronic shortage of trained health-care providers; chronic understaffing impedes these countries’ ability to adequately train health workers in HIV care. A variety of factors contribute to this shortage. First, removing physicians and nurses from active clinics for training purposes intensifies the strain on clinical care systems. Second, professional programs for physicians and other health workers are lacking in some countries. For example, several countries in Africa and the Caribbean—including Botswana, Lesotho, Namibia, Swaziland, and the Bahamas—do not have medical schools and must send students outside the country for basic professional training (see http://imed.ecfmg.org; Table 1, next page). Third, the economic crisis in several African countries has affected recruitment of new graduates from medical and nursing schools. Finally, trained workers (and potential recruits) commonly leave the public health sector for better compensation, benefits, working conditions, and job satisfaction found in other sectors and other countries—the “brain drain” phenomenon—further exacerbating the human resource crisis.⁷⁻¹²

Faced with these challenges, and with the rapid pace of HIV treatment expansion, few resource-limited countries have sufficient internal resources to address their health workers’ training needs. As a result, most countries have collaborated with external partners to develop health-care-worker training programs and/or to bring in expatriate specialists to provide training, at least in the initial phase of scale-up. Often, these training efforts are poorly coordinated with national training priorities, lack evidence to support their effectiveness, and are driven largely by foreign partners.
result, many training redundancies exist alongside large unmet training needs.

We gathered information on global HIV training through a thorough review of the published peer-reviewed literature, Internet sites, program reports related to training for HIV treatment in resource-limited countries, a survey of HIV training efforts in countries with a high HIV disease burden, and discussions with appropriate professionals in selected countries. In this chapter, we review challenges and approaches to popular methodologies and applications of clinical HIV training in order to address the question: what is the optimal approach to training the health workforce for an expanding HIV-treatment program in a resource-limited setting?

Table 1. Medical Schools in Selected Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Medical Schools</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>230</td>
</tr>
<tr>
<td>China</td>
<td>171</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>16</td>
</tr>
<tr>
<td>Tanzania</td>
<td>4</td>
</tr>
<tr>
<td>Haiti</td>
<td>3</td>
</tr>
<tr>
<td>Cambodia</td>
<td>2</td>
</tr>
<tr>
<td>Kenya</td>
<td>2</td>
</tr>
<tr>
<td>Jamaica</td>
<td>1</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1</td>
</tr>
<tr>
<td>Rwanda</td>
<td>1</td>
</tr>
<tr>
<td>Bahamas</td>
<td>0</td>
</tr>
<tr>
<td>Botswana</td>
<td>0</td>
</tr>
<tr>
<td>Lesotho</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are from the international medical education directory of the Foundation for the Advancement of International Medical Education and Research (http://imed.ecfmg.org).

BACKGROUND

Training Appropriate to the Model of Care

The design of a national health-worker training program to support the expansion of quality HIV treatment should be tightly linked to the way in which HIV care and treatment are delivered in the country. Many national programs, such as those of the Bahamas, Botswana, and Uganda, initiated HIV treatment by following a “vertical” specialty HIV-clinic model in which the majority of HIV treatment is provided by HIV specialists. Training according to this approach targets the creation of multidisciplinary HIV-care teams that provide care predominantly, or exclusively, for patients with HIV.

At the other end of the spectrum is the public health model of care delivery, in which HIV care and treatment are provided by primary health-care providers who are trained in basic aspects of HIV care for adults and children and taught to recognize conditions that warrant referral to a specialized setting. Training in advanced aspects of HIV care is reserved for a small cadre of specialists. A hybrid of these two models occurs when a national program starts its treatment program by following the specialty model but decentralizes HIV services to peripheral facilities as treatment scales up. In this case, HIV care and treatment may be provided in a primary health-care setting by primary care clinicians, or by an HIV-care specialist.

In the vertical model, training in HIV care relies on a highly centralized training program driven by a small group of expert trainers, with a core curriculum that can be quickly and easily updated to keep pace with changes to practice and guidelines, and short intensive trainings for small groups of trainees. Parallel systems are often established for training in laboratory methods, counseling and
patient education, data collection, and pharmacy and supply management. As programs decentralize into a public health model, training decentralizes accordingly. Short, intensive trainings in a central setting become less practical. The cadre of trainers and curricula must be expanded, and systems must be implemented to allow for curricula review, updates, and distribution of continuing medical education (CME) and continuing nursing education (CNE) materials. The World Health Organization’s (WHO’s) Integrated Management of Adult and Adolescent Illness (IMAI) training strategy relies on a set of generic training materials that stress training within the public health model of care delivery and is designed for adaptation to fit the training needs of a particular setting. This approach stresses referral mechanisms, team building, clinical mentoring, and clinical monitoring within the context of both chronic and acute care.16

**Training Decisions amidst a Crisis in Human Resources for Health**

The human-resources-for-health crisis in resource-limited countries is a substantial obstacle to scaling up HIV-treatment programs and is directly relevant to health-workforce training. Neither Mozambique nor Rwanda nor Tanzania, for example, has more than 5 physicians, 43 nurses, or 3 pharmacists for every 100,000 people (Table 2).17 The United States, by comparison, has a density of 256 physicians, 937 nurses, and 88 pharmacists for every 100,000 people.17 Chen et al have linked low national staffing ratios to poorer

<table>
<thead>
<tr>
<th>Country</th>
<th>Physicians</th>
<th>Nurses and Midwives</th>
<th>Pharmacists</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>256</td>
<td>937</td>
<td>88</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>188</td>
<td>184</td>
<td>40</td>
</tr>
<tr>
<td>China</td>
<td>142</td>
<td>96</td>
<td>27</td>
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<tr>
<td>Bahamas</td>
<td>105</td>
<td>447</td>
<td>n/a</td>
</tr>
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<td>Jamaica</td>
<td>85</td>
<td>165</td>
<td>n/a</td>
</tr>
<tr>
<td>India</td>
<td>0</td>
<td>127</td>
<td>56</td>
</tr>
<tr>
<td>Botswana</td>
<td>40</td>
<td>265</td>
<td>19</td>
</tr>
<tr>
<td>Haiti</td>
<td>25</td>
<td>11</td>
<td>n/a</td>
</tr>
<tr>
<td>Cambodia</td>
<td>16</td>
<td>85</td>
<td>4</td>
</tr>
<tr>
<td>Kenya</td>
<td>14</td>
<td>118</td>
<td>10</td>
</tr>
<tr>
<td>Lesotho</td>
<td>5</td>
<td>62</td>
<td>3</td>
</tr>
<tr>
<td>Rwanda</td>
<td>5</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>Mozambique</td>
<td>3</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Tanzania</td>
<td>2</td>
<td>37</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Human Resources per 100,000 People in Selected Countries

Latest available data. Data are from the Global Health Atlas of the World Health Organization.17
health outcomes, and it is likely that this link extends to HIV care.

**Training Tailored to Each Health Sector Cadre**

The HIV health-care workforce includes doctors, clinical officers, nurses, pharmacists, laboratory technicians, phlebotomists, counselors, program managers, data clerks, ancillary staff, and community health workers. The function of each category of health worker depends on the local model of care delivery and is influenced by tradition, legislation, and local regulations. Variation in healthcare-worker roles can be an obstacle to adapting generalized training tools and curricula to a specific setting. A study in the United States found that nurse practitioners and physician assistants who specialize in HIV care provide better care than non-HIV-expert physicians and provide care that is comparable to that of HIV-specialist physicians—a finding that could support the expanded role of nurses and clinical officers in HIV treatment in resource-limited settings.

**Common Challenges**

As noted, many countries lack adequate preservice training institutions for health-care workers and must send clinicians outside the country for professional training. Postgraduate migration to other countries is common, exacerbating the human resource crisis. In a setting where the demand for health workers outweighs the supply available, it can be difficult to entice workers to staff underserved areas, such as rural sites. It can be hard to retain health workers when they themselves may feel the impact of HIV, either through their own infection, for which they may or may not be getting the appropriate treatment, or that of family members. Finally, for busy clinics, it can be a challenge to allocate time to training amid demands that staff time be devoted to patient care.

**DESIGNING A TRAINING PROGRAM**

There is scant evidence to support the effectiveness of one training methodology over another. Below, we present some of the advantages and disadvantages of the predominant training methodologies that have emerged ad hoc in the past few years.

**Preservice Education**

Adding or enhancing relevant coursework during preservice education for health professionals (e.g., medical schools, nursing schools) takes advantage of preexisting programs without taking professionals away from the workplace as trainers or trainees. It helps address health-workforce needs and ensures an adequate skill set among graduating professionals. However, it does not address the needs of those who have already completed their professional education, nor does it provide immediate solutions to urgent needs.

**Didactic Training**

Most training programs have emphasized centralized didactic training as the core training method. Didactic training, delivered as lectures in a classroom setting, is often used to convey large amounts of information at one time. Held in a centralized location, it typically lasts a week or two, and can accommodate large numbers of trainees—requiring fewer trainers and resources than other methods and allowing for standardization of the training’s content. The classroom style is a familiar approach for many trainees, yet the translation of classroom knowledge to clinical practice can be challenging, especially if the curriculum is divorced from the practical circumstances facing trainees or among trainees with limited experience. Trainees may not retain knowledge if it is not immediately applied to clinical practice. And, like all methods that take trainees and trainers away from their workplace, didactic training can temporarily exacerbate the strain on clinical care services.
While some programs send multidisciplinary teams of health workers to didactic trainings, others focus didactic training exclusively on one discipline—such as physician trainings or nurse trainings. Often, workers from one clinic who attend the training are expected to bring the information back to their clinic and train the remaining staff, although this may not always take place.

Training of Trainers
A training-of-trainers methodology is generally implemented when programs wish to provide didactic training at decentralized sites. Groups of health professionals are trained as “experts” and then expected to lead or facilitate future trainings. This approach attempts to expand the pool of trainers and leverage resources to build training capacity. An important downside of this method is the potential dilution of information as trainers get further removed from the original trainer’s expertise and information, which can impact the quality of training and the resulting clinical outcomes. Some trainers may require training in educational methods and pedagogy in addition to training in the management of HIV infection.

Refresher Course
It can be difficult for trainees with limited experience to absorb information from a didactic training. Trainees often benefit from practical experience at their own sites, followed by a refresher course. This affords trainees an opportunity to develop skills, before returning for ongoing training, that may add complexity and build on their classroom and practical experiences. It gives programs an opportunity to provide trainees with updated information and affords trainees the opportunity to solve problems together.

Distance Learning
Using computer-based or video-based technology is another way to train health-care workers in resource-limited settings. This approach allows trainees to remain at their workplace and has the added advantage of reaching a wide, geographically disparate audience with simulated cases that allow providers to test their knowledge without negative consequences to patients. These courses are inherently technology- and resource-intensive—the application of this method may be limited in settings with no access to the Internet—and require a certain degree of comfort with technological applications, but they reduce the need for trainers and allow trainees to move at their own pace.

Off-Site Clerkships (“Attachments”)
Some programs, such as those in Botswana and Kenya, complement didactic courses with opportunities to shadow experienced providers. During these off-site clerkships, or “attachments,” trainees spend a block of time with a mentor at the mentor’s clinical facility, which, ideally, is similar to their home clinic. Trainees gradually assume clinical responsibilities under supervision. The mentored environment allows the trainee to practice a skill with the comfort of having an experienced mentor to address questions and difficulties, and reinforces information provided during the didactic course. If the caseload and experience of the mentor are inadequate, or if the attachment site differs significantly from the practice sites of the trainees, this type of training may be less relevant. Finally, attachments can take trainees away from their jobs for an extended period of time.

On-Site Mentoring (“Preceptorship”)
On-site mentoring, or “preceptorship,” programs typically send experienced HIV-treatment professionals (nationals and/or expatriate health professionals) to sites of less-experienced providers for an extended
THE DEVELOPMENT AND APPLICATION OF A DISTANCE LEARNING TOOL FOR HIV CARE AND TREATMENT

Fransje van der Waals

Health[e]Foundation, the Netherlands

Health[e]Foundation is a not-for-profit organization that focuses on training and educating health-care workers in the care of patients living with HIV by means of a distance-based electronic (e-learning) system. The system, known as HIVeDucation, is an interactive, HIV/AIDS clinical management program that is tailored to the needs of clinicians and other health-care workers in regions severely affected by the HIV epidemic. The program has been designed to equip health-care workers with the practical tools they need to initiate and maintain patients on antiretroviral therapy (ART). The goal of the program is to train a new generation of specialized clinicians and health-care workers who can function as local role models who are capable of informing and advising their colleagues.

Programs are started in each country in collaboration with local stakeholders (e.g., public or private hospitals or other groups, such as research groups or medical schools). The first programs were launched in Thailand and Uganda, since these countries had relatively high computer literacy and had already started offering ART. Once the model proved successful, training was conducted in Mozambique, India, Surinam, Indonesia, and Malawi, followed by Kenya, Tanzania, Senegal, Cameroon, Eastern Europe and Bangladesh.

The HIVeDucation training program has several components, including computer-based clinical training, on-site workshops, and continuing medical education. The program combines computer-based self-study courses, clinical case studies, e-assisted tutoring, on-site workshops, and the creation of peer consultation networks. Electronic PDF files of all treatment guidelines and other relevant literature are provided. Participants are also trained in clinician-patient communication skills, counseling on issues of stigmatization and discrimination, and approaches to adherence education and palliative care by using exercises and role-play. Each workshop is tailored to the specific needs of the participant group.

CONTENT AND FORMAT

The HIVeDucation training program is composed of two main elements:

1. Up-to-date general information on HIV/AIDS, including pathogenesis, presentation and management. International experts write the HIV/AIDS modules and update them on an annual basis.

2. Localized country-specific information, including epidemiology, prevention programs and management guidelines. Modules can be added or removed from the program to provide a country-specific course.
In each country where HIVeDucation runs a training course, the Ministry of Health is asked to provide a country-specific epidemiology module to inform the participants about the local HIV/AIDS epidemic, the specific prevention programs that are being implemented in the country, and country-specific HIV testing and treatment guidelines. Several clinical cases per country have been designed with the assistance of local clinicians so that they reflect local resources and situations.

**TRAINING METHOD**

In developed countries, many continuing medical education (CME) programs for physicians as well as nurses are provided via the Internet in e-learning format (i.e., as computer-based learning programs). Our intention was to develop high-quality training for as many health-care workers in resource-limited settings as possible in a short period of time. We decided to develop an e-learning training tool specifically for health-care workers (HCWs) in the field of HIV/AIDS—not only for doctors and clinical officers, but for nurses, midwives and counselors as well. Distance learning has the advantage that HCWs are trained at the workplace, where they can learn at their own pace and in their own setting. This has a double benefit for the health center in that participants can do their training during the course of daily patient care and they can then instantly implement their newly acquired knowledge.

Since the Internet is not consistently available in every setting, we devised a special software program so that participants are able to work offline (via a USB memory stick) and only connect to the Internet to download and upload information to our server. Participants can connect their personal USB-stick to the Internet automatically when it is available. In the absence of Internet access, the information stays on the USB-stick until a connection is made. When connected, participant test scores (the training program is problem-based) are sent to the HIVeDucation database and emails are sent to the e-tutor. At the same time, participants receive updates and new modules from the server. World-renowned experts in the field, who are all committed to update the content of their module on a yearly basis, have written the modules. All modules contain pre- and post-module questions and results. Several references cited during the course are available as PDF files. Depending on the country where the training is given, modules can be added or removed from the course to provide country-specific information.

**IMPLEMENTATION**

The training program starts off with an on-site “kick-off meeting”. During this meeting, members of the HIVeDucation team introduce the program so that participants can learn about the background of the program and the problem-based learning method, and have the opportunity to practice with a hands-on computer exercise. A virtual “participant portal” is set up for each class so that participants have a customized space on the Internet that serves as a point of reference and a communication conduit throughout the training. After the kick-off meeting, participants undertake the self-study course, which usually takes about 12 weeks.

At the completion of training, an on-site three-day workshop takes place that serves as a final review and reinforcement of the course content. The on-site program is tailored to the
needs of the group and generally includes presentations by local and international experts, as well as people living with HIV.

LESSONS LEARNED

- Training teams of HCWs works well to promote teamwork and improve workflows.
- Conducting training for a group of hospitals in one geographical area promotes future networking.
- Computer illiteracy is no hindrance—learning curves of all groups (with different educational backgrounds as well as computer experience) are similar. For example, we trained midwives over the age of 55 who were proud to become not only computer savvy but also to be more involved in HIV/AIDS care.
- Blended learning (i.e., a combination of on-site and online training) is a must—participants work toward the on-site workshop, with support by email and or cell phones motivating them from a distance. Most participants want to have their computer-based learning finished before the on-site workshop.
- Focus groups are a great method for evaluating and improving the program, as well as for encouraging participants to start communicating with one another. We start all three-day workshops with focus group sessions.
- Teamwork, triage and collaboration within the AIDS care team, as well as the hospital, are oftentimes new and attractive concepts for participants. Certificates and diplomas are very important in most countries. HIVeDucation is nationally acknowledged, which increases participant motivation.

COSTS

The costs associated with distance learning are relatively high due to the high cost of the e-learning platform management system and the servers that support it, as well as production of the “offline” USB stick. We were able to start the program with grants from the Dutch AIDS Fonds, Roche and Gilead. Once the program was developed, it was supported by grants from Cordaid, the Dutch AIDS Fonds, and in 2006 a generous five-year grant was received from

period of time (several days to several months) to offer on-site mentoring. The preceptorship training methodology has the same advantages as attachments and also offers training specifically tailored to the trainee's work situation. Preceptorships can be particularly time-, labor-, and resource-intensive, and can require a large number of skilled mentors. While expatriate mentors are not always knowledgeable about local conditions, language, or policy, and may need to be licensed and/or registered to work as mentors, national mentors are in very short supply because of the human resource crisis and the fledgling nature of treatment programs in resource-limited countries. Most countries currently rely heavily on expatriate preceptors. WHO has developed recommendations for clinical mentoring in resource-limited settings. These guidelines include helpful information on planning, budgeting, and the monitoring and evaluation of a national clinical mentoring system as well as guidance on the selection, training, and preparation of clinical mentors.
the Dutch Government. Even with this support, 35% of program costs have to be covered by other sources. We generally receive a small fixed fee per participant from the in-country training partners, after which health[e]Foundation takes care of all remaining costs, such as kick-off meetings, USB memory sticks, IT support, e-tutors, three-day workshop venue, per diems, and facilitator fees.

FUTURE PROGRAMS

TBeDucation is a new program that is similar to HIVeDucation. It focuses on the management of TB in HIV-infected patients. The program is given to all participants after a three-day workshop. It is not a program aimed at experts in TB, but is suitable for all practitioners who see many HIV/TB co-infections but who, until now, have only been trained in HIV/AIDS.

Pediatric HIVeDucation is developed by the Pediatric European Network for Treatment of AIDS (PENTA) as a collaborative training program. PENTA/ESPID has a distance-based learning program available via the Internet combined with a workshop. It will be adapted for use in Africa and Asia and put on USB memory sticks by the Health[e]Foundation. We aim to deliver the program to as many health-care workers who are connected to both PENTA/ESPID and the Health[e]Foundation, and possibly to an even wider range of HCWs. Plans are to launch it in Thailand, Cameroon, Senegal, and Kenya.

CommuniteDucation is another new development. The program contains basic information in the form of animations, comics, movies, and other multimedia to inform and promote discussions within communities affected by HIV/AIDS. We hope that the program will be used by schools, positive living groups, workplaces, peer educators, and others and facilitated by trained HCWs.

Initial steps have been taken to develop new programs on neglected tropical diseases and malaria.

HIVeDucation is now available in English, Spanish, and Portuguese. Translations into French, Russian, and Chinese are expected to be available soon.

For more information about HIVeDucation, please visit: http://www.healthefoundation.eu.

Consultation

Some programs have developed a consultation system that allows newly trained providers to ask questions of experienced providers through direct phone calls, e-mail, call centers, or frequent site visits by the mentor. Consultation systems provide a support network that builds the confidence of newly trained providers. In Uganda, for example, the AIDS Treatment Information Centre hosts a call center that responds to providers’ treatment questions.21 Similarly, the Prince Leopold Institute of Tropical Medicine has developed an Internet-based program, TELEmedicine, to enable its experienced providers to respond via e-mail to inquiries made by clinicians in resource-limited settings.4 One drawback to a phone or e-mail system of consultation is its reliance on communication technology.

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Case Conferences
Another way to train providers is through case conferences: regular meetings to discuss complex problems in HIV care and to provide updates on practices or guidelines. Case conferences encourage a team approach to HIV care, help establish a network of HIV-care providers for informal consultation and/or referrals, and can reach a wide audience, especially with advanced Internet-based conferencing software, where it is available.

CME/CNE Programs
CME/CNE programs exist in countries with robust medical associations. Preexisting CME/CNE systems can be used as a vehicle for HIV training but are generally used to supplement a preexisting knowledge base, not to train inexperienced providers.

ESTABLISHING A NATIONAL TRAINING PLAN

Tailoring a National Training Plan to a Program’s Unique Circumstances
When establishing a national training plan, planners should consider their options and the appropriate combination of training methodologies in the context of their program’s unique circumstances, including the size of the population requiring treatment, the care delivery model, the extent of local expertise, the existing public health infrastructure, whether staff to be trained work in urban or rural areas, health-care-worker-to-population ratios, political will, nongovernmental organization involvement, available technology, and resources.

Forecasting Training Needs
Training programs would also benefit greatly from accurate forecasts of the demand for health workers: the number of necessary staff needed immediately, the number of staff needed over time as programs scale up treatment, the number of site locations, and the optimal number and mix of staff at each site. Such forecasts would allow planners to determine the extent to which an investment in hiring and training additional health workers would affect HIV care and the extent to which it is critical to budget- and resource-allocation decisions.

In August 2006, WHO estimated that over four million health workers would be needed in 57 countries to fill the gaps created by health worker shortages. When strategizing how to reach three
and death from HIV infection. Although it can be difficult to implement such solutions in resource-limited settings, some programs have chosen to train two individuals for every position, assigning each to spend half of his or her time at the HIV clinic and half elsewhere in the hospital or clinic. This reduces reliance on one individual, allowing each to miss clinical time without significant disruption. Without a buffer system to replace trained individuals, or the flexibility to train additional staff quickly, unexpected staff shortages create bottlenecks in clinic operation, slowing down the flow of patients and straining other staff. A forward-thinking national training plan will not only anticipate the loss of staff but will also incorporate ways to avoid it. Approaches might include augmenting salaries, recruiting staff to work in their home districts, improving staff-to-patient ratios, and providing adequate supplies.

Additional Considerations

Other considerations to be addressed when designing a training plan include training frequency, technological requirements, training site, the target audience, and content material. Planners should decide whether training sessions will be concentrated or spread out over time, and whether they will rely on technology such as computers, video, and Internet connections. Designers of training plans must consider the optimal components of a training site, for example, proximity to a healthcare facility, an environment similar to what the trainees will experience at their home clinic, or the use of the home clinic itself as the training site. Planners must assess the training previously received by workers and decide whether to train one health cadre at a time or to train multidisciplinary teams together. Content material should match the reality on the ground, reflect local practice, and account for the availability of drugs and diagnostic capabilities.

Anticipating and Taking Steps to Prevent Staff Turnover

Training plans should anticipate common experiences—such as the permanent loss of trained health workers who take more lucrative jobs or burn out, the temporary loss of health workers who take leave or attend trainings, and worker illness
Optimal Model for a National Training Program

There is no single model for a national training program, given the differences among countries and HIV treatment programs. However, the elements mentioned above, such as the model of care delivery, the role of each health-care worker, and the advantages and disadvantages of popular training methodologies in the context of the particular country, are critical considerations for the design of any national training program.

CONTEXTUAL EXAMPLES: LESSONS LEARNED WHILE PLANNING AND IMPLEMENTING TRAINING PROGRAMS

Lesotho

In 2005, the government of Lesotho recognized the need to complement its decentralized national didactic trainings with an on-site clinical mentoring (preceptorship) program. As free antiretroviral drugs and laboratory testing became available and new treatment sites were rapidly added, the government determined that the newly trained staff were not fully confident in their ability to initiate treatment and would benefit from practical on-site teaching and guidance. A clinical mentoring program was established in response, relying mostly on expatriate volunteer expert HIV clinicians. Identified district hospitals received a doctor-and-nurse team for a period of six weeks to six months, depending on the progress of the clinic. As treatment expanded from the district hospitals to rural health centers, nurse mentors were also sent to the surrounding health centers where the training need for nurses was greater. Through consultation, case presentations and review, coaching, and encouragement, but not clinical care, the mentors helped guide their colleagues to clinical competence and confidence in their ability to function independently. In February 2008, after two years of relying on foreign mentors, the Lesotho AIDS Directorate hired five local nurse mentors. The transition to a local model involved extensive training for these clinical mentors, including being paired with an experienced foreign mentor.

The government of Lesotho and its implementation partners learned several lessons in the process of rolling out the clinical mentoring program. The Ministry of Health and Social Welfare (MOHSW), in collaboration with the Clinton Foundation, learned the importance of site preparation and clarification of the clinical mentor’s role prior to the mentor’s arrival. The MOHSW found it important to establish from the outset that the clinical mentors (doctors and nurses) were not there to relieve the workload, but rather to assist the clinic staff to identify barriers to scale-up and possible solutions. Written communication from the Ministry of Health (or comparable authority) to the administration of the facility clearly outlining the roles and responsibilities of the mentors and the local staff can be critical to the success of the program.

The initial barriers to scaling up HIV treatment and care are often facility-based: issues relating to pharmacy, labs, medical records, referral systems, and administrative support. The clinical mentor must be willing and able to work with the staff to design solutions to these problems, as these issues are best dealt with before new patients are enrolled. Once a site starts providing ART, clinical mentors can serve a valuable role in encouraging the local clinicians to communicate to the Ministry of Health the additional challenges they face, such as difficulties with medication or test kit stock-outs, sample transport issues, reporting of lab results, or infrastructure weaknesses.

While regular case reviews and team meetings should be multidisciplinary, the best results of the program in Lesotho came when doctors mentored
may have been trained in PMTCT. In one district with 15 PMTCT sites, 168 nurses, out of a total of 214, had been trained in PMTCT. Yet less than half of those nurses are engaged in any way with pregnant women, and the percentage of women receiving antiretroviral prophylaxis for PMTCT continues to be low. In that same district, no one had received training in pediatric ART or DTC (a provider-initiated testing program). The provincial ART officers and district health management teams continue to urge donors to fund trainings that are targeted to the needs of the district.

An emphasis on effectiveness and efficiency should be stressed; uncoordinated, donor-driven, classroom-only training will rarely be effective and efficient. Trainees should be carefully chosen based on their role within the health-care system. Time and money should not be wasted on training people for roles they will not have. Didactic training should be complemented by on-site support and mentoring. Donors should work closely with the local health-care managers to define training needs and fund them appropriately. Government and donors must work together to determine whether increased training is resulting in improved access to care and quality of care, and use this information to revise and improve training programs.

India
The India HIV/AIDS Nurse Training Program was initiated by the National AIDS Control Organization (NACO) in an effort to improve the knowledge and skill level of nurses employed in government ART center hospitals. The Indian Nursing Council (INC) organized a national consultation on HIV/AIDS nursing and gathered together Indian nursing leaders and educators to design the program, which addressed four questions: What is the current role of the nurse in the care of patients with HIV/AIDS? What is the optimal role of a nurse in this setting? What does a nurse need to know to be
able to function effectively in that role? How can a training program be designed and implemented in order to disseminate the necessary knowledge and develop the clinical skills of Indian nurses?

This expert group submitted its recommendations to the INC and NACO, and they were accepted as the guiding principles of this training project. The International Training and Education Center for HIV (I-TECH) was contracted to design the curriculum according to NACO/INC requirements. A team of Indian nursing faculty served as advisors and provided frequent feedback and suggestions. It was the consensus of this advisory group that all nurse training must be practical and patient-focused. The training program emphasizes the role of the nurse in all aspects of HIV prevention, care, and treatment.

A key component of the program is a review of the nursing assessment process and practical application. After a classroom review and discussion of the nursing assessment of the patient with HIV/AIDS, the trainees are taken to the inpatient unit or ART center to interview and assess a patient under the guidance of an instructor. Nurses are expected to be able to stage a patient, determine whether the patient is eligible for ART, and identify nursing interventions appropriate to that patient. On the last day of the training, the nurses present their patients to the group, allowing trainers to assess how well the trainees have understood the material and can apply it to a real patient.

A lesson learned from the development of the India HIV/AIDS Nurse Training Program is that training programs should be based on the expressed needs of the health-care workers trained. The involvement of Indian nurses in the design of the program and as part of the training team ensured that the training would meet the needs and support the role of nurses in the Indian health-care system. This proved to be much more effective than having a physician, professional educator, or public health expert design the training program without input from nurses. Not including the cadre of health-care worker to be trained in the training design can result in material that is too basic or too complex, inappropriate for the practical role of the health-care worker, uninteresting, or impossible to implement due to infrastructure and resource issues at the local health-care facility. Employing an experienced nurse as the trainer was deemed essential by the expert advisory committee of Indian nurses.

For health-care professionals, in-service training is not about learning a set of facts or skills, but about incorporating new information into an existing practice. The preexisting expertise of the clinician should be the basis for incorporating new knowledge related to the care of patients with HIV/AIDS. Didactic training must include some practical demonstration by the trainee that the material has been understood and can be applied in a clinical setting. Case studies, role plays, and other exercises aimed at demonstrating the trainee’s ability to apply new information in a clinical setting are essential.

China

The Lixin Training Center in rural China is the site of an HIV/AIDS clinical mentorship program for Chinese doctors, jointly sponsored by the Centers for Disease Control and Prevention (CDC) Global AIDS Program and the Clinton Foundation. This program supports China’s Center for Disease Control and Prevention as well as the Anhui Province Bureau of Health and the local Lixin County Bureau of Health. Chinese physicians come to Lixin County, Anhui Province, for three months at a time, for practice-based training with an American HIV clinician and a clinical assistant/translator. The training is a mix of outpatient care, inpatient care, didactic lectures, and a training-of-trainers module in which trainees create and deliver their own presentations.
The Lixin Training Center, the first rural practice-based training center in China, places the training where there is a large volume of patients needing care. Prior to the establishment of the Lixin Training Center, the training centers in China were primarily urban-based, where there were few patients, or didactic in nature. The Lixin training program focuses on practical clinical care in a resource-limited setting, where trainees see patients independently and then are mentored in both inpatient and outpatient settings. Continuity of care and follow-up of patients over time is emphasized. One goal of this program is to create a paradigm shift in Chinese outpatient care from a predominantly acute care model to a primary care / chronic disease management model. As of January 2007, 42 Chinese physicians had been trained. The trainers and trainees have cared for more than 800 HIV-positive patients in Lixin, with more than 400 on antiretrovirals. Following their training, the training center graduates have gone on to treat 1,000 more patients.

This practice-based mentoring approach successfully trained competent HIV clinicians who demonstrated an understanding of the shift in the patient model toward comprehensive care and chronic/longitudinal patient management. Some graduate trainees went back to their local sites and spearheaded ambitious new systems and trained doctors at those local sites, mirroring the Lixin Training Center and multiplying the success of the program.

While some graduate trainees were instrumental in spreading the model back to their home sites, some trainees were not allowed to take positions of local leadership in HIV care and clinical training upon their return home. Implementers learned that consultation with local political and healthcare leadership is crucial to identifying appropriate candidates for training. Also crucial is careful selection of trainees who are motivated to learn and to provide care to HIV-positive patients when they return home.

CONCLUSION

Training a robust health workforce is critical for building sustainable HIV-treatment programs. The care delivery model, the roles played by different types of health workers, the number of workers needing training, resources available for training, and the phase of program development all significantly affect training design and should be considered when deciding how to best train the health workforce in resource-limited countries. Evidence to support these decisions will help policymakers and planners of training programs answer the overarching question: what is the optimal approach to training the health workforce for an expanding HIV-treatment program in a resource-limited setting?

ACKNOWLEDGMENTS

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A
LTHOUGH THE GLOBAL HIV/AIDS response has fallen short of meeting the World Health Organization (WHO) “3 by 5” target of starting 3 million people on antiretroviral therapy (ART) by 2005, the initiative did galvanize an unprecedented global commitment to expand access to HIV care and treatment in low- and middle-income countries. With this commitment came a new emphasis on a public-health response to HIV, as opposed to the previously favored “specialist” approach—an important shift needed to address a devastating generalized epidemic. The “3 by 5” initiative; the President’s Emergency Plan for AIDS Relief; and the Global Fund to Fight AIDS, Tuberculosis and Malaria definitively demonstrated the feasibility of delivering ART in even the most resource-limited settings, cooperating to support programs that did exactly that.1-3 Yet despite the provision of antiretroviral medications (ARVs) becoming more affordable for low- and middle-income countries in recent years, long-term access to this life-sustaining treatment remains limited by the ability of health systems to deliver quality care in a reliable manner to all who need it. Chief among the limitations of these health systems is a lack of sufficient health-care personnel with the training and experience to administer these medications to provide lifelong care at the community level for adults and children living with HIV.

Building capacity within the health systems of communities that face the task of scaling up HIV therapy in settings of high disease prevalence and/or limited resources is a tremendous challenge. This chapter will discuss the development of training programs for health-care personnel to meet this challenge.

PLANNING AND PROGRAM DESIGN
The specific human resource (HR) needs of different countries depend on a number of factors, including the staffing levels within the existing system, the prevalence and geographic distribution of HIV disease in the population, the planned model of service delivery (integrated vs. vertical) for the HIV treatment program, the available personnel, the health-system training capacity, and the financial resources available to support HR needs. Designing an appropriate national training program for health-care personnel to meet the needs of a particular country’s ART scale-up plan will have to take all of these factors into account.
Thus, country-specific planning, based on an assessment of the context in which training is to take place, is the essential first step to a successful HR training program for ART scale-up. Such assessment and planning is typically undertaken by the government health officials tasked with charting the national response to the HIV epidemic. In some cases, expert consultants are brought in with the support of government and nongovernmental aid agencies to assist in this process, particularly in countries where health officials are greatly overstretched and the magnitude of the epidemic requires an emergency response. Inclusion and involvement of all possible stakeholders that may contribute to the overall health system is very important from an early stage in the planning of the scale-up of HIV treatment. Such lifelong care is unlikely to be sustainable as a stand-alone program; thus, integration and communication across programs and between agencies is one of the keys to long-term success.

ASSESSING THE TRAINING CONTEXT
The context in which an HIV treatment program will be developed is very important to the planning and design of the training program for health-care personnel in HIV care. A number of conditions must be considered to ensure that a program will meet the needs of the environment where it is to be implemented. These conditions will be described in this section and include administrative conditions, characteristics of the health system as well as the population it serves, and existing resources for training in general and the HIV treatment program in particular.

Administrative Issues
No public health program can begin without consideration of the administrative environment in which it is to be implemented. The public sector plays a vital role in planning for long-term HIV care, particularly in poverty-stricken areas where the population cannot afford to pay for routine health care.

It is important to assess the attitudes, existing policies, and capacity of the administration responsible for public health when the scale-up of training for HIV care is being planned. What is the distribution of responsibility for health care? Does it fall to local authorities, or is it managed centrally? Where are decisions taken? How are budgets distributed? It may be very well for a central health authority to decide that HIV treatment is a priority, but if the allocation of personnel occurs at the district level, then it is important to involve the district-level decision makers in the planning for the training of personnel.

In addition to ensuring that the appropriate decision makers are involved in the planning process for training scale-up, it is important to know the existing attitudes and policies regarding the diagnosis, care, and treatment of HIV.

Table 1 summarizes these administrative issues.

The answers to these questions will allow for a greater understanding of the framework in which a training program is to be developed. Often, a training program must work to build capacity not only among the health-care workers at the ground level but also among the administrative personnel and systems that will support the ongoing treatment program. The need to build administrative capacity, however, must be balanced against the urgent need in a region to start an HIV care and treatment program, due to the particulars of the epidemic and the availability of resources. There is a necessary tension between the need for rapid HIV treatment scale-up and ensuring that the capacity exists within the system to support ongoing quality HIV care and prevention. One should not be ignored in favor of the other.
Antiretroviral treatment, like the management of any lifelong chronic disease, will require patients to have routine follow-up, with regular access to pharmacy, laboratory, prevention, and social work services. In many resource-limited settings, provision of such services for long-term care has not been seen as a priority. Additional challenges arise because HIV, unlike other chronic diseases such as diabetes and hypertension, can be transmitted to others. And although similar to TB in that it is also transmissible, potentially fatal, and capable of developing resistance to medications, HIV often kills people during their young, most productive years, with devastating impact on populations. Cost-benefit analyses clearly demonstrate the consequences to a nation’s economy of an untreated HIV epidemic. Although recent political

<table>
<thead>
<tr>
<th>Table 1. Administrative Issues to Consider in Designing a Training Program</th>
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<tbody>
<tr>
<td><strong>Issue</strong></td>
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<tr>
<td>Is there a documented policy stating that HIV-positive people are entitled to care and treatment supported by the government?</td>
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<tr>
<td>Have adequate funds been budgeted and is there capacity within the government for administration of such funds?</td>
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<tr>
<td>Has sufficient planning and budgeting been devoted to supply-chain management for long-term HIV care, and is there capacity within the government for this?</td>
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<tr>
<td>Is there a policy regarding confidentiality of medical information?</td>
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<tr>
<td>Are there policies preventing discrimination against individuals based on their HIV status in the workplace, the health-care system, and the community?</td>
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<tr>
<td>Are there policies regarding HIV testing in the health sector, government sector, education sector, military, police, etc.?</td>
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<tr>
<td>Are there policies for protecting health-care workers and ensuring access to adequate safety equipment and postexposure prophylaxis?</td>
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<tr>
<td>Are there policies regarding necessary training and supervision to prescribe, sell, or distribute antiretrovirals?</td>
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<tr>
<td>Is there significant misinformation, stigma, or discrimination within the government sector toward HIV and populations affected by HIV?</td>
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</table>

**Health-System Issues**

Antiretroviral treatment, like the management of any lifelong chronic disease, will require patients to have routine follow-up, with regular access to pharmacy, laboratory, prevention, and social work services. In many resource-limited settings, provision of such services for long-term care has not been seen as a priority. Additional challenges arise because HIV, unlike other chronic diseases such as diabetes and hypertension, can be transmitted to others. And although similar to TB in that it is also transmissible, potentially fatal, and capable of developing resistance to medications, HIV often kills people during their young, most productive years, with devastating impact on populations. Cost-benefit analyses clearly demonstrate the consequences to a nation’s economy of an untreated HIV epidemic. Although recent political
developments have allowed most countries to offer universal access to first-line medications for HIV, widespread use of second- and third-line therapy remains economically nonviable. It is in the best interests of a society to prevent the development and transmission of drug-resistant HIV, and to implement HIV treatment properly, if it chooses to undertake ART scale-up.

Planning for lifelong treatment of HIV infection must consider issues of sustainability and ongoing access to treatment services. Thus, it is important to examine the existing public-health infrastructure and the challenges to chronic disease management within the current system. A thorough assessment of the current adequacy of staffing levels, diagnostics and supplies management, and incorporation of the chronic care model in the existing system for the care of other chronic diseases, such as diabetes, will give an indication of the training needs to make ART scale-up possible.

These issues are summarized in Table 2.

The primary purpose of an evaluation posing these questions (see Tables 1 and 2) is to determine whether patients who start ART will be able to have ongoing access to uninterrupted care within the existing system. For training purposes,

<table>
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<th>Table 2. Health-Care System Issues to Consider in Designing a Training Program</th>
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<tr>
<td><strong>Issue</strong></td>
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<tr>
<td>What is the structure of the general health-care delivery system (centralized vs. decentralized)?</td>
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<td>What level of care is provided at the community level?</td>
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<td>Where are pharmacy and laboratory services available?</td>
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<tr>
<td>How good is the transport infrastructure, and how will that affect patient travel, sample transport, and supply management?</td>
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<tr>
<td>Are current service sites well stocked with needed supplies?</td>
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<tr>
<td>What is the existing system for referral and consultation?</td>
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<td>What is the existing system for patient medical records?</td>
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<tr>
<td>What is the existing system for determining eligibility for services/reimbursement?</td>
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<tr>
<td>Are existing nationwide treatment programs (e.g., TB, antenatal care, diabetes, hypertension, sexually transmitted infections) integrated within institutions or managed in a vertical, stand-alone fashion?</td>
</tr>
<tr>
<td>How is continuing education of existing health-care personnel implemented?</td>
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</table>
it is important to be sure that health-care workers are given training in ART that is appropriate for the level of health-care system in which they will work. This assurance is the key to combating “training fatigue” among overextended workers. Training fatigue often occurs when workers are called away from their duties for a generic training program only to find that they are unable to implement these generic strategies in their current work environment.

Patient Population Issues
A solid understanding of the population served by an HIV treatment program will inform the tailoring of the training program to ensure maximum relevance to trainees. Information regarding the epidemiology of HIV in the country will help define the populations that will need treatment and thus the services that will be most needed. For instance, it is important to determine how much of the epidemic is focused among the poor, who will need access to public sector services and nutritional support; whether patients are concentrated in rural or urban areas; and whether levels of literacy will allow written health-promotion materials to be used and in what languages materials should be developed. It is also important to know the prevalence and incidence of HIV among women of childbearing age and the availability of perinatal services, as well as the HIV prevalence and incidence in children, as all of these factors will shape the design of an HIV treatment program. The presence of a concentrated epidemic among disenfranchised members of the community, such as injecting drug users (IDUs) and sex workers, will require that the training program address services specific to the needs of these populations. Finally, it will be important to learn about the epidemiology of comorbid conditions and opportunistic infections (OIs).

HIV-Specific Issues
Often, the scale-up of HIV-related services will take place in an environment where work has already begun in tackling the epidemic. Learning about the existing programs, the groups and individuals working on them, the extent of what has been tried, and the challenges faced will be very helpful in preventing duplication, engaging potential allies, and avoiding conflicts in the planning of a training program to build capacity for ART scale-up. These issues are presented in Table 4.

Gathering information on all of the topics enumerated in the preceding sections will allow for a solid foundation for the design of a program of large-scale training to support the nationwide scale-up of HIV treatment.

MODELS FOR SCALE-UP OF TRAINING IN HIV TREATMENT SETTINGS

Centralized Training Models

Centralized training for centralized treatment programs (i.e., vertical program or specialist model). Training can eventually become more decentralized, with training and clinical rotations for trainees taking place at the main site. This model is appropriate for settings with relatively low HIV prevalence, sufficient infrastructure and resources for patient transport, limited available personnel, and/or sufficient communications and medical records infrastructure for patient tracking.

Centralized training at a central treatment site using the team approach. This approach involves bringing a multicadre team from new sites to a central training hub, followed by on-site expert preceptorships to facilitate the launch of the program at new sites (i.e., vertical program). This is appropriate for settings with very high HIV prevalence, ample human resources, and well-supported programs that are able to fund the
extended training of health-care workers hired only for the treatment program, as well as transport, accommodation, and salaries of external experts for on-site precepting.

**Decentralized Training Models**

**Decentralized training with ongoing mentorship.** In this train-the-trainers model, a team of health-care professionals consisting of members from each cadre of an ART care team come to a central training site from regions where the program is to be rolled out. They are trained in ART care, how to train colleagues in ART care, and the specific features of the national program. Training is in the form of workshops that combine didactic with experiential learning. After attending the workshops, trainers return to their regions to conduct local trainings for scale-up of the ART program. This model is usually supported with ongoing mentorship by the central training team and external experts.

This model is appropriate for settings with a high burden of HIV, a significant shortage of human resources, the need to integrate the program into existing services, and/or the need for training that requires minimal travel and missed workdays.

**Decentralized in-service training using a facility-based team approach.** In this model, a designated care team at each facility is trained by a team of experts, who conduct the training through a series of on-site, in-service workshops. These consist of didactic and case-based learning, followed by a visit to an established site to observe hospital-based care. This model is appropriate for settings with a large population, relatively low HIV prevalence, many public health-care facilities over a large geographic area, or where there is a need for widespread scale-up to established facilities.

**Decentralized training using ongoing distance-learning workshops.** This model involves the delivery of didactic lectures and case-based learning to a wide number of health-care professionals of varying cadres using telecommunications technology. This is appropriate for settings with high HIV prevalence, a widely dispersed population, poor infrastructure for transport of patients, adequate existing decentralized health services, and a suitable communications infrastructure to support teleconferencing.
### Table 4. Training Environment and Resource Issues to Consider in Designing a Training Program

<table>
<thead>
<tr>
<th>Issue</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there a distinct government program for the scale-up of HIV services (including or specific to ART)?</td>
<td>Significant investment may already have been made. Note barriers to progress thus far.</td>
</tr>
<tr>
<td>Does the government consider the planned training program to be an extension of the ART scale-up program or a separate program?</td>
<td>Coordination enhances program credibility. Be careful of duplication of efforts, claims on resources, power shifts, and political alliances.</td>
</tr>
<tr>
<td>Is the funding for the ART scale-up program different from the funding for the training program?</td>
<td>Clarity in funding and budgeting is essential for ongoing sustainability.</td>
</tr>
<tr>
<td>Has any training already been done, or is any training already planned?</td>
<td>Be careful of duplication of efforts, claims on resources, and power shifts.</td>
</tr>
<tr>
<td>Are there any other government or nongovernmental organizations working on training for ART scale-up (including pharmacy, laboratory, data management, and supply-chain management for the ART program)? What gaps remain to be filled by the current training program?</td>
<td>Coordination and cooperation with existing groups enhances the credibility of the training program. Be careful of duplication of efforts, claims on resources, and power shifts. Clarity in funding and budgeting is essential for ongoing sustainability.</td>
</tr>
<tr>
<td>Are the management and oversight different? If so, what is the relationship between the organizations, and how will communication be formalized?</td>
<td>Clarity in roles, responsibilities, and communication is essential for ongoing sustainability.</td>
</tr>
<tr>
<td>How will data be shared on the implementation of the training and treatment programs for evaluative purposes?</td>
<td>Documentation of agreements on data collection and management will facilitate implementation and evaluation efforts.</td>
</tr>
<tr>
<td>Is there unanimity behind the adoption of a single set of guidelines for HIV treatment? Have these guidelines been developed, or is there a plan for the development of guidelines in advance of the training?</td>
<td>Training content will be based on guidelines. Unanimity and clarity of guidelines will prevent duplication of training and confusion of health-care workers. Coordination enhances program credibility.</td>
</tr>
<tr>
<td>Were any previous trainings conducted using different (earlier) guidelines or protocols?</td>
<td>Addressing any protocol changes will prevent confusion of health-care workers.</td>
</tr>
<tr>
<td>Is there an existing program of oversight and evaluation for the health-care system, or for the HIV program in particular? Is there a plan for ongoing evaluation and improvement of program capacity? Where does the responsibility lie for management, implementation, and funding of the evaluation piece for the training program being planned?</td>
<td>Coordination enhances program credibility. Documentation of agreements on data collection and management will facilitate implementation and evaluation efforts. Clarity in roles, responsibilities, and communication, as well as funding and budgeting, is essential for ongoing sustainability. Quality will depend on evaluation and remediation.</td>
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FROM THE GROUND UP: LAYING A STRONG FOUNDATION

provide technical consultants for the development of treatment guidelines.

Vertical vs. Integrated Programs
It is rare to have sufficient numbers of staff to create a stand-alone HIV program (also known as a vertical or parallel program). In most developing countries, the best alternative is to build on any existing infrastructure of decentralization.

Central-Level Capacity Building
In some settings, a comprehensive training program for the roll-out of ART will have to include education, training, or capacity building at the central or administrative level. This may take the form of policymaker education workshops, assistance in guidelines development, or the seconding of staff within the administration for the management of the program. Some examples of where this has been done successfully include Botswana, where staff were seconded to the government by African Comprehensive HIV/AIDS Partnerships (ACHAP) for program development; Lesotho, where consultants from the Clinton Foundation and WHO worked with the HIV/AIDS directorate to outline the program and successfully apply for funding; and India, where the Centers for Disease Control and Prevention (CDC) and the Clinton Foundation support administrative staff positions within the national AIDS program and the clinic from remote locations when needed. The program also became a center for preservice training of physicians and nurses. Over time, as enrollment has grown, the program has been able to decentralize to provide HIV care at remote primary-care sites. Staff are trained centrally via workshops coordinated by the Caribbean HIV AIDS Regional Training Network and overseen by the central program staff. Clinicians are trained with clinical rotations at the original clinic (some have received prior preservice training at the main clinic).

ADDED CONSIDERATIONS FOR PROGRAM DESIGN

Preservice Training
Because of the high rates of attrition of healthcare professionals in many developing countries, vacant positions will often be filled by new graduates. Thus, it is important to ensure that HIV pathogenesis and treatment are well covered in nursing and medical schools, as well as orientation to referral and reporting systems used within the program. However, this is worth prioritizing within the training roll-out only if there is a solid strategy for recruitment and retention of graduates and if the jobs are funded and available within the program.

SAMPLE TRAINING MODEL: BAHAMAS

The HIV treatment program was begun in Nassau with a single, very motivated physician and his staff. The initial training of the main physician was undertaken at his own initiative, with the help of experts outside the country. This physician became proficient in the care of both adults and children living with HIV and then undertook training of his own staff and sought support for the program. The program employed an aggressive system of contact tracing and adherence support as well as securing funding to assist patients with transport to the clinic from remote locations when needed. The program also became a center for preservice training of physicians and nurses. Over time, as enrollment has grown, the program has been able to decentralize to provide HIV care at remote primary-care sites. Staff are trained centrally via workshops coordinated by the Caribbean HIV AIDS Regional Training Network and overseen by the central program staff. Clinicians are trained with clinical rotations at the original clinic (some have received prior preservice training at the main clinic).
SAMPLE TRAINING MODEL: BOTSWANA

Botswana’s national HIV treatment program, MASA, began with the establishment of a state-of-the-art treatment facility in the nation’s capital. The treatment model is based on the hospital as a “fixed-capacity multiplier,” able to initiate care and stabilize patients, with patients continuing follow-up at four satellite clinics. Health-care personnel are trained with a series of didactic workshops using the KITSO (Knowledge, Innovation, and Training Shall Overcome AIDS) program, followed by shadowing of the clinicians in the central clinic sites (medical doctors, four weeks; nurses and laboratory personnel, two weeks). Satellite clinic staff must pass a test before their facility can be certified as a treatment site. Once ready to open a peripheral site, staff are joined by international consultants brought in by African Comprehensive HIV/AIDS Partnerships (a collaboration between the government of Botswana, the Bill and Melinda Gates Foundation, and Merck), who then remain for three to six months to oversee the local team in running the clinic and treating patients.

(e.g., TB DOTS [directly observed therapy short course] and antenatal care programs) and train the personnel in these programs for appropriate HIV-related care. For example, TB DOTS workers can also be trained for adherence support in HIV treatment, and both DOTS workers and antenatal care workers can be trained as important resources for prevention counseling and HIV screening in the community. This approach also helps to reduce stigma by demystifying HIV care. In other words, HIV is not singled out and set apart from other diseases, as is common in vertical programs.

Testing and Counseling
Recent years have seen tremendous progress in “know your status” campaigns. Building seamless links between treatment programs and testing programs is essential to increasing treatment access and providing added motivation for the public to get tested. It would be unethical to provide testing without linking individuals who test positive to appropriate care and support.

Social Services
Because HIV treatment is lifelong, any treatment program must take into account the social-service issues that may present obstacles to ongoing care for patients. A comprehensive training program should include training for social work personnel in HIV-related issues and should highlight services that exist within the program and the larger community.

Prevention Services
The advantages of combining HIV transmission prevention with the provision of ART are many. Because patients will be in regular contact with their treatment providers, there will be many opportunities to educate them and reinforce the need for protection to prevent reinfection or the infection of others. Training on prevention counseling (including “prevention for positives”) and supply management for support of prevention strategies (e.g., condom use, family planning, deliberate safe conception) should be included in the training of personnel in ART clinics.
Prescribing and Dispensing
Different health-care systems may have varying regulations regarding prescribing and dispensing medication. This must be taken into account when considering the task sharing of personnel for ARV provision and the respective training needed for the different cadres. Additionally, some training of management personnel may also be needed to facilitate the understanding and planning needed to ensure uninterrupted supplies of medications to dispensing sites within the program.

Chronic Care
Monitoring ART, diagnosis and management of OIs, monitoring for and prevention of complications, and prevention of secondary transmission are all required for the ongoing management of stable HIV infection. Long-term chronic care will need to be undertaken at the primary care level, and consideration must be given to training and other needs related to the sustainable provision of chronic care at this health service level.

Laboratory Capacity Building and Sample Transport
Chronic management of HIV will require regular monitoring of basic laboratory tests, including CD4 lymphocyte count, according to the schedule set forth in the treatment guidelines. Decisions regarding task shifting and decentralization of care will have to take into account the feasibility of providing laboratory services at varying levels of the health system. The training program may be called upon to include the training of laboratory personnel as well as the training of all cadres in the standardized plans for sample collection, transport, and reporting.

Referral Systems and Communications for Consultation and Mentorship
The cornerstone of any decentralized program is a reliable system of communication for referral and consultation. The lifelong management of patients on ART will require health-care systems to devise strategies of decentralization and task shifting so that stable patients can be managed as close to home as possible without compromising the quality of care. The training of lower cadres of health-care workers will need to emphasize when to call for advice or assistance, and it is important that such mentorship be dependably available when needed. The training of all cadres should include training in the referral system, including the roles and responsibilities of personnel at each level. Also, it is recommended that individuals who will be at the higher levels of the referral chain be included in the training as content consultants and training facilitators.

**SAMPLE TRAINING MODEL: LESOTHO**

The government of Lesotho collaborated with WHO’s Integrated Management of Adult/Adolescent Infection program for its initial program scale-up. Training of trainers was performed over two weeks and comprised a number of didactic and interactive sessions by international experts and local people living with HIV, plus hospital-based clinical training. Trainers then returned to their sites and trained fellow workers in the program, supported by the central HIV/AIDS directorate. Ongoing clinical mentorship has been provided by international HIV clinicians supported by the International Center for Equal Healthcare Access and the Clinton Foundation.
WORKFORCE CAPACITY

Sample Training Model: India

India's National AIDS Control Organization (NACO) has recently begun the large task of scaling up the country's AIDS treatment program from a relatively small number of sites in large urban hospitals to planning for the roll-out of a standardized program of care in all states. Together with the assistance of experts from WHO, CDC, International Training and Education Center on HIV (I-TECH), and the Clinton Foundation, NACO has developed a curriculum for training personnel to establish ART sites at public hospitals throughout the country. The curriculum engages personnel from clinician and nursing cadres and offers education and training for administrators in the national program.

Record Keeping and Data Management

As with any chronic disease, HIV management requires that a provider be able to follow a patient’s progress over time and that good records be kept of the history of the illness for that individual. In many resource-constrained settings, most health care is provided on an acute basis; thus, the idea of keeping durable patient records is relatively uncommon. A challenge for HIV training programs is to introduce and reinforce the importance of chronic health maintenance and the use of written and electronic patient records to guide management. It is a very practical and useful strategy to have standardized forms for recording patient-level information, as well as facility-level information, and to include training on the use of those forms in the training of personnel for HIV care.

Evaluation Plan

Because of the public-health implications of HIV treatment resistance, maintaining quality of care in resource-limited settings takes on great importance. Thus, monitoring and periodic evaluation of program quality must be included in plans for training. This planning will require agreement of stakeholders (funding and implementing partners) on desired outcomes of the program, indicators to be measured, intervals for evaluation, and plans for addressing the findings of an evaluation. It is helpful to include plans for evaluation in the development of the training program so that elements of monitoring and data collection can be included in the training of management and administrative personnel as well as guiding the training content.

The Case for Careful Planning

Effective antiretroviral treatment, like the management of any lifelong chronic disease, will require patients to have routine follow-up, with regular access to pharmacy, laboratory, prevention, and social work services. In many resource-constrained countries, provision of such services for the long-term care of chronic disease has not been an economic priority. But long-term care of HIV, as explained previously, poses a particular challenge in that HIV can be transmitted to others, even by those without symptoms or on treatment, and when individuals do not have regular access to services, resistance to medications can develop and such resistance can be transmitted. The implications of this for planning treatment programs cannot be overstated. Using sub-Saharan Africa as an example, experts say that for every individual who was placed on anti-AIDS drugs last year, five more were newly infected, and the region’s rate of new infections has not improved since the late 1990s.
The specter of drug-resistant HIV looms large in this part of the world, where second- and third-line treatments will be much less feasible to provide to large numbers. It is in the best interests of a society to prevent the development and transmission of drug-resistant HIV, and to implement HIV treatment properly if the decision is made to undertake ART scale-up.

In recent years, tremendous progress has been made in improving access to HIV treatment in developing countries. For example, 28% of those in need of ART in sub-Saharan Africa were receiving it in 2007, compared with just 2% in 2003. There is currently great donor interest in global HIV programming, resulting in many organizations having much to offer to advance the goal of increased access to HIV treatment. Efforts that assist in bringing quality HIV care to existing health systems must often face the fact that these systems are severely lacking in resources for other basic health services. This situation can be extremely challenging, as these shortages must be taken into account and addressed before new services are scaled up. Although the severity of the HIV epidemic brings urgency to the cause, there is still a need for careful planning and consideration of all variables to ensure the long-term success of new or expanded HIV care programs. There is also a need to integrate HIV care with other existing services (e.g., TB, antenatal clinic [ANC]) whenever possible so that available health-care resources are used efficiently.

**INTERVENTIONS FOR TRAINING SCALE-UP**

**Promoting Local Ownership: Policymaker Education and Guideline Development**

Local ownership of a training scale-up program is essential for its success and long-term sustainability, particularly if the program is being initiated and supported by an external international organization. Ownership and “buy-in” may come from the central government as well as local health-care administrators involved in the implementation of the treatment program. Interventions to promote local ownership should be based on an assessment of the administrative conditions in which the training program is to take place (see Table 1). These interventions may take the form of high-level meetings, frank discussions with important community leaders and policymakers about the challenges of the HIV epidemic and the need for training scale-up, workshops with members of various departments and nongovernmental organizations (NGOs) to develop strategies.
and plans, or even “education tours” for key officials of successful HIV treatment programs to give them an idea of what is possible in their region.

Guideline development or revision may also be undertaken at this time. This should be done with input from local experts as well as international technical advisors. Local experts are a tremendous resource for understanding the particular characteristics of the epidemic in their region and for information on drug and diagnostics availability. Local experts can also provide key insights into the population to be served. For these reasons, their early engagement in the development of the training content is vital. International technical advisors bring their knowledge from years of practice using ART for chronic HIV care and experience with the evolving epidemic.

Systematically Evaluating the Existing Health-Care System

With the cooperation and participation of local counterparts, the next step in planning a nationwide training program to support ART scale-up is a formal evaluation of the existing health-care system by those designing the training program (whether local government officials or external expert consultants), with a focus on training needs for ART scale-up (see Table 5). This evaluation should extend to all levels of the health system that will be required for quality long-term HIV care and include the input of national, regional, and district health authorities as appropriate.

The outcome of this evaluation may form the basis of a report to local stakeholders and policymakers regarding the identified training needs and the proposed design of the training program. The design of the training program should also be informed by the broader assessment of existing access to care described in the previous section. Often, the details of the ART program design are worked out in this process, bringing the planning more in line with on-the-ground realities, such as staffing and laboratory capacity. A common example of this is when policymakers have initially planned for a vertical program of HIV care but come to realize that staffing constraints will not support a stand-alone HIV program.

Designing the Plan for Training Scale-Up

A training program for health-system personnel in HIV care is not possible without a well-considered national plan for the sustainable delivery of chronic HIV care. This plan should be clearly elucidated in a guideline or policy drawn up by the responsible policymakers. The plan should map out the responsibility for HIV care at the various levels of the health-care system as well as plans for the budgetary and systematic support of care at each level. The capacity for HIV care at various levels of the health-care system will dictate the training content appropriate for different cadres of workers at the different levels. However, the treatment plan does not necessarily indicate the way that this systemwide training of health-care personnel should be carried out.

There are a number of models that may be used to approach the national scale-up of training for a new HIV treatment program. These models, centralized and decentralized, were explained and examples given in the previous section. In choosing among these models, the best approach will be determined by the number and distribution of personnel to be trained, as well as by how the system can best accommodate the large-scale training of staff. For example, in areas with severe HR shortages, staff to be trained may not be able to take time away from existing duties to travel to a central training site and/or may be limited in the amount of time available at a stretch. In other cases, staffing numbers may be less of a problem than the urgent need to get training completed quickly; thus, a shorter-duration, more centralized approach may be advised.
## Table 5. Training Considerations for Specific Health-System Components

<table>
<thead>
<tr>
<th>Health-System Component</th>
<th>Considerations</th>
<th>Implications for Training</th>
</tr>
</thead>
</table>
| **Administration**      | ■ Capacity to acquire and administer funding within the system  
■ Policies in place  
■ Accountability | ■ Training needed for administrators, seconding of staff  
■ Workshops/education/guidelines development  
■ M&E plan, indicators, and outcomes |
| **Staffing**            | ■ Feasible distribution of tasks for ART provision: by cadre, level of health system  
■ Numbers: staffing levels, attrition, labor pool/supply  
■ Prior training or experience with HIV (disease burden at sites)  
■ Existing positions for necessary staff (e.g., counselors, data clerks) | ■ Availability of varying levels of trained staff will influence ART treatment program design and ultimately training program content  
■ Availability of staff for training, utility of preservice emphasis, incentives, certifications, promotion opportunities  
■ “Training fatigue,” relevance of content |
| **Care model: acute vs. chronic** | ■ Capacity for acute care: diagnostics, drugs, equipment at various levels  
■ Capacity for chronic care: medical records, communications, staffing, supplies | ■ Identify areas of strengthening needed to provide adequate acute and chronic aspects of ART  
■ Will influence planning for distribution of tasks within HIV care and content of training |
| **Supply management**   | ■ Adequate staffing at various levels | ■ Training needed to ensure stable supply of ART drugs and diagnostics |
| **Communications: capacity for referral and consultation** | ■ Adequate transfer of patients and information between various levels of system | ■ Training on systems and procedures for referral/consultation at each level is a significant element of training |
| **Medical records systems** | ■ Maintenance of confidential individual records  
■ Adequate reporting between levels of the system (inpatient, lab, pharmacy)  
■ Capacity for collecting monitoring data | ■ Training on medical records systems is a significant element of training program at each level |
| **Monitoring and evaluation (M&E)** | ■ Challenges to existing reporting  
■ Capacity for data management  
■ Use of information: feedback/follow-up | ■ Training in monitoring tools and data collection are a significant element of training program at each level  
■ Plan for ongoing mentorship based on findings of M&E |
Adapting and Developing the Training Curriculum

Just as the training model must be specific to the needs of the health system in which the staff are being trained, so should the training content be adapted for the needs of the program. Bearing that in mind, some essential topics may be considered core elements of a curriculum in HIV treatment scale-up. The specific training content for each cadre at the respective levels of the health system will vary, with the following key concepts composing a minimum basic knowledge set to be covered by the training program as a whole.

- **Epidemiology.** This should include the epidemic today, such as global, regional, and national figures for adults (men and women) and children living with HIV; people newly diagnosed with HIV; and HIV-related deaths (as per Joint United Nations Program on HIV/AIDS [UNAIDS]). The known history of the HIV epidemic in the local context is also useful.

- **Basics of HIV.** This should include the essentials of the human immune system, HIV life cycle, and natural history and progression of the disease.

- **Reducing HIV transmission.** This can include the clinician’s role in prevention through education, diagnosis and treatment of sexually transmitted infections (STIs), preventing and managing occupational exposure, and case detection of asymptomatic HIV (including during pregnancy), with referral for prevention of parent-to-child transmission (PPTCT) and neonatal prophylaxis.

- **Recognizing and testing for HIV.** This can include elements of testing and counseling, test specifics, and explanation of the window period.

- **Presentations of HIV.** This can include case recognition, sexual history taking, and details of OI diagnosis and treatment.

- **ART.** This can include how and why drugs work, goals of therapy, introduction to principles of resistance, availability of ART drugs in the local context, national protocol for ART (including guidelines for pregnancy and TB), drug reactions and interactions, routine monitoring, adherence support, and identifying clinical, virologic, and immunologic failure.

- **OIs.** This can include prevention, prophylaxis, and recognition and syndromic management of major and minor OIs according to national guidelines and available resources.

- **Pediatric HIV.** This can include prevention, recognition, diagnosis, and management of pediatric infection per national guidelines, with discussion of breastfeeding, immunization, and diagnostic and pharmaceutical resources available.

- **Orientation to services provided under the new program.** Services may include voluntary counseling and testing, PPTCT, ART, OI treatment, and laboratory services. Understanding of consultation and referral systems should also be discussed.

Developing Training Materials

Once a plan has been designed for the scale-up of the training program, materials must be developed and reproduced in adequate numbers. The content of the training with regard to medication choices, service provision, and clinical and lab monitoring of HIV should be dictated by the country’s HIV treatment guidelines. A variety of different materials will be developed for a comprehensive, systemwide training program, and it is important to consider all of these in planning and budgeting for training.

The following are important considerations to be made when planning and designing training materials.
Use of Training Materials as References

It is useful to consider what elements of the training content will be most essential to ongoing everyday implementation of the treatment program and to consider creative ways to make the information useful as a reference. For instance, books or binders are useful references when they contain details of protocols, clinical descriptions and photographs, and/or medication information and equipment specifications. Posters and wall charts can also prove useful to help trainees implement the new knowledge they have acquired. These job aids may present algorithms, regimens, emergency protocols, or patient education outlines. Pocket manuals can be useful for easy reference to important lists, formulas, contact numbers, treatment and diagnostic algorithms, and dosing information. CD-ROMs can be given out during or after training for the provision of reference literature, digital images, and self-guided refresher courses. Finally, Web sites can be developed for the provision of clinical, educational, and research updates, medication specifications, and diagnostics information.

Developing Evaluation Materials

Based on the agreed-upon goals and indicators to be measured in evaluating the HIV treatment program and the corresponding health-care worker training program, materials must be developed for use during and after the training. These materials may include some or all of the following:

- Training program evaluation
- Registration forms for recording demographics of participants
- Baseline knowledge (pretest) and current practice surveys
- Course satisfaction forms
- Knowledge posttests
- Treatment program evaluations (to train participants for ART program data collection)
• Patient information forms
• Registers
• Referral forms
• Laboratory forms
• Reporting forms

Training Roll-Out
After thorough planning and preparation, implementation should proceed according to the training model developed. The training model, as discussed earlier, refers to the physical location (centralized or decentralized) and mode of information delivery, as well as the groupings and order in which all health-care workers will pass through the program. Given the HR constraints of most countries rolling out ART scale-up programs, care must be taken in planning trainings to ensure that all staff are able to be trained in sequence while not depleting the sites of staff during training.

Recommended approaches include the following:

• **Training by team.** Teams from several sites that include a representative of each cadre are sent sequentially for workshop-style training at a regional training location until the full staff of each institution has been trained.

• **Training by cadre.** In-service trainings are conducted for groups of each cadre over a relatively long period of time rather than in an intensive workshop setting.

• **Training by institution.** This approach is typically used during institution-based in-service trainings, rotating through small groups over a longer period of time. Stakeholders or funders sometimes require this type of training for proof of feasibility or justification of budget. In cases of disagreement between stakeholders on policy issues (e.g., feasibility of sample transport strategy, need for supply-chain management, acceptability of routine testing strategy), a pilot can allow data to be collected to guide possible revision of the national plan as indicated. Where serious discrepancies exist between regions in infrastructure or HR capacity, staged roll-out can allow for needed capacity building.

**IMPLEMENTING HIV TREATMENT PROGRAMS**

The work of the training program does not end with the completion of training and the start of implementation of the treatment program. Once training has been completed, the scale-up of the HIV program can begin. This entails not only beginning to provide HIV treatment with ARVs but also to implement the program to supervise trainees and to collect data for monitoring and evaluation, all of which have implications for the training program. Activities that are needed after the conclusion of training include the following:

• **Initiation of the HIV care program.** It is generally recommended that this take place as soon as possible after completion of the training. Often, there are logistic or systematic constraints that impede the initiation of care at the site, underlining the importance of close collaboration with administrators and the inclusion of central-level capacity building in a training program.

• **Supportive supervision and mentorship.** The training program should include plans for ongoing supportive supervision of trainees as they begin to implement the program. Some programs (such as Botswana's MASA) have international expert mentors on-site for the initial weeks of ART provision. Others have close supervision by the experts from the local referral center. It is recommended that a long-term, ongoing program of routine clinical mentorship be planned, with a built-in mechanism for feedback and supplemental training as needed to maintain program quality.
• **Data collection.** Roll-out of the program should mark the start of data collection for the ongoing monitoring of the ART program. The early days of the program are the essential time for data consultants and information technology experts to note and correct any problems in these systems.

**Evaluating Training**

Donald Kirkpatrick has described a framework for evaluating professional training development programs. Kirkpatrick’s model, which has been used as the basis for evaluating the Health Resources and Service Administration’s AIDS Education and Training Center, comprises four measurement levels:

- Participants’ reaction to the training, surveyed at the conclusion of the training and six months later, measuring satisfaction and comfort with preparation for treatment provision
- Learning—improvement in knowledge of HIV pathogenesis, treatment, and the program—measured before and after the training and at six months
- Changes in behavior that result from the training assessment of clinical practice performed by mentors at the treatment site
- Final results of the training—improved access to care, satisfactory clinical treatment outcomes, and improvement in the standard of care as measured by the patient monitoring system and the indicators monitored for the evaluation of the treatment program

This is just one suggested framework for analyzing the data collected during the training program and implementation of the HIV treatment program. It will also be important to return to the statement of goals established for the training program at its outset and analyze the measured indicators accordingly.

**Feedback, Revision, and Follow-Up Training**

Following the evaluation of the training program, an important next step is to address the findings of the analysis. Monitoring and evaluation provide a valuable opportunity to discover areas where supplemental training is needed or aspects of the training program that need revision before further scale-up. These activities include the following:

- **Postpilot revision or staged scale-up.** Typically, the time frame of evaluation is short, not allowing for analysis of clinical outcomes but rather focusing on operational issues of the training program and implementation logistics. Information gained can be used to generate recommendations for revision of the program before implementing further.

- **Ongoing continuing medical education (CME).** Weaknesses revealed through analysis of monitoring and evaluation data can be used to formulate a program of ongoing CME for providers and possibly can reveal the need for further education of administrators and policymakers.

- **Mentorship.** A solid program of mentorship should provide the opportunity for mentors to give individual-level feedback to their mentees and to foster them in their ongoing professional development. Such relationships contribute greatly to the strength of the care network and the success of the referral and consultation system.

- **Stakeholder reports.** Good data collection, analysis, and evaluation allow a program to demonstrate to funders and other stakeholders what they have accomplished through the training program. Good monitoring and evaluation is a useful tool to make the case for next steps and subsequent program needs.
TRAINING AND TREATING AT THE SAME TIME: EXPERIENCES WITH NATIONAL HIV/AIDS TRAINING IN NIGERIA

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Institute of Human Virology, Nigeria

NIGERIA, UNLIKE MANY OTHER countries in sub-Saharan Africa, is fortunate to have a large number of doctors and nurses graduating from local institutions. However, at the start of the rapid expansion phase of the President's Emergency Plan for AIDS Relief (PEPFAR)-supported treatment effort in Nigeria in 2004, there were very few locally active clinicians with in-depth experience managing patients living with HIV. At that time, HIV and AIDS had yet to become a focus of the country’s medical school curriculum.

In early 2005, the PEPFAR-supported University of Maryland Institute of Human Virology ACTION (AIDS Care & Treatment in Nigeria) program began the rapid scale-up of HIV/AIDS treatment services throughout the country. As the single largest supporter of ART services in Nigeria, the ACTION program urgently needed to develop a core group of clinicians knowledgeable in the treatment of HIV infection, as well as related complications. At first, a basic curriculuma was used and teachers were flown to the capital, Abuja, from academic medical centers in the United States to teach the five-day course. Approximately 60 doctors, nurses, and pharmacists representing five large Nigerian government teaching hospitals were trained in the first two trainings. The course covered the basics of HIV pathophysiology, the WHO first-line ARV pharmacopeia, adherence issues, toxicities, and opportunistic infection diagnosis and management. At the completion of the first round of training, medical officers initiated the ACTION program’s first patients on ART, in March 2005.

Subsequent five-day introductory trainings were conducted as the program expanded into new centers and required new clinical staff as well as replacements for staff who transferred out of the program. The curriculum was modified each time it was taught to reflect the realities faced by participants in their local settings.

Program staff soon realized that a five-day introduction to the basic concepts of HIV/
AIDS medicine was insufficient preparation for clinicians who needed to manage severely immunosuppressed patients and prescribe complicated drug regimens. For instance, although the course covered ART failure and some fundamentals of protease inhibitor–based therapy, it became apparent that physicians were reluctant to begin second-line treatment, even when faced with clear cases of treatment failure.

Follow-up training, including more intensive supervision and confidence building, was obviously needed but the task was daunting. How could the program train a nationwide network of providers in a country more than twice the size of California with very limited expert personnel? A preceptor program using clinical experts from outside Nigeria to mentor newly trained Nigerian clinicians was then developed based on models of successful programs from other settings. To recruit experts from abroad, advertisements were placed on the Web sites of the Infectious Diseases Society of America and the British HIV Association for experienced board-certified physicians with an active practice in AIDS management who were prepared to come to Nigeria for one to six months.

The preceptor program includes a mixture of classroom didactic training followed by case-based learning. Several physicians from a variety of countries have participated in the program since its inception and have provided valuable mentoring and case-based instruction. At the end of 2007, the ACTION program had provided ART to 42,000 patients, and clinicians were gradually becoming more confident in the management of complex conditions, such as treatment failure. In fact, graduates of the program have begun to train their colleagues within their network of ART sites, setting up trainings at the tertiary “hubs” and inviting providers from the secondary and primary “spokes.” In addition, the Nigerian government is promoting a WHO-sponsored short course in AIDS management throughout the country.

Efforts are now under way to increase the amount of HIV/AIDS management instruction contained in the undergraduate and postgraduate curricula of Nigerian medical schools and medical credentialing societies. It is hoped that this will help establish a career path for clinicians interested in the field of HIV/AIDS. Development of a national program of medical knowledge assessment will then be necessary to ensure a basic minimum standard for providers of HIV/AIDS care. It is expected that these measures, coupled with increased investment in public services, may lead to a strengthening of morale in the public sector and a consequent increase in commitment to the provision of quality HIV/AIDS care and treatment services throughout the country.
REFERENCE LIST


Supporting National ART Scale-Up in Botswana through Standardized, Multiphased Training

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B OTSWANA, A SOUTHERN AFRICAN country of 1.7 million people, is among the countries most severely affected by the AIDS pandemic. In 2001, in the face of the growing threat posed by HIV—identified by former president Festus Mogae as a national crisis—the government of Botswana announced that it would provide antiretroviral therapy (ART) free of charge to eligible patients. This initiative, at the time without precedent in Africa, posed significant challenges to Botswana’s already overburdened public health-care system, especially in terms of the additional demands this would place on health-care personnel, infrastructure, and training programs. In spite of these challenges, the government of Botswana responded to the emergency by introducing a national ART program in January 2002.1

The lack of trained medical personnel, identified early on as a key challenge, continues to be a major obstacle to the timely and effective rollout of ART programs in Botswana and other African countries.2–6 Unlike high-income countries with low HIV prevalence, where HIV care is often provided by specialists, most African nations must marshal their entire health-care sector to confront the pandemic.7 The expedited and targeted training of a critical mass of health-care workers, followed by more broad-based workforce education, is of paramount importance to the success of ART programs in particular and to health-care sectors in general.8–10

The need to strengthen health-care worker capacity was identified by the Botswana Ministry of Health (MOH) and confirmed by a training needs assessment conducted in 2001. In response, Botswana embarked on the first phase of a national antiretroviral (ARV) training program.

PHASE 1: THE KITSO AIDS TRAINING PROGRAM

The KITSO AIDS Training Program, also known simply as KITSO, was created in 2001 by the MOH and the Botswana–Harvard School of Public Health AIDS Initiative Partnership for HIV Research and Education (BHP), with financial support from the African Comprehensive HIV/AIDS Partnerships (ACHAP), a collaboration between the government of Botswana, the Bill & Melinda Gates Foundation,
and the Merck Company Foundation / Merck & Co. Inc. KITSO is the Setswana word for “knowledge” and also serves as an acronym for “Knowledge, Innovation, and Training Shall Overcome” AIDS.

With the help of a private donation and the partnership of the MOH and BHP, the initial KITSO AIDS Training Program was developed in 2001 after a countrywide needs assessment. In 2002, Botswana announced the provision of free ART to all eligible citizens according to national treatment guidelines. Since Botswana did not have a medical school, the MOH partnered with BHP and ACHAP to devise and implement a standardized program to train Botswana’s health-care workers in HIV care and ART. Following the needs assessment and extensive stakeholder consultations, the KITSO AIDS Training Program was implemented by a newly formed national faculty who, with support from international advisers, designed country-specific training courses in HIV care and treatment.

In 2004, the MOH expanded KITSO’s didactic training by incorporating additional training partners in the country through a preceptorship program. Under the supervision and mentoring of a preceptor, newly trained health-care workers gained valuable hands-on experience in the practical application of their didactic training. In 2003, the training underwent further improvements with the development and implementation of the BHP–President’s Emergency Plan for AIDS Relief (PEPFAR) Master Trainer and Site Support Program (see section on Phase 2).

The KITSO training program has a number of distinguishing characteristics that have led to its success (see Box 1). According to the Botswana MOH, KITSO has been instrumental in Botswana’s national ART roll-out. KITSO training lectures have also been customized and used by ART training programs in several other countries, including Tanzania and Lesotho. KITSO lectures have also been translated for use in China.

### Program Design

The KITSO training modules serve as the national standard of training in HIV care and treatment throughout Botswana’s public and private health-care systems and are fully integrated with Botswana’s national HIV/AIDS treatment guidelines. The curriculum is also regularly updated by national and international experts to ensure that health-care professionals gain competency and confidence in the latest national standards of HIV care and treatment. Curriculum development and course implementation have been informed by the urgent need to train Botswana’s health-care workers in good clinical HIV care practice, without requiring long periods of staff release for training.

The MOH requirements to receive KITSO certification include full attendance at all sessions and completion of both a baseline assessment (pretest) and final examination (posttest) with a requisite passing grade. Health-care workers who meet the MOH requirements receive certificates of successful course completion. The KITSO-BHP team oversees training implementation, curriculum development, content updates, course examination, and certification.

### Box 1. Distinguishing Characteristics of the KITSO Training Program

- Botswana’s national training program directed by the MOH
- Country-specific curriculum, developed in Botswana for practitioners and patients in Botswana
- Standardized training modules that have been implemented by many training partners in a consistent fashion to train a high volume of health staff
- Responsiveness to the evolving training needs of Botswana’s health sector since its inception in 2001
An experienced and knowledgeable faculty provides instruction for KITSO-BHP courses. Faculty members are drawn from the KITSO team, BHP, ACHAP Clinical Preceptorship Program, the PEPFAR Master Trainer Program, and other development organizations. The course faculty includes national and international experts in the fields of HIV/AIDS prevention, treatment, care, education, and research.

Training for National ART Roll-Out

The first year of Botswana’s roll-out of ART to 31 treatment sites across the country was accomplished through a stepwise approach. The initial 31 sites included a main infectious disease care clinic (IDCC) that was integrated into the existing hospital (“mother site”) and linked to between two and five designated satellite clinics that conducted HIV screening and referrals. Treatment sites were first established in areas of high population density and easy accessibility, followed by the roll-out of ART to smaller and more rural sites. By March 2009 there were 31 hospital mother sites and 112 satellite ART sites.

The training of a critical mass of health-care workers at treatment sites was an essential step to the successful national roll-out of ART. Core treatment teams, which were prioritized for training, consisted of 20 staff members from the hospital IDCC and four staff members from each satellite clinic. The team was commonly comprised of 2 to 4 doctors, 10 to 12 nurses, 2 to 4 pharmacy staff, and 1 to 2 social workers. The approach that was used to deliver didactic training and clinical mentoring for each site is summarized in Box 2.

### Box 2. Steps in the Roll-Out of Training for Core Treatment Teams

**Step 1.** Core treatment teams received training in “AIDS Clinical Care Fundamentals” (ACCF) in either a facility-based or centralized format, depending on the size of the treatment site. Large treatment sites able to release sizable groups of health-care workers for training were offered facility-based training, while smaller treatment sites with limited staff were pooled with other facilities of similar size to receive centralized training over a period of four to six weeks (e.g., releasing 5 staff members per week over four weeks to train a total of 20 staff members). The training format for smaller facilities enabled simultaneous training of core treatment teams from multiple sites, while avoiding the interruption of health-care services that would have been caused by taking all health-care workers for training at one time. In Phase 2, the BHP-PEPFAR clinical master trainers also provided ACCF training to health-care workers at ART sites during site support visits.

**Step 2.** After the successful completion of ACCF training, one doctor, one nurse, and one pharmacy staff member from each treatment site were attached to one of two referral hospitals for the “Integrated Practical Attachment.” At the conclusion of the attachment training, participants returned to their treatment sites equipped to begin provision of ART and to provide basic mentorship to other health-care workers at that facility. PEPFAR clinical master trainers provided follow-up site and telephone support to all ART sites as part of Phase 2.

**Step 3.** As each treatment site’s opening date approached, the “Laboratory Fundamentals” module was conducted at the facility. With the support of PEPFAR laboratory master trainers, CD4 and viral load capacity testing was expanded to decentralized laboratories; master trainers also provided on-site and telephone support and mentoring. For support staff, the satellite module “Introduction to HIV & Biosafety” was implemented alongside the laboratory training, usually on consecutive days. (Note: All laboratory training now falls under the BHP-PEPFAR Laboratory Master Trainer program [see section on Phase 2].)

**Step 4.** Before the launch of each treatment site, an experienced ART practitioner (i.e., preceptor) from the ACHAP Clinical Preceptorship Program was assigned to the treatment site for three to six months to assist with final preparations and the ART launch, as well as to provide ongoing logistical assistance, clinical mentoring, and lectures. (Note: Currently, support for needs assessment, readiness assessment, preparation, launch, and mentoring is being performed by the BHP-PEPFAR clinical master trainers.)
Botswana’s health-care workers with the information and skills they need to begin providing basic ART and other HIV care services. Training is carried out using either a facility-based or centralized format, depending on the staffing needs of individual health-care facilities. This baseline module covers a total of 15 topic areas (see Box 3) and includes both adult and pediatric content. The module is comprised of lectures, case study discussions, practical exercises, and question-and-answer sessions, and concludes with a final examination. Following the initial training of core health-care worker teams for each treatment site, ACCF is now being provided

**KITSO-BHP Curriculum**

KITSO consists of didactic and practical core modules to facilitate ART roll-out, three advanced modules to consolidate and extend the HIV/AIDS knowledge and experience of Botswana’s health-care workers, and two satellite modules for non-medical staff (see Figure 1).

*Didactic Core Modules*

AIDS Clinical Care Fundamentals (ACCF), a four-day didactic training course for doctors, pharmacists, nurses, pharmacy technicians, and social workers, has served since 2001 as a gateway course to provide Botswana’s health-care workers with the information and skills they need to begin providing basic ART and other HIV care services. Training is carried out using either a facility-based or centralized format, depending on the staffing needs of individual health-care facilities. This baseline module covers a total of 15 topic areas (see Box 3) and includes both adult and pediatric content. The module is comprised of lectures, case study discussions, practical exercises, and question-and-answer sessions, and concludes with a final examination. Following the initial training of core health-care worker teams for each treatment site, ACCF is now being provided

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**Figure 1. KITSO-BHP curriculum**

<table>
<thead>
<tr>
<th>Physicians &amp; Pharmacists</th>
<th>Nurses &amp; Other Health Professionals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core Module</strong></td>
<td><strong>Core Module 2</strong></td>
</tr>
<tr>
<td>AIDS Clinical Care Fundamentals</td>
<td>Laboratory Fundamentals*</td>
</tr>
<tr>
<td><strong>Core Module 3</strong></td>
<td></td>
</tr>
<tr>
<td>AIDS Clinical Care Fundamentals Refresher/Update</td>
<td></td>
</tr>
<tr>
<td><strong>Advanced Elective Module</strong></td>
<td><strong>Advanced Elective Module</strong></td>
</tr>
<tr>
<td>Advanced HIV/AIDS Care &amp; Treatment</td>
<td>Medication Adherence Counseling</td>
</tr>
<tr>
<td><strong>Advanced Elective Module</strong></td>
<td></td>
</tr>
<tr>
<td>Sexual &amp; Reproductive Health in HIV Infection</td>
<td></td>
</tr>
<tr>
<td><strong>Satellite Trainings</strong></td>
<td></td>
</tr>
<tr>
<td>Introduction to AIDS Clinical Care</td>
<td>Introduction to HIV &amp; Biosafety*</td>
</tr>
<tr>
<td>One-Day Training for Nonmedical Professionals</td>
<td>Setswana Course for Nontechnical Staff</td>
</tr>
</tbody>
</table>

*These modules were phased out after initial ART roll-out to the 31 main treatment sites.*
to all health-care workers in Botswana. Staff reassignment, resignation, and replacement create a continuing need for the baseline training provided by the ACCF module. Between July 2001 and December 2008, 6,304 participants completed this module. During that period, 66% of trainees were from the nursing professions and 16.4% were medical doctors (Figure 2).

“AIDS Clinical Care Fundamentals Refresher/Update,” a two-day refresher course first implemented in January 2008, was developed in response to the high demand for refresher training. It also serves to update previously trained health-care staff on the most recent changes to the national treatment guidelines. Incorporating information from the new guidelines along with care and treatment fundamentals, the training covers HIV testing, ART eligibility, principles of ART, management of toxicities, management of treatment failure, prevention of mother-to-child transmission (PMTCT), and treatment of TB and other opportunistic infections.

“Integrated Practical Attachment,” designed as a hands-on follow-up to ACCF, utilized the high-volume ART clinics established at Botswana’s two referral hospitals for clinical mentoring in adult and pediatric ART. (Note: This module was subsequently replaced by the BHP-PEPFAR Clinical Master Trainer program in 2004 [see section on Phase 2].) Doctors, nurses, and pharmacy staff were taught under the guidance of experienced national clinicians, who in turn were supported by international experts from various MOH collaborators. Doctors were attached for four weeks of mentorship, during which time they maintained a clinical logbook and developed the confidence and skills to treat patients independently while receiving expert supervision and support. Nurses and pharmacy staff were attached to the same ART clinics for two-week rotations to gain experience in the national protocols for adherence counseling, treatment initiation, and treatment follow-up.

“Laboratory Fundamentals,” a one-day didactic and practical module, was designed for laboratory personnel and health-care workers involved in the collection and processing of laboratory specimens for the ART program. This training included practical background on the testing protocols for the ART program, sample collection, labeling, testing procedures, results interpretation and reporting, and basic biosafety. (Note: The “Laboratory Fundamentals” module was replaced by the

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**Box 3. Topic Areas Covered in the “AIDS Clinical Care Fundamentals” Module**

- Introduction to the Botswana National ARV Program
- HIV Epidemiology and Pathophysiology
- Laboratory Diagnostics in HIV/AIDS Care
- Principles of ART in the Botswana National Program
- Pediatric- and Adolescent-Specific Issues in HIV/AIDS Clinical Care
- Pediatric- and Adolescent-Specific Issues in HIV/AIDS Psychosocial Care
- ARV Drug Side Effects and Toxicities
- Drug-Drug Interactions in ART
- Treatment Failure and Its Management
- Adherence in ART
- Adult and Pediatric Opportunistic Infections and Other Complications in HIV Disease
- Prevention of Mother-to-Child Transmission (PMTCT)
- Postexposure Prophylaxis (PEP)
- TB and HIV Coinfection
- Summary of the Major Changes in the 2008 Botswana National Guidelines
FROM THE GROUND UP: LAYING A STRONG FOUNDATION

training in ART and advanced treatment challenges, as well as in-depth information in the areas of HIV virology and immunology. The course familiarizes participants with the full range of ARV drugs and provides strategies for the management of treatment failure, interpretation of drug resistance, assays, design of “salvage” regimens, and the understanding of short- and long-term ARV side effects and toxicities. Extensive case study discussions incorporate actual patient cases provided by course participants to illustrate and reinforce optimal care and treatment strategies.

Advanced Modules
Following the national roll-out of ART, KITSO introduced two new courses, “Advanced HIV/AIDS Care and Treatment” and “Medication Adherence Counseling,” to build on ART providers’ prior training and hands-on experience. Both courses were designed to provide responsibility-specific continuing and advanced training support for health-care workers from ART sites. These highly interactive courses, conducted in a centralized format, build specialized knowledge and skills integral to the long-term success of Botswana’s ART program.

“Advanced HIV/AIDS Care and Treatment” is an intensive five-day course for doctors and pharmacists who have successfully completed ACCF and have subsequently gained clinical experience in ART. The course combines lectures and interactive case discussions to provide comprehensive training in ART and advanced treatment challenges, as well as in-depth information in the areas of HIV virology and immunology. The course familiarizes participants with the full range of ARV drugs and provides strategies for the management of treatment failure, interpretation of drug resistance, assays, design of “salvage” regimens, and the understanding of short- and long-term ARV side effects and toxicities. Extensive case study discussions incorporate actual patient cases provided by course participants to illustrate and reinforce optimal care and treatment strategies.

The course covers adult, adolescent, and pediatric HIV care, with input from the Botswana-Baylor Children’s Clinical Center of Excellence and the pediatric departments of the two referral hospitals in Botswana: Princess Marina Hospital and Nyangabgwe Hospital. Special emphasis is placed on primary care for children living with HIV and on disclosure issues, especially for children and adolescents. Each advanced course features an evening

Figure 2. ACCF cumulative training numbers by profession, 2001–2008

<table>
<thead>
<tr>
<th>Profession</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors</td>
<td>1,033</td>
</tr>
<tr>
<td>Nurses, Nurse-Midwives &amp; Family Nurse Practitioners</td>
<td>4,001</td>
</tr>
<tr>
<td>Pharmacy Staff</td>
<td>556</td>
</tr>
<tr>
<td>Laboratory Staff</td>
<td>127</td>
</tr>
<tr>
<td>Other Health-Care Workers</td>
<td>587</td>
</tr>
<tr>
<td>Total</td>
<td>6,304</td>
</tr>
</tbody>
</table>
Responsive and Flexible Implementation

The KITSo model of training has mirrored the MOH’s general approach to national ART roll-out. Training was initially a centralized, vertical effort to equip core treatment teams to participate in the ART roll-out. KITSo courses are now offered in centralized, regional, and facility-based formats by KITSo faculty, BHP master trainers, and other training partners.

Since July 2001, KITSo-BHP has adapted its curriculum in response to the evolving training needs of health professionals in Botswana. Responsiveness and flexibility have enabled KITSo-BHP to problem solve and respond in a targeted fashion to the training goals as defined by the MOH and program stakeholders.

Teaching Tools

To augment the didactic courses offered by KITSo, the program has developed a number of valuable teaching tools, including CD-ROMs, a video lecture series, pill charts and pediatric dosing charts, and PMTCT flow charts. In 2002 a video-cassette series, bound course readings, and case studies were developed for use as training tools. Five CD-ROMs have been developed: Course for Physicians: Antiretroviral Therapy (2001), Lessons from Botswana: A Comprehensive Instructional Guide on HIV and AIDS Medicine for Health Professionals (2002), HIV and AIDS Care and ARV Therapy (2003), AIDS Clinical Care Fundamentals (2006), and AIDS Clinical Care Fundamentals (with the 2008 national ARV guidelines). These teaching tools provide narrated PowerPoint lecture slides.

Distance Education

Since January 2007, KITSo-BHP has formally established distance education through CD-ROMs as a means of providing the ACCF course to relevant health-care workers. After reviewing the CD-ROM and course materials, health-care workers come to
Gaborone for one day to participate in case discussions and take the final examination. The criteria for certifications are the same as for those taking the full in-class training.

**KITSO AIDS Training Program Achievements**

Nurses and doctors receiving ACCF training take different final examinations tailored to their clinical responsibilities. In an analysis of exam scores for the period 2003–2006, both professions demonstrated marked improvement in knowledge, as illustrated by the improved scores between the baseline assessments and final examinations. The mean change in pre- and post-test score was significantly higher for nurses ($P<.001$) than for doctors, most likely due to lower baseline knowledge among nurses and the fact that doctors regularly achieved the maximum scores (ceiling effect) at the time of final examination.

As part of site preparation, 553 health care workers were trained in “Laboratory Fundamentals,” and 687 support staff participated in “Introduction to HIV & Biosafety.” In addition, 95 health-care workers completed “Integrated Practical Attachment” during the initial roll-out period.

The advanced modules, “Medication Adherence Counseling” and “Advanced HIV/AIDS Care and Treatment,” more recent additions to the KITSO curriculum, have been conducted for 683 and 470 health-care workers, respectively. Through December 2008, 1,457 nonmedical professionals had completed the satellite module “Introduction to AIDS Clinical Care.” During this same period, 733 physicians and pharmacists were trained in the “AIDS Clinical Care Fundamentals Refresher/Update.”

**Program Assessment and Review**

Over the past eight years of the program, KITSO-BHP’s curriculum development and implementation have been enhanced by reviews conducted by the MOH, stakeholders, faculty, participants, and external evaluators. As KITSO-BHP’s funder, ACHAP has twice sponsored external evaluations that included the KITSO-BHP training efforts. In May 2003, Health and Development Africa, a South Africa–based consultancy, conducted an evaluation and subsequently released a report entitled *Evaluation of the KITSO AIDS Training Program and Clinical Preceptorship Program*. In 2004, John Snow International (UK) conducted a review of KITSO-BHP as part of its midterm evaluation of ACHAP-supported programs.

In 2006, KITSO-BHP and the MOH jointly conducted a long-term program evaluation to assess the impact and reach of KITSO training. Site leaders from 17 ART sites were interviewed and 494 former training participants completed survey questionnaires and knowledge assessments. The final evaluation report was released by the MOH in January 2008, the key findings of which are summarized in Box 4.

**PHASE 2: THE BHP-PEPFAR MASTER TRAINER AND SITE SUPPORT PROGRAM**

As the number of ART sites and enrolled patients increased throughout the country, it became evident that an expanded master trainer and site support system was needed. In response to the MOH’s demonstrated need for additional capacity building, Harvard School of Public Health, in conjunction with the MOH and BHP, initiated the BHP-PEPFAR Master Trainer and Site Support Program in March 2003 as the second phase of country-specific training and capacity-building activities.

BHP-PEPFAR is a multipronged project aimed at developing sustainable training capacity in the clinical care and treatment of people living with HIV, expanding decentralized CD4 and viral load laboratory testing, and strengthening the MOH’s monitoring and evaluation capacity to monitor the
Clinical Master Trainer Program

The Clinical Master Trainer (CMT) program provides site-specific, ongoing training and mentoring, and on-site and telephone support to designated MOH ART sites. These activities help ensure that health-care professionals stay current on all aspects of HIV treatment and care, that they are strengthening and reinforcing their skills on a continual basis, and that they are receiving sufficient technical support. The MOH devised the original framework for the project based on the belief that the best way to achieve these goals was to create sustainable training capacity at the sites themselves through the identification and training of site-level master trainers, including a physician, nurse, and pharmacist, at each ART site. BHP-PEPFAR has established a clinical master trainer corps, currently consisting of six physicians (including two pediatricians), two pharmacists, and four nurse-midwives, all of whom are highly experienced in HIV treatment and care for both adults and children. These core master trainers—some of the most experienced HIV/AIDS practitioners in the country—train and provide ongoing site and telephone support to the site-level master trainers. The approach used is based on a modified, country-specific version of the World Health Organization (WHO) Integrated Management of Adult and Adolescent Illness (IMAI) guidelines. Building on the KITSO didactic training, the program has become an important catalyst in the government’s effort to create a comprehensive, integrated, and decentralized HIV/AIDS treatment program from what had been a more traditional series of vertical programs addressing specific aspects of HIV/AIDS care (e.g., ARV, PMTCT, TB treatment and prevention, sexually transmitted infections, etc.). The components crucial to the program’s successful implementation are summarized in Box 5.

Laboratory Master Trainer Program

The Laboratory Master Trainer (LMT) program was developed to support the government’s goal of establishing decentralized laboratories capable of performing CD4 and viral load testing. This was done in order to relieve the burden and time delays at the country’s two national HIV reference laboratories in Gaborone and Francistown. Currently, the government of Botswana, along with ACHAP and the Centers for Disease Control and Prevention—Government of Botswana Partnership (BOTUSA), is constructing or expanding and equipping the new laboratories.


- 90% of KITSO-trained physicians were actively prescribing ART.
- 85% of respondents reported that they were working in a capacity that allowed them to use the skills and information taught by KITSO.
- 89% of respondents stated that they had provided instruction to their colleagues: 64% had provided theoretical instruction, while 48% had provided practical instruction to untrained co-workers.
- Facility leadership across the sample sites reported that KITSO training had improved patient care, particularly the management of opportunistic infections, adherence counseling, and the management of ARV drugs and side effects.
- Results of the knowledge retention test were below expectations. This is believed to be a result of the limitations of didactic courses and highlights the need for continuing education opportunities, performance feedback, and mentoring beyond the six KITSO courses evaluated.

The efficacy of the national ART program (“Masa”). The PEPFAR-funded project consists of three program components, which are detailed in the following sections.
Under BHP-PEPFAR’s national laboratory director, six core laboratory master trainers provide training in conducting CD4 and viral load tests, using a similar master trainer/site support approach as the CMT program. The MOH has recently asked the LMT program to add training in hematology and chemistry, as well as training on rapid HIV testing of adults and dried-blood-spot testing of infants. Program activities include site needs assessments for each decentralized laboratory, centralized attachment training at the Botswana-Harvard HIV Reference Laboratory (BHHRL) in Gaborone for site laboratory master trainers, on-site support to the new trainees in launching these tests at the decentralized laboratories, follow-up support and evaluation visits to each laboratory, and telephone support through a toll-free line.

**BHP-PEPFAR Program Achievements**

To date, the clinical master trainers have provided on-site support and training in care and treatment at all 31 hospital mother sites and their associated 112 satellite clinics (in addition to ongoing support at the IDCC/Princess Marina Hospital). Seventy clinics have been upgraded to ART sites and are being fully supported and mentored. During support at IDCC and other ART sites in the past five years, 17,654 patients were directly attended by physician master trainers and 7,548 patients were attended by nurse master trainers.

**Task Shifting**

In 2007, task shifting was implemented to mitigate the critical shortage of pharmacists, pharmacy technicians, and doctors/prescribers for the ART roll-out in Botswana. By adding pharmacists to the clinical master trainer corps, clinical and pharmacist master trainers have taken a lead role in training nurses in ARV prescribing and dispensing. These trainers provide comprehensive training and site support during the critical stages of ART roll-out and the upgrading of ART sites to become prescribing and dispensing sites. To date, a total of 63 nurses have attended the monthlong prescribing and dispensing course and 127 have attended the four-day dispensing course.

**Management of Treatment Failure**

Due to the success of the national ART roll-out and the continuous upgrading of clinics to full
prescribing and dispensing capacity, sites need to be vigilant in the areas of treatment failure and management. In partnership with the Masa program, all sites supported by clinical master trainers have been set up with treatment failure registries. The National Monitoring and Evaluation Committee, formed in 2007, is currently drafting the national protocol on early warning indicators.

**Telephone Site Support**

The telephone site support program allows clinic staff to receive real-time support from the master trainers. Both clinical master trainers and laboratory master trainers track all calls, which concern issues such as ART complications and necessary changes in drug regimens; pediatric HIV management; and reagent, equipment, and logistical laboratory issues. Site calls to the Monitoring, Evaluation, and Quality Improvement (ME&QI) Unit staff at the MOH deal mostly with reporting uniformity and deadlines, meeting and workshop notification, and new pharmacy data collection. More than 3,300 calls were fielded by representatives of the three BHP-PEPFAR components (i.e., CMT, LMT, and M&E) in the last year.

**Laboratory Decentralization**

Efforts by the laboratory master trainers to decentralize laboratory services have resulted in 23 sites now performing CD4 counts and 10 sites now performing viral load testing. Infant HIV diagnosis (DNA polymerase chain reaction [PCR]), which had previously been performed only at the BHHRL, was initiated at Jubilee HIV Reference Laboratory during 2008. More than half of the CD4 tests performed nationally are done at decentralized laboratories; this has significantly decreased the turnaround time of results, demonstrating the success of the decentralization process. During 2008, 160,877 CD4 and 30,650 viral load tests were performed in decentralized laboratories.

**ME&QI**

Clinical master trainers emphasize quality assurance and improvement initiatives in their site training. A quality improvement sensitization workshop for district and site leadership was held in June 2008 with 45 attendees. In addition, district health teams, Ministry of Local Government staff, and ART site managers participated in the Harvard-PEPFAR Tri-Country Conference, which focused on the quality management and improvement of HIV care and treatment programs.

Since January 2008, QI of HIV/AIDS services has been part of the mandate of the M&E Unit, now referred to as the ME&QI Unit. The ME&QI Unit continues to expand its role not only to cover ME&QI activities within the Masa program, but to have a greater role in integrating programs within the MOH Department of HIV/AIDS Prevention and Care (DHAPC). BOASA II, a new electronic application developed by the ME&QI Unit, links to the existing stand-alone Masa databases and produces standardized monthly clinical and pharmacy reports. The BOASA application was implemented in all Masa site hospitals in March 2008. To date, more than 45 million records have been extracted. The software development team of the ME&QI Unit continues to provide both site and telephone support. BHP-PEPFAR also supports 10 data entry clerks (DECs) who have been posted throughout the country. The DECs are in the process of updating data and improving data quality at ART sites. Early warning indicators have been identified and data collection mechanisms finalized.

**SUMMARY**

Training is a necessary prerequisite for the scale-up of HIV care and treatment programs. In Botswana, there has been an increase in both the number of health-care workers completing the ACCF course and the number of patients receiving ART. With over 112,000 people currently receiving ART in the
BEGINNING IN JULY 2005, BHP-PEPFAR began supporting the government of Botswana in establishing a Monitoring, Evaluation, and Quality Improvement (ME&QI) Unit within the national ART program (“Masa”). In July 2007, at the request of the Department of HIV/AIDS Prevention and Care (DHAPC) director, the unit expanded its role to become the official M&E unit of the DHAPC. The resultant ME&QI Unit, headed by an M&E specialist, is comprised of two data managers, a data manager understudy, a data quality officer, and 10 data entry clerks deployed to ART sites.

The ME&QI Unit is developing a uniform manual and computerized ART patient tracking system that will provide data on indicators for the national ART program. This process involved the development of standardized indicators, reporting instruments, and a uniform reporting schedule. The unit upgraded the BOASA electronic reporting application to include production of the pharmacy reports. This upgrade was deployed to 28 ART sites that have started producing standard pharmacy reports. The ME&QI Unit also tracks private sector patients, including those “outsourced” from the public to the private sector through the newly established public-private partnership (PPP) program. The unit is now working on linking data from ARV pharmacies, laboratories, the TB program, and other HIV/AIDS programs. To facilitate this process, a data warehouse server was purchased and is currently located within the MOH. While the system initially focused on the ART program, plans for eventual expansion to other HIV/AIDS programs will create a comprehensive M&E system serving the needs of the newly created MOH DHACP.

The DHAPC is working with the ME&QI Unit to identify indicators and develop standardized instruments and reporting mechanisms as well as an overall M&E plan for the DHAPC. The ME&QI Unit will also set up a national QI team and coordinate QI efforts in the MOH programs, as well as those of other stakeholders.

Beginning in July 2005, BHP-PEPFAR began supporting the government of Botswana in establishing a Monitoring, Evaluation, and Quality Improvement (ME&QI) Unit within the national ART program (“Masa”). In July 2007, at the request of the Department of HIV/AIDS Prevention and Care (DHAPC) director, the unit expanded its role to become the official M&E unit of the DHAPC. The resultant ME&QI Unit, headed by an M&E specialist, is comprised of two data managers, a data manager understudy, a data quality officer, and 10 data entry clerks deployed to ART sites.

The ME&QI Unit is developing a uniform manual and computerized ART patient tracking system that will provide data on indicators for the national ART program. This process involved the development of standardized indicators, reporting instruments, and a uniform reporting schedule. The unit upgraded the BOASA electronic reporting application to include production of the pharmacy reports. This upgrade was deployed to 28 ART sites that have started producing standard pharmacy reports. The ME&QI Unit also tracks private sector patients, including those “outsourced” from the public to the private sector through the newly established public-private partnership (PPP) program. The unit is now working on linking data from ARV pharmacies, laboratories, the TB program, and other HIV/AIDS programs. To facilitate this process, a data warehouse server was purchased and is currently located within the MOH. While the system initially focused on the ART program, plans for eventual expansion to other HIV/AIDS programs will create a comprehensive M&E system serving the needs of the newly created MOH DHACP.

The DHAPC is working with the ME&QI Unit to identify indicators and develop standardized instruments and reporting mechanisms as well as an overall M&E plan for the DHAPC. The ME&QI Unit will also set up a national QI team and coordinate QI efforts in the MOH programs, as well as those of other stakeholders.
of the MOH to build health-care worker capacity and assure the quality of HIV care and treatment in Botswana.

Flexibility in the implementation of training has made it possible to train a high volume of staff without disruption of overall health-care services. Training staff from large urban and semi-urban health-care centers, as well as from small rural facilities, requires different logistical approaches in training implementation. Other ART initiatives in the region will need to develop their own strategies according to their individual needs and resources.\textsuperscript{3,6,9,10,16} Operations research on optimal training methodologies, the effectiveness of various follow-up mechanisms, and long-term patient outcomes is warranted.\textsuperscript{9}

Another important feature in the design and implementation of KITSO has been the close collaboration of national faculty with international HIV experts. This ongoing process began in 2001 and resulted in the creation of training modules that present up-to-date medical and scientific information within the context of existing national guidelines and available diagnostic capacities. This mutual exchange of expertise has built capacity in all aspects of ART and has helped clinicians in Botswana to develop their own experience and expertise. When the national ART program was officially launched in January 2002, a core of capable clinicians was already in place. Training continued ahead of the roll-out timetable, preparing sites in sequence for their involvement in the national program.

Efforts to scale up ART programs in sub-Saharan Africa have been constrained by a lack of trained medical personnel, stemming from both acute staff shortages and general inexperience and lack of training in ART. Recruitment of additional health-care workers is often a slow process and in many cases is not an option. Innovative task shifting, which can increase available health-care capacity among existing staff, can help to rapidly address unmet patient care needs; however, this approach necessitates an even greater emphasis on standardized and expanded training efforts.\textsuperscript{3,6,9,10,16}

**ONGOING CHALLENGES**

With ART now available throughout the country, Botswana is well positioned to further increase access to ART by extending ARV prescribing and delivery of comprehensive ART services to existing, affiliated satellite clinics, even if physicians are not available in these clinics. Some satellite clinics have already begun to provide ART, and training of all staff in these facilities is currently under way. There is an ongoing need at these sites for continuing education, refresher courses, advanced training, and timely information regarding revisions and amendments made to national treatment protocols.

The long-term need for ART in Botswana and elsewhere requires that adequate knowledge of HIV care and treatment be integrated into the pre-service training curricula for all health professionals. The retention of trained staff with ART experience is critical to the program’s long-term success. KITSO-trained health-care workers have been recruited into HIV/AIDS programs in other countries, a fact that underscores the successes of Botswana’s training and treatment efforts. However, this recruitment hampers the expansion of the Botswana program, especially in the context of a generally understaffed health system. In addition, care should be taken to avoid transferring staff with ART experience to locations and duties that do not utilize their specialized knowledge and skills.

Finally, training programs such as KITSO and BHP-PEPFAR cannot remain static. In order to be successful, training programs must reflect the continual advances in HIV care as well as the evolving needs of the health sector they serve.
KITSO and BHP-PEPFAR seek to be flexible and responsive as new research emerges and as Botswana’s training needs change. For example, in view of the fact that a majority of patients in the ART program are women, and in view of many women’s renewed desire to have a child following restoration of health on ART, a new module on HIV and women’s health is now being developed to focus on special care and treatment considerations for women living with HIV, including family planning issues.

CONCLUSION
As a standardized, national training program coordinated by the MOH, the KITSO AIDS Training Program and the BHP-PEPFAR Master Trainer and Site Support Program collaboration is a model of HIV/AIDS care training for rapidly expanding the capacity of a national health system to respond to the HIV pandemic. KITSO and BHP-PEPFAR have been indispensable elements in Botswana’s national roll-out of ART. Through timely implementation of a standardized curriculum, broad collaboration, high-quality and country-specific instruction, effective monitoring and evaluation, and strong MOH leadership and coordination, the KITSO/BHP-PEPFAR approach could serve as a training model for many countries in the early stages of national HIV care and ART program implementation.

ACKNOWLEDGMENTS
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The authors would like to acknowledge the leadership and guidance of the Botswana Ministry of Health and the Botswana–Harvard School of Public Health AIDS Initiative Partnership for HIV Research and Education (BHP), the commitment and dedication of KITSO faculty members and the KITSO-BHP team, and the contributions of all training partners participating in the broader KITSO AIDS Training Program, particularly the BHP-PEPFAR Master Trainer and Site Support Program, the Botswana-Baylor Children’s Clinical Center of Excellence, the University of Pennsylvania, the ACHAP Clinical Preceptorship Program, and the Private Practitioner Association of Botswana.

KITSO-BHP has been made possible through support from ACHAP and the Botswana Ministry of Health. BHP-PEPFAR has been made possible through support from the Health Resources and Services Administration / HIV/AIDS Bureau (HRSA/HAB), as part of its international AIDS activities as an implementing organization for PEPFAR.
REFERENCE LIST

Development and Implementation of Training Packages for PMTCT and Pediatric HIV Care

Linda S. Podhurst, Mary Jo Hoyt, Farai Dube, Nomfundo Nhlapo, Lucy Connell, and Robert Ayisi

COMPREHENSIVE PROGRAMS FOR THE prevention of mother-to-child transmission of HIV (PMTCT) in conjunction with effective linkages to pediatric HIV care and treatment can reduce significantly the number of children who become infected with HIV while improving outcomes for those already infected. To facilitate the provision of these critical services, it is essential to expand the pool of health-care workers trained in PMTCT and pediatric care. Such training activities, which can take a number of forms, are important for the success of the widespread scale-up of PMTCT and pediatric HIV care now under way. The severe shortage of skilled health-care workers in many developing countries remains a major barrier to the development and expansion of lifesaving children’s health services.

Frontline health-care providers in a position to provide PMTCT and pediatric HIV care services are often already overburdened by heavy patient caseloads and severe staff shortages. Ideally, PMTCT services can be offered in all settings that provide reproductive health care, including those that utilize traditional birth attendants. Pediatric HIV care serves a much smaller population than PMTCT and can be provided by relatively fewer clinicians. However, training for pediatric services lags significantly behind training for PMTCT and adult HIV care and treatment programs. The provision of pediatric HIV care requires specialized training, as well as a shift in traditional models of service provision, so that chronic care can become the norm rather than the exception. Until very recently, most pediatric health care in resource-limited settings has focused on well-child and acute care, with limited services for the care of children with chronic illnesses.

This chapter discusses strategies and experiences in developing training materials and approaches for the implementation of training programs for PMTCT and pediatric HIV care. Training is an important tool for addressing the technical and emotional demands placed on health-care workers when HIV prevention and treatment services are added to their existing workloads. Training programs give health-care workers opportunities to acquire knowledge and skills while teaching them how to take on new roles and cope with the emotional demands of HIV care. The following section highlights how the planning of training programs and related materials development can address the needs of the target population and the specific
services to be delivered. Later in the chapter, case studies provide examples of successful training initiatives.

**DEVELOPMENT OF TRAINING MATERIALS**

The processes used to develop training materials vary greatly depending on program characteristics (see Table 1). The process for materials development should reflect the scale and scope of the training needs. Centralized, national leadership may be especially important during the development of large-scale training efforts, such as training to support nationwide scale-up of comprehensive PMTCT services, whereas regional or local leadership is sufficient for the development of training programs for smaller or more localized initiatives. This section describes three model processes for training materials development that strike varying balances between national and international participation. The descriptions are meant to serve as useful reference points for understanding the variety of processes that can be used. Naturally, variations of these models involving different mixes of national and international cooperation are also possible.

**Materials Developed by National or Regional Experts**

A rapid method for responding to the need for training materials is development by a small, dedicated group of national or regional experts in a specific area of expertise (e.g., perinatal HIV transmission or pediatrics). These experts may come together in a number of ways, such as clinicians and/or educators working to address the needs arising in clinical settings. Experts convened regionally or nationally by the government to work with the country’s ministry of health are often referred to as a technical working group (TWG). There are significant strengths that emerge from this approach to training materials development:

- Practitioners are invested in the materials, and their investment often generates buy-in for the recommended procedures to facilitate service delivery.
- Content is likely to reflect country-specific cultural norms, values, and priorities.
- Materials development is a capacity-building activity that encourages developers to
  - focus on the clarity of the protocols for service delivery;
  - identify and address gaps;
  - integrate national policies for consistency with training;
  - identify and develop policies that have not yet been addressed (e.g., confidentiality within the national strategy for HIV/AIDS and its application to PMTCT, or disclosure policies for pediatrics); and
  - change clinical practice to increase coordination of PMTCT and pediatric care.
- Involvement of a TWG is likely to focus on the population-specific considerations of targeted patient groups (i.e., pregnant women, their partners and families, as well as HIV-exposed and -infected children), with training content tailored to patient and health worker needs.

However, there are some potential drawbacks to the development of materials exclusively by national or regional experts without input from international partners or resources:

- The balance and quality of the materials may be skewed due to the varying availability and inclusion of experts (e.g., nutrition experts may place substantial emphasis on details of infant feeding rather than on less familiar content about antiretroviral prophylaxis or counseling and testing).
- Focus of materials may be less multidisciplinary than materials developed with international input (e.g., materials development may be dominated by physicians, because contributions
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<th>National/Regional</th>
<th>National/International Collaborative</th>
<th>International</th>
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<tr>
<td><strong>Advantages</strong></td>
<td>Local practitioner investment in materials</td>
<td>Inclusion of international standards and evidence-based data</td>
<td>Comprehensive coverage of pilot-tested, efficacious materials</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Potentially limited available expertise and skewed emphases on content and practice areas</td>
<td>Potential for contradictory perspectives between partners</td>
<td>Potential for unrealistic (not practical) standards and protocols</td>
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<tr>
<td><strong>Content</strong></td>
<td></td>
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<tr>
<td><strong>Buy-in</strong></td>
<td>Buy-in from local practitioners, to facilitate service delivery</td>
<td>Buy-in from national experts, to integrate country perspective into international standards</td>
<td>Buy-in from international experts, to invest in proven standards and protocols</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potentially unequal partnerships and inclusion of content that is of questionable relevance</td>
<td>Potential lack of interest among local clinicians and trainers</td>
</tr>
<tr>
<td><strong>Cultural relevance</strong></td>
<td>Reflection of country-specific norms, values, and priorities</td>
<td>Consideration of infrastructure, resources, and cultural norms</td>
<td>Influence of international norms and increased awareness of human rights issues</td>
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<tr>
<td></td>
<td></td>
<td>Cultural variability among partners and potential for intensified negotiations</td>
<td>Potential for insufficient consideration of cultural values, or failure to reflect health-care infrastructure</td>
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<tr>
<td><strong>Approach</strong></td>
<td>Attention to population-specific considerations with targeted training content</td>
<td>Collaborative, multidisciplinary approach</td>
<td>Inclusion of wide-ranging multidisciplinary expertise in training methods</td>
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<td>Inhibition of meaningful international collaboration due to cost and logistics</td>
<td>Potential lack of country expert consultation</td>
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Table 1. Approaches to Training Materials Development: Advantages and Limitations (cont.)

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<th>National/Regional</th>
<th>National/International Collaborative</th>
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<tr>
<td><strong>Advantages</strong></td>
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<tr>
<td><strong>Capacity-building potential</strong></td>
<td>Opportunities to clarify protocols, identify and address services gaps, and develop new policies</td>
<td>Potential for capacity building for international and national partners</td>
<td></td>
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<tr>
<td><strong>Limitations</strong></td>
<td>Potentially limited access to current resources</td>
<td>Barrier of value differences</td>
<td></td>
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<tr>
<td><strong>Timing considerations</strong></td>
<td>Potential for quick development and implementation of new strategies</td>
<td>Efficient revision process, due to reduction of potential biases from the outset</td>
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</tr>
<tr>
<td><strong>Funding opportunities</strong></td>
<td>Funding from partners with particular regional/national development focus</td>
<td>Optimal funding opportunities if national/regional and international standards are incorporated</td>
<td></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>International funding may depend on whether international standards are considered</td>
<td>Potential for lack of funding for partners with regional/national development focus</td>
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<tr>
<td><strong>Limitations</strong></td>
<td>Potential for lack of funding for partners with regional/national development focus</td>
<td>Funding opportunities from entities that emphasize meeting international standards</td>
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</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Lost capacity-building benefit for national/regional partners and TWG</td>
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*Source: François-Xavier Bagnoud Center, 2007.*
from nurses or other allied professionals may be undervalued or seen as inferior, rather than valued for their unique content and perspective).

- There may be limited access to the most up-to-date resources and to experienced PMTCT or HIV clinicians or educators. Reference books may be the only resources available in a particular setting; these texts may not reflect the latest internationally recognized guidelines or training methodologies.

**Materials Developed Collaboratively by National and International Experts—Harmonization**

Midway on the continuum of materials development processes is the harmonization model. In this model, national experts (e.g., the TWG) collaborate with a select group of international experts to develop training materials. This model has the potential to build on the strengths of the national expertise and materials and address some of the potential drawbacks of an exclusively national development process. The collaborative nature of this process is a significant advantage of the model, which may result in some or all of the following positive outcomes:

- International standards and evidence-based data are introduced by international partners; such standards and data are reviewed and incorporated when appropriate for the setting, as guided by national partners.
- There is access to a broader range of expertise that includes experience in various training methodologies.
- Knowledge and experience shared in the act of collaboration builds capacity among both international and national experts.
- Exchange of perspectives reduces the potential for a biased emphasis on certain areas.
- Appropriate consideration can be given to the impact of infrastructure, resources, and culture.
- Process of integrating materials results in enhanced buy-in from national experts.
- Collaboration may encourage a multidisciplinary approach.

At the same time, the following challenges may arise from the harmonization process:

- The need to negotiate content and perspectives is time consuming.
- Negotiations may be intensified by cultural variability between partners.
- Value differences may present barriers (e.g., the question of whether an HIV-positive woman should have a baby).
- Unequal partnerships may result in the inclusion of content that is not acceptable in the national context, and implementation may be compromised by lack of buy-in.
- Access to international collaboration may be limited due to cost and logistics.

The development of comprehensive, evidence-based training materials to prepare health-care workers to implement PMTCT and pediatric HIV care and treatment programs presents an enormous human capacity and fiscal challenge for resource-limited settings. The availability of internationally developed training materials that can be adapted to address national needs and integrated with existing materials provides a useful starting point for the collaborative materials development process. Generic training packages can be extremely helpful in this context. The U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have lent considerable support for the development of training materials that meet international standards. They have done this through the development of the PMTCT Generic Training Package (PMTCT GTP), the

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*Available at http://www.womenschildrenhiv.org/wchiv?page=gtp-01-00.
Integrated Management of Childhood Illness (IMCI), the Integrated Management of Adolescent and Adult Illness (IMAI), and the Complementary Course on HIV/AIDS. These training packages target frontline health-care providers in resource-limited settings and serve as a training template that national experts can rapidly adapt to meet local needs. Where training materials already exist, the GTP, IMCI, IMAI, and other materials can be used to quickly strengthen and update the contents of national materials. The Kenya harmonization case study (presented later in this chapter) provides a comprehensive example of how the PMTCT GTP was used in the development of a national training curriculum. The International Maternal Pediatric and Adolescent AIDS Clinical Trials (IMPAACT) network Global Training Program case study (presented later in this chapter) provides an example of a collaborative partnership to address gaps and enhance existing national training programs for PMTCT and pediatric HIV care.

Materials Developed by an International Partner

At the other end of the continuum is a model in which materials are developed by an international partner and then implemented nationally and regionally. WHO has developed a number of such products that provide guidance on the gold standard for disease management worldwide. They include the Clinical Care Essentials, seven essential manuals on clinical care that provide key knowledge to health-care professionals, and HIV and Infant Feeding Counselling: A Training Course. Unlike the PMTCT GTP, however, these materials do not include specific guidance about where and how to insert local policies and guidelines; nor do they provide guidance for areas in which national practices need to be considered and addressed. For resource-limited settings, this model of materials development, which features the significant involvement of one or more international partners, offers the advantage of minimal fiscal and time investment at the national level. Key strengths of this model include the following:

- Materials are widely used in a range of international settings, have often been pilot-tested, and have some proven efficacy.
- The product benefits from a broad range of multidisciplinary expertise.
- Widespread availability of content expertise allows for more comprehensive coverage of issues using evidence-based data.
- Training expertise may facilitate use of a broader range of educational methodologies.
- Additional human resources provided by international partners facilitate more rapid completion of materials.
- External funding may depend on meeting international standards, and these materials provide the information needed to meet those standards.
- The materials preparation process allows clinicians to benefit from external sources of information or support.
- Exposure to and influence of international norms fosters increased awareness of human rights issues that have an impact on affected groups.

The strengths may be compromised by challenges that result from the absence of national expertise, such as the following:

- Standards and protocols may not be relevant to or realistic for the setting.

\*Available at http://www.who.int/bookorders/WH/destart.jsp?sessionid=1&colidan=1&colcol=93&codch=204.
\*Available at http://data.unaids.org/Publications/External-Documents/who_fch_cah_00-3_en.pdf.
• Policy and service delivery priorities may not be adequately understood and appropriately addressed.
• Resource constraint considerations and cultural values may not be sufficiently considered.
• Content may not reflect the local health-care infrastructure.
• Country-expert consultation networks may not be incorporated into materials.
• The capacity-building benefit from national TWG involvement is lost.
• Clinicians and trainers may not be interested in a product that they have not played a role in developing.

PMTCT AND PEDIATRIC HIV CARE TRAINING

Conducting a Needs Assessment for PMTCT and Pediatric HIV Care Training
The materials development process begins with a needs assessment to learn about the training needs of the target audience as well as to catalogue existing content to ensure that the training program responds effectively to a given set of regional or national requirements. The mechanism used to conduct the needs assessment varies; in general, rapid strategies are used to meet the urgent need for training. For PMTCT programs, the assessment will look at the training needs associated with the scale-up of PMTCT services and will guide the development of sustainable, large-scale national training programs and a national training plan. For pediatric HIV care programs, the assessment will examine the ways in which the number of trained health workers with the capacity to provide pediatric HIV care can be expanded, as well as methods that can be used to clinically mentor and support the development of expertise among other health workers. Rapid assessment strategies include these:

• Direct observation of site(s) using a detailed checklist to gather information about staffing, space, reference materials, equipment, laboratory, pharmacy capacity, and so on
• Open-ended interviews with frontline providers and key stakeholders (see “Developing a Training Plan” for key questions to discuss)
• Desk review of related policies, guidelines, strategic planning documents, and training materials

From the time the needs assessment is initiated until dissemination and roll-out of the final training materials, it is of the utmost importance to engage with and elicit feedback from a broad range of stakeholders. Whoever ultimately makes decisions on training policies and the content of training materials will benefit enormously from the opportunity to discuss the training development process with the many partners committed to quality PMTCT and pediatric service delivery. The success of training materials is measured by their utilization by various partners. Seeking, respecting, and incorporating the input of partners in-country is the key to broad acceptance of training materials that provide a consistent “take-away” message for the delivery of services to pregnant women and families affected by HIV. Ultimately, the success of training programs is indicated by the scale-up of PMTCT services staffed by trained health-care workers with quality assurance reviews of clinical practice indicating that clients and families are receiving targeted services according to established policies and procedures (e.g., voluntary counseling and testing, antiretroviral prophylaxis and treatment, infant feeding counseling, etc.).

Developing a Training Plan
The training plan takes into account the training infrastructure, available resources, time frame, and monitoring and evaluation plan. The responsible partners and timeline for each part of the plan are
Development of Training Content

The materials developed need to be evidence-based and provide a comprehensive, accurate description of national policies, procedures, and protocols. When it is expected that training will be utilized on a long-term basis, an expert advisory group, such as the TWG or a separate panel of experts, monitors developments in PMTCT and pediatric care to ensure that materials are updated as needed; existing policies, procedures, and protocols are changed; and new policies are developed as required. A comprehensive package of training materials will include manuals and tools for the trainer and participants during the training course as well as clinician support tools (i.e., job aids) that can support the application of newly acquired skills in the clinical setting.

The trainer manual for a direct training or a training-of-trainers course should be comprehensive enough to allow an experienced trainer to confidently conduct the training after reviewing the manual contents. The objectives for each session must be stated clearly. Consistent, quality training can be facilitated by slides that include trainer notes, interactive activities that include trainer instructions and support materials, role-plays that are fully described and/or scripted, and ready-to-use evaluation materials.

The provision of high-quality pediatric HIV care services requires a considerable number of specific and diverse skills, from intensive counseling and patient education to management of pediatric phlebotomy. Because of the unique aspects of pediatric HIV care, adult HIV care experience alone is not sufficient preparation for addressing the specific needs of infants and children. Training involving the transfer of information without a practical component is also inadequate in settings where health-care services are primarily delivered by nurses or other midlevel providers. Such providers need more...
comprehensive training since they generally have little to no experience in pediatric HIV management and limited access to on-site supervision by experienced clinicians. While training programs for PMTCT may adequately prepare participants for clinical practice by providing opportunities to apply their skills in the training setting, opportunities to practice in the work setting under the supervision of a mentor are highly desirable. If mentoring is performed as part of the training, materials that offer guidelines for mentoring and learning goals for trainees are helpful tools for increasing the likelihood that participants will further develop and apply their newly acquired knowledge and skills in the work setting. The case study of the Enhancing Children’s HIV Outcomes (ECHO) project in South Africa (later in this chapter) offers an illustrative example of a successful mentoring program.

Implementation of Training
It is often challenging to identify experienced and highly skilled trainers who are also experts in the required content areas. In addition to content expertise and clinical experience, training skills are an important selection criterion for trainers. Ideally, experienced trainers are competent in an array of training methodologies, and trainers with less experience are paired with highly skilled trainers. Local or regional trainers familiar with the settings of the trainees are also highly desirable. An advisory group that represents stakeholders is a potential source for identification of qualified trainers. A common pitfall to be avoided is the selection of trainers based on seniority or rank rather than training skills.

The trainer orientation process focuses on training methodologies as well as content mastery. Providing practice sessions with peer “teach-back” opportunities can be an effective interactive learning exercise that enhances didactic content. Ideally, highly experienced trainers with content expertise orient the less experienced trainers. They can help guide the less experienced trainers on strategies for the use of training materials and mixed training methods, go over model sections of the curriculum that incorporate the various methods, and offer an opportunity for trainers to teach back course content and receive feedback. Extensive trainer preparation helps less experienced trainers feel more confident in their abilities, while increasing their personal investment in achieving a high standard of quality.

Selection of a training venue that affords adequate space and a comfortable learning environment for the target audience is another important component of successful training implementation. Off-site training prevents participants from being interrupted by clinical responsibilities but requires administrative involvement and planning for adequate staffing coverage. Staffing coverage is easier to facilitate during a regional training, which involves select participants from a number of regional health facilities, rather than situations in which large numbers of staff from a single program or site attend all at once. Additionally, on-the-job preceptorships not only provide opportunities to address the clinical application of training but also reduce the problem of staff shortages since training can be received while on the job.

Qualified trainers set the tone of the training experience by describing the plan for the training, ground rules, and time frame. Careful monitoring of time for each segment of the training, paying attention to participants’ verbal and nonverbal messages, and frequent check-in for understanding of take-away messages are key attributes of a good trainer. Clinicians attending PMTCT and pediatric HIV trainings are often overburdened by heavy workloads and inadequate staffing at their worksite. To be useful, training must realistically
Methods to Address the Gap between Training Programs and Clinical Care

The ongoing evaluation process serves to provide information about gaps that may exist between training programs and the actual delivery of clinical care. Training strategies that can be implemented to bridge such gaps include on-site clinical preceptorships and targeted clinician support tools and job aids for use in the work setting. On-site clinical preceptorships for PMTCT services pair experienced clinicians with trainees for periods ranging from a half day to a full week with the express purpose of providing guidance in the management of challenges presented by real patients in the clinical setting. For pediatric care, midlevel clinicians inexperienced in the management of pediatric patients in general or inexperienced in the care of HIV-exposed and infected children need more involved preceptorships over longer periods of time. Successful sites have a mix of experienced and inexperienced clinical staff. When this mix is not possible, weekly or semimonthly site visits by an experienced clinician—for the purposes of reviewing cases and addressing problems—can be critical to the ongoing delivery of high-quality services.

Targeted clinical support tools are user-friendly, accessible materials that address common problems that trainees will likely encounter (e.g., understaffing) and identify and discuss strategies to overcome those challenges.

Evaluation is an integral component of training. Evaluations conducted during initial or pilot trainings provide a way to obtain feedback that will inform the revision and finalization of training materials and presentations. The involvement of participants, trainers, and observers in the evaluation process provides diverse perspectives that are particularly useful. Course evaluations that assess attendees’ achievement of learning objectives and the usefulness of training activities help to determine whether the training has addressed the identified needs of the participants and can facilitate continuous quality improvement. Pre- and post-tests are also useful in that they help document both where training is most needed and the effectiveness of the training in addressing participant needs. However, pre- and post-tests cannot address all course content, and constructing valid test questions can be difficult. Therefore, this approach works best as one component of a broader, more comprehensive approach to training evaluation.

The tracking of process indicators (e.g., number, location, and role of trainees) monitors progress in developing capacity to deliver PMTCT or pediatric HIV services. Evaluations can also be used to measure progress toward provider competencies and to monitor and guide the clinical development of trained health-care workers. Midterm evaluations measure the extent to which training has resulted in sustained practice change on the job. Evaluation tools that measure to what extent learning is transferred to the clinical/work setting, and to what extent positive changes are maintained over time, are especially important. Long-term evaluations assess whether changes in health-care providers’ knowledge, skills, and behaviors resulted in positive patient outcomes.
DEVELOPMENT OF GENERIC TRAINING PACKAGES

The PMTCT GTP developed jointly by WHO and the U.S. Department of Health and Human Services–Centers for Disease Control and Prevention (HHS-CDC) is a useful focal point for a discussion of how generic training materials for resource-limited settings are developed. The PMTCT GTP includes trainer and participant manuals comprising nine modules, accompanying slides for each module, clinician support tools (i.e., pocket guide and wall charts), and a program and course director guide. Available in English, French, Russian, and Spanish, the GTP has been adapted for use in resource-limited settings in Africa, Asia, the Caribbean, and South America.

The GTP can be used in a number of ways to fully support or supplement national PMTCT training activities. Here are some typical uses:

- The GTP is fully adopted as the national package with minimal country-level input.
- GTP modules are used to supplement, update, and revise existing country materials.
- The GTP serves as a framework for a fully integrated package; extensive country-specific materials are developed to provide a comprehensive, cohesive national training package.

The GTP begins with an introduction and overview that provide an orientation to the teaching methodologies and a sample course schedule for the nine modules, which are as follows:

- Module 1: Introduction to HIV/AIDS
- Module 2: Overview of HIV Prevention in Mothers, Infants, and Young Children
- Module 3: Specific Interventions to Prevent MTCT
- Module 4: Infant Feeding in the Context of HIV Infection
- Module 5: Stigma and Discrimination Related to MTCT
- Module 6: HIV Testing and Counselling for PMTCT
- Module 7: Linkages to Treatment, Care, and Support for Mothers and Families with HIV Infection
- Module 8: Safety and Supportive Care in the Work Environment
- Module 9: PMTCT Programme Monitoring and Field Visit Guide

The successful dissemination and implementation of the GTP in more than 40 countries on three continents suggests that this training package meets diverse needs. The widespread use of the package points to the need for further investment in the development of generic training materials for resource-limited settings. A vital component of the success of generic training materials is the roll-out plan that provides a detailed description of a set of activities to engage potential users by introducing the materials, facilitating the development of an action plan, and providing technical assistance for implementing the action plan. The roll-out plan may include training exchanges and workshops targeting key countries preparing to scale up services.

The development of a national curriculum based wholly or in part on a generic training package begins with a decision by the ministry of health to lead the process. The first step entails identifying and convening a TWG comprising multidisciplinary stakeholders with expertise in PMTCT. Among these stakeholders are clinical experts, frontline care providers, program managers, and people living with HIV, in addition to a range of organizations (e.g., nongovernmental organizations, bilateral and multilateral partners, community- and faith-based groups). The role of the TWG is to provide leadership for the development of the training plan, the guidelines, the training package, and the monitoring and evaluation plan. The TWG
is responsible for regularly reviewing and updating PMTCT documents, establishing sustainable training strategies to effectively build capacity within the PMTCT program, and ensuring that policies and protocols are feasible and acceptable given the local cultural context.

The implementation of the GTP in a given country entails one of two related processes: adaptation or harmonization. In countries that do not have existing PMTCT training materials (or that have only limited materials), adaptation best describes the process that will be used. According to this process, the GTP serves as the basic working document, which is then amended to reflect country-specific information, such as national policies, protocols, algorithms, and program descriptions. For countries that already have training materials and established policies and protocols, the process used is harmonization. In this process, the national training materials serve as the basic working document and the GTP format is used to structure the material, address any gaps in the existing curricula, and ensure that all information is up-to-date.

Throughout both the adaptation and harmonization processes, the development of materials is under the supervision and guidance of the ministry of health, which identifies membership and assigns responsibilities to the TWG, the lead agency, partners, and stakeholders. The adaptation or harmonization of GTP training materials to meet national guidelines, resources, and needs can be described in an eight-step process, as shown in Table 2.

CASE STUDY #1: ADAPTING THE WHO/HHS-CDC PMTCT GENERIC TRAINING PACKAGE: THE KENYA HARMONIZATION EXPERIENCE

In 1998, the Network of AIDS Researchers in Eastern and Southern Africa (NARESA) PMTCT project was developed to conduct operations research that evaluated the feasibility of implementing a PMTCT program in three Ministry of Health (MOH) hospitals in Kenya. NARESA developed a curriculum for the pilot sites, and that curriculum was then used in the national scale-up of PMTCT from 1999 to 2004 to train 1,500 health-care workers. In 2000, the National AIDS and STD Control Programme (NASCOP) created the PMTCT TWG to facilitate and monitor PMTCT scale-up and implementation in Kenya. The TWG was charged with

- standardizing national PMTCT training materials and systems;
- establishing effective coordination of PMTCT programs;
- updating national PMTCT guidelines and policies;
- developing an operational plan for roll-out of PMTCT training for health-care workers; and
- implementing a sustainable trainee follow-up system.

The Kenya PMTCT scale-up plan led to the need for a service provider curriculum. Thus, the TWG was mandated by the MOH to harmonize the existing training materials (i.e., the NARESA pilot site curriculum) into a standardized national training package. Once NASCOP had created a draft curriculum, the CDC Global AIDS Program (GAP) training experts were invited to assist in the process of finalizing the materials. GAP training experts reviewed the content and format of both the original pilot site NARESA curriculum and the draft NASCOP national curriculum and presented a proposal for the integration of those two documents into a comprehensive, standardized national curriculum.

The CDC training experts invited the François-Xavier Bagnoud (FXB) Center at the University of Medicine and Dentistry of New Jersey (UMDNJ) to collaborate in the process of harmonizing the NARESA and NASCOP curricula with the PMTCT
## Table 2. Sample Harmonization Process for the PMTCT Generic Training Package

<table>
<thead>
<tr>
<th>Harmonization Step</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Prepare the curriculum outline</td>
<td>Analyze existing documents and training materials, comparing strengths and gaps with the GTP. From this analysis, prepare a list of proposed modules that identify key content and session topics.</td>
</tr>
<tr>
<td>Step 2: Develop a draft of the primary technical document</td>
<td>The primary document is usually the trainer manual, which ideally serves as the source for the participant manual and clinician support materials. If, as the trainer manual is developed, the TWG members do not have content-area expertise in vital areas such as infant feeding, testing and counseling, and antiretroviral management, that information is gathered in consultation with experts in those areas.</td>
</tr>
<tr>
<td>Step 3: Review and revise the trainer manual</td>
<td>The complete first draft of the PMTCT trainer manual is then reviewed by the ministry of health (MOH) and members of the TWG. This key step provides the opportunity to learn and build consensus on content. The trainer manual is revised based on the comprehensive review by the MOH and the TWG.</td>
</tr>
<tr>
<td>Step 4: Develop participant manual, accompanying slides, and clinician support materials</td>
<td>The participant manual can then be extracted from the trainer manual with an emphasis on conveying clear take-away messages with well-reasoned, easy-to-understand rationales for implementing the PMTCT program. Based on the needs assessment, job aids for clinicians, such as complementary pocket guides and wall charts based on trainer manual content, are helpful components of the training package.</td>
</tr>
<tr>
<td>Step 5: Pilot test the curriculum</td>
<td>For the pilot test, experienced trainers are selected and oriented to the training materials. In addition to the content review, the trainer orientation for the pilot test describes the roles and responsibilities of the trainer and the expected outcomes of the pilot test. The pilot-test participants are selected to represent multidisciplinary health-care workers with varying levels of PMTCT experience. Observers providing detailed evaluations of the pilot test are ideally key stakeholders planning to implement the national curriculum. Evaluations of the pilot test are completed, module by module, by participants, trainers, and observers, so that specific feedback can be collected for the final revision of the curriculum.</td>
</tr>
<tr>
<td>Step 6: Revise, finalize, and launch the curriculum</td>
<td>Careful analysis of the pilot-test data informs the revision of the curriculum. After final review and approval by the TWG and the MOH, the curriculum is ready to launch. A formal launch to present and promote the curriculum is an effective strategy to institute a national adaptation of the materials by multiple stakeholders.</td>
</tr>
<tr>
<td>Step 7: Monitor and evaluate</td>
<td>The monitoring and evaluation (M&amp;E) activities developed at the outset as part of the training plan are then implemented. Ongoing assessment of the training process, trainer competence, and participant knowledge and skills will contribute to the ultimate goal of effective delivery of PMTCT services.</td>
</tr>
<tr>
<td>Step 8: Provide follow-up training</td>
<td>Offering ongoing refreshers and supplemental courses helps to ensure the quality of PMTCT service delivery; the M&amp;E data drive the content of ongoing training programs.</td>
</tr>
</tbody>
</table>

Source: François-Xavier Bagnoud Center, 2005.
Challenges and Lessons Learned

Through the experience of harmonizing the national training materials with the PMTCT GTP, solutions to some cross-cutting challenges have emerged (which are summarized in Table 3).

Lessons learned in the Kenya harmonization process include the need for consensus building among key stakeholders. To accomplish this, the MOH mandated that the PMTCT TWG and other content experts provide input on the technical aspects of the training materials. The TWG members worked collaboratively to build consensus on technical content. Another key concern in Kenya was the need to reduce the number of training days needed to adequately prepare health-care workers to deliver PMTCT services. The pilot test and subsequent implementation of the Kenya national PMTCT curriculum demonstrated that the PMTCT content could be delivered in a six- or seven-day course if conducted by a well-trained facilitator.

Successful harmonization experiences have emphasized the importance of trainer involvement in the development of training materials. Technical experts are crucial to the process, but they may include more material than is practical to communicate. Trainer involvement often results in more focused, pragmatic content decisions. In the training implementation process, it has been helpful to make the training materials available to participants prior to the training in a self-study format so that the training experience can focus more intensively on skills building so as to facilitate transfer of knowledge to the clinical setting. Given the multiple burdens on national governments and health-care workers in resource-limited settings, careful thought should be given to the development of training materials to ensure that they include practical tools and methods for negotiating the often challenging realities of the clinical setting.


**Table 3. Challenges and Solutions to Training Material Development**

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
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</thead>
<tbody>
<tr>
<td>Creation of country-specific training materials</td>
<td>◼ Coordination among a representative, multidisciplinary group of PMTCT professionals to identify gaps between guidelines and practice and propose strategies to bridge those gaps</td>
</tr>
<tr>
<td>◼ Example: Integrating actual practices (that are often influenced by the lack of resources) with national and international PMTCT policies and guidelines</td>
<td>◼ Inclusion of clinic visits in the process of training materials development to learn the particulars of constraints encountered in the clinical setting</td>
</tr>
<tr>
<td>◼ Provision of more than one opportunity for training materials review prior to the pilot test</td>
<td></td>
</tr>
<tr>
<td>Clarification of stakeholder expectations</td>
<td>◼ Development of a detailed timeline for the training materials development and implementation process at the outset</td>
</tr>
<tr>
<td>◼ Example: Addressing the pressure to meet unrealistic time-frame goals for training health-care workers</td>
<td>◼ Implementation of training for maximum impact on PMTCT service delivery by starting at facilities in areas with the highest HIV burden, facilities ready to implement services, and those with the largest patient loads</td>
</tr>
<tr>
<td>◼ Determination of the appropriate balance between training-of-trainer and direct training opportunities</td>
<td></td>
</tr>
<tr>
<td>Allowance for sufficient training preparation</td>
<td>◼ Development of a comprehensive, well-designed trainer orientation process that includes opportunities to model and teach back both content and training methodologies</td>
</tr>
<tr>
<td>◼ Example: Meeting the need to familiarize trainers with content and training methodologies</td>
<td></td>
</tr>
<tr>
<td>Attention to design and quality assurance</td>
<td>◼ Allocation of sufficient time for formatting, reproduction, and quality assurance of training materials</td>
</tr>
<tr>
<td>◼ Example: Eliminating grammatical and typographical errors, inconsistencies, and poor layout that can confuse trainers and participants and have an impact on confidence in the training materials</td>
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</table>

Source: François-Xavier Bagnoud Center, 2008.

**CASE STUDY #2: THE PEDIATRIC AIDS CLINICAL TRIALS GROUP/INTERNATIONAL MATERNAL, PEDIATRIC, AND ADOLESCENT AIDS CLINICAL TRIALS NETWORK GLOBAL TRAINING PROGRAM**

In recent years, a significant amount of HIV-related clinical research has moved from the United States and Europe to resource-limited settings. The significance of this movement for training in HIV care lies in the fact that while research is essential to ensure the safety and effectiveness of new therapies, site participation in research protocols can serve as one way to gain external support for the development of clinical care expertise through training. Sites cannot safely or ethically conduct clinical trials in the absence of a solid foundation of high-quality care that meets current international guidelines, and research networks can contribute to efforts to reach an acceptable standard of care.
When the Pediatric AIDS Clinical Trials Group (PACTG) network began establishing international sites in 2003, it was recognized that the network needed to direct additional support toward clinical training programs at research sites to support quality of care both within and outside of clinical trials. To establish a global training program that would support the development of clinical care infrastructure at research sites, PACTG initiated a collaborative agreement with the FXB Center at UMDNJ to lead the training effort. In 2006, the program was transitioned and reestablished as the IMPAACT Global Training Program.

The methods used to develop and implement training to support clinical care in the context of clinical trials allow blending of local, regional, national, and international expertise. A needs assessment survey consisting of a comprehensive list of skills and knowledge required to provide family-centered PMTCT and pediatric care, as well as to gain a general understanding of research, is distributed to a wide range of staff at sites before the scheduled needs assessment site visit. The survey serves as a point of reference to help identify site-specific training needs. Once the survey has been completed, there is an extensive discussion of survey results with site staff, and care and resources at the site are observed to ensure that the training plan addresses the unique needs and priorities of the individual site and utilizes local resources. Where expert resources for training do not exist locally, a regional approach to identifying program faculty is generally used to fill gaps in expertise. The regional approach benefits sites by helping to establish supportive connections among sites with similar resources and populations.

Challenges and Lessons Learned

The expanded role for nurses was identified as a common challenge among most of the research sites. In the United States, advanced HIV nursing practice is supported by the Association of Nurses in AIDS Care, which has a certification program for HIV nursing, and by the easy availability of government-supported education and training through the AIDS Education and Training Centers across the United States. In addition, U.S.-based nurses have greater access to graduate education programs, which allow for advanced training leading to a license to provide specialized services beyond the scope of the general nursing practice. In the PACTG global training program, this challenge has been addressed by careful mentoring of site research nurses and by providing training that includes content on training techniques (training of trainers), leadership, and in-depth coverage of the basic pediatric curriculum for HIV care and treatment.

Another challenge is the need to include training for the establishment and support of community advisory boards (CABs) for the research program. Training for CABs has included not only a basic overview of PMTCT and pediatric HIV care but also training on research methodology, research ethics, informed consent, and protocol review, as well as basic skills in meeting management, communication, and the overall role of community representatives in the research network. The effort to support the CABs culminated in the development of a 10-module training curriculum that specifically targets community representatives and covers all relevant topics. The curriculum makes wide use of clear and simplified language, graphics that support the training content, and interactive activities that solidify content while helping to build the CAB as a team.

*The HIV Prevention Treatment Network (HPTN) joined with PACTG to become the International Maternal, Pediatric, and Adolescent AIDS Clinical Trials (IMPAACT) network in 2006 as part of the restructuring of AIDS clinical trials networks by the National Institutes of Health.*
An important response to the challenges of this training has been the consistent use of a multidisciplinary training team. At a minimum, physicians, nurses, and community representatives are included, but the teams have often included social workers, psychologists, and pharmacists. This approach has been important in modeling a multidisciplinary approach to care and nursing leadership while sensitizing trainers and trainees to the skills, needs, and challenges of these various disciplines. All members of the training group are assisted in developing interactive learning strategies aimed at changing the actual delivery of care rather than just transferring knowledge. A strong mix of methods that include real case studies, community participation and input, panel discussions, role-play, and other interactive activities has been rated highly by participants in evaluation forms.

Outcomes
This project has provided 15 training programs at six research sites in South Africa, Zimbabwe, and Thailand, reaching more than 1,200 participants. Program evaluations have demonstrated significant knowledge gain, and comments from participants have been consistently positive. The multidisciplinary approach has changed the role of some of the nurses within the research teams to one of collaborative partner and group leader. Nurses have joined protocol teams and network committees, have demonstrated capacity and confidence in managing patients and families, and are contributing to training initiatives at newly established sites. The positive effect on community participation in the network has led to broader community support for research, a better informed and functioning CAB, a better informed community, and good relationships with community groups. Investigators have indicated that the program has helped them to gain support from clinical staff in the form of patient referrals, better communication about research participants who are seen or cared for by nonresearch clinicians, and a general sense of interest in and support for the research program among the health-care community. The success of the training program to date has made it possible to identify people who have been through the training program (including training-of-trainers courses) and have gained experience managing research patients who will then participate as trainers.

CASE STUDY #3: ENHANCING CHILDREN’S HIV OUTCOMES PROJECT, GAUTENG PROVINCE, REPUBLIC OF SOUTH AFRICA

Bringing pediatric HIV care to the community level presents specific training challenges in many resource-limited settings, including South Africa. Clinicians who provide HIV care and treatment in community settings are usually nurses, not pediatric specialists, and the complex care of HIV-infected infants and children is beyond their usual scope of practice. Training for existing child health professionals must offer new information and skills focused on the delivery of specialized pediatric HIV care and treatment (see Table 4, next page).

In addition, efforts to increase access to treatment and maintain and improve quality of care for HIV-exposed and -infected infants and children are often blocked by the severe shortage of qualified health workers.

The Enhancing Children’s HIV Outcomes Project
In November 2003, the South African government released the Operational Plan for Comprehensive HIV and AIDS Care, Management, and Treatment for South Africa (CCMT). Yet by late 2004 it was clear that few of the estimated 240,000 children living with HIV in South Africa were accessing treatment through the CCMT program, and the
The following examples of successful clinical mentoring through the ECHO program demonstrate the flexibility of this approach in addressing the unique needs and demands of diverse clinical sites and illustrate some of the challenges and lessons learned through this program.

### Challenges and Lessons Learned: Discoverers Clinic

The Discoverers Clinic, a private site supported by a charitable organization, is one of the sentinel sites for the ECHO project and has contributed greatly to the project’s success. Initially, the Gauteng Department of Health partners were skeptical of working together with a nongovernmental organization. At the clinic itself, there were major concerns as to how long the ECHO mentoring team would stay in the clinic and how ART services could be sustained once the ECHO team departed, given staff shortages and lack of clinic space. Counselors were very reluctant to counsel children, and all of the staff believed working with children would be more difficult than provision of HIV care and treatment to adults. The nurses, who had not received training in primary care or the IMCI, believed that their scope of practice did not include independent management of ART. But as is typical in resource-limited settings, the lack of available physicians demanded that routine care provided by nurses be expanded to include pediatric ART.

The majority of the children who were receiving treatment did so through the hospital-based antiretroviral therapy (ART) clinics linked to academic institutions. Through a situational analysis, it was determined that there was an urgent need to scale up and improve access to pediatric ART care and to increase the availability of ART at primary and secondary health facilities in communities where affected children and families live in order to address perceived barriers to pediatric ART service delivery. The ECHO project was officially launched by the Wits Paediatric HIV Clinics in October 2005 with support from a US$1 million annual grant from the U.S. President’s Emergency Plan for AIDS Relief. The aim of the ECHO project was to scale up pediatric ART, improve the quality of pediatric HIV care, and ensure the sustainability of services. The ECHO project uses a mobile clinical support team (MCST) model whereby teams from central academic sites strengthen more-peripheral facilities to provide care to the estimated 50,000 children living with HIV in Gauteng Province. The advantages and disadvantages of different approaches to training and capacity building, summarized in Table 5, were considered during the planning of this project (the table also includes insights gained through implementation of the MCST model).

Today, the ECHO project has expanded to support 13 accredited ART sites in Gauteng, three in Limpopo Province, and one in Mafikeng Province.

### Table 4. Unique Aspects of Pediatric HIV Care to Be Addressed through Training

<table>
<thead>
<tr>
<th>Health workers require special training in the following areas:</th>
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</thead>
<tbody>
<tr>
<td>■ Diagnosis of pediatric HIV infection (particularly in infants)</td>
</tr>
<tr>
<td>■ Feeding of HIV-exposed infants</td>
</tr>
<tr>
<td>■ Natural history of pediatric HIV infection</td>
</tr>
<tr>
<td>■ Diagnosis and management of tuberculosis in infants and children (along with prevention and management of opportunistic infections)</td>
</tr>
<tr>
<td>■ Standards of primary care of HIV-infected infants and children</td>
</tr>
</tbody>
</table>

**Source:** François-Xavier Bagnoud Center, 2008.
<table>
<thead>
<tr>
<th>Approach to Capacity Building</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide additional full-time staff to all new accredited ART facilities in order to treat more children</td>
<td>Makes skilled staff readily available.</td>
<td>Creates parallel system.</td>
</tr>
<tr>
<td></td>
<td>Allows for rapid scale-up.</td>
<td>Runs counter to the fundamental tenet of supporting and strengthening the public health system.</td>
</tr>
<tr>
<td></td>
<td>Provides relief for overburdened site staff.</td>
<td>Limited by budget constraints.</td>
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<tr>
<td></td>
<td></td>
<td>Exacerbates existing space shortage at outreach sites.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approach may not be sustainable.</td>
</tr>
<tr>
<td>Strengthen capacity to deliver care (through training) at only the large, central, hospital-based sites</td>
<td>Builds upon a core of existing trained staff.</td>
<td>Runs counter to the patient-centered approach needed for chronic disease management, which requires the provision of services at facilities reasonably close to patients’ homes or workplaces.</td>
</tr>
<tr>
<td></td>
<td>Adequate space is available.</td>
<td>Approach may not be sustainable.</td>
</tr>
<tr>
<td></td>
<td>Facility can accommodate additional staff and patients.</td>
<td></td>
</tr>
<tr>
<td>Create mobile clinical support teams (MCSTs) to build capacity at outreach sites</td>
<td>Offers training coupled with direct, hands-on clinical care.</td>
<td>Local team resistance to accepting the burden of pediatric ART care and beliefs that ART care should be limited to tertiary settings may pose barriers to implementation.</td>
</tr>
<tr>
<td></td>
<td>Strengthens the role of nurses.</td>
<td>Must reach consensus.</td>
</tr>
<tr>
<td></td>
<td>One-on-one teaching allows individualized attention to mentee strengths and weaknesses.</td>
<td>Can’t always address system or infrastructure dysfunction.</td>
</tr>
<tr>
<td></td>
<td>Pace of learning can be adjusted.</td>
<td>Lack of motivation on the part of mentees, or development of overdependence on MCST to provide motivation.</td>
</tr>
<tr>
<td></td>
<td>Builds capacity for cross-pollination of ideas and development of a regional collaborative learning network.</td>
<td>Risk of local team dependence on the MCST for service provision—must have clear exit strategy.</td>
</tr>
<tr>
<td></td>
<td>Can utilize tertiary care centers for additional support and training.</td>
<td>Ongoing monitoring, evaluation, and follow-up may not be sustainable.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of a single individual may compromise the entire program at individual sites.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perception that the work is too difficult and outside the normal scope of practice.</td>
</tr>
</tbody>
</table>

Source: François-Xavier Bagnoud Center, 2008.
this case, the clinic was able to add a nurse with the additional training, and she became the primary recipient of MCST assistance.

The initial skepticism and resistance of the staff quickly turned to optimism and openness when the ECHO team began seeing HIV-infected children with the primary care nurse and the clinic staff. The training at this site took the form of one-on-one case demonstrations and discussions, with a series of didactic lectures given every two weeks to the whole team. The primary care nurse also went to a tertiary-care hospital once a week for a period of six weeks to see patients alongside a mentor in that setting. The South African National Pediatric Guidelines for HIV Care were a primary focus of this training. Within months, the clinic’s nurse was initiating ART in infants and children with the weekly support of the MCST, and within a year she managed a stable cohort of children on ART with support provided by telephone only.

**Challenges and Lessons Learned: Taung Hospital in the North West Province**

The ECHO project started providing outreach support to Taung Hospital in October 2005. At that time, Taung Hospital was certified to provide ART and had an adult HIV clinic with more than 1,000 patients on treatment—no children were being treated at that time. The single physician at the site had not cared for a pediatric patient in more than 10 years. Due to the staff’s inexperience in treating children, basic pediatric care and phlebotomy had to be addressed before launching into HIV care and treatment. The nursing staff and the pharmacist were also new to pediatric primary care and needed training in basic skills. This case is an example of the advantages of the mentoring program, since the mentor team was able to adjust the training program to meet the unique needs of the site, rather than rigidly presenting a predetermined curriculum in a fixed amount of time.

At Taung Hospital, the ECHO MCST also visited with partners for adult care from the Reproductive Health Research Unit (RHRU) in order to create a linkage between that unit and the pediatric HIV clinic. This strategy helped to promote the family-centered model of HIV care and treatment and made it possible for RHRU personnel to provide relief staffing at the hospital, freeing the physician for training. To introduce the pediatric HIV clinic effectively, children and their caregivers were scheduled to be seen on the same day. This was made possible by coordinating visits by the RHRU and ECHO teams.

At each visit, the mentor gave didactic presentations before clinic sessions to highlight the basic approach to pediatric antiretroviral treatment and to address topics that the clinical team identified as needing clarification. The MCST counselor transferred skills to the on-site counselor through co-management of families and also helped the on-site counselor develop a system for addressing missed visits and patients that have been lost to follow-up. The training at this site took the form of one-on-one case demonstrations and discussions, with a series of didactic lectures given every two weeks to the whole team. The primary care nurse also went to a tertiary-care hospital once a week for a period of six weeks to see patients alongside a mentor in that setting. The South African National Pediatric Guidelines for HIV Care were a primary focus of this training. Within months, the clinic’s nurse was initiating ART in infants and children with the weekly support of the MCST, and within a year she managed a stable cohort of children on ART with support provided by telephone only.
every week, reserving only the most complicated cases to be seen alongside the ECHO team during its monthly visit. As of September 2006, ECHO support ended for the Taung clinic, but the team continues to hold a weekly family clinic.

The long distances patients traveled to access clinic services also posed a challenge at this clinic. They made it impossible to book the standard frequent appointments for adherence and clinical reviews following initiation of therapy. The team found that it was critical to mobilize the entire care team to make the most out of every visit in order to try and overcome the challenge of infrequent follow-ups. This has been a successful strategy. To date, the weekly family clinic cares for 109 pediatric patients on ART, and 104 of those children remain stable on treatment.

CONCLUSION
The first Global Forum on Human Resources for Health convened by WHO in March 2008 called for immediate and sustained action to resolve the critical shortage of health workers around the world, setting out the essential steps that need to be taken over the next decade to turn the crisis around. Chief among those measures was a call to all countries to give top priority to training health personnel from within their own country. Training is a key strategy for the scale-up of HIV services in resource-limited settings. Because frontline HIV health workers are already overburdened, it is essential to find and implement efficient strategies to ensure that they have the knowledge and skills to effectively provide much-needed PMTCT and pediatric HIV care services. Well-designed and executed training approaches can address the demands placed on health-care workers. The approaches and case studies in this chapter describe processes that have successfully addressed the training needs of frontline health workers. Development and adaptation of generic training materials has proven to be a valuable resource for efficient transfer of knowledge. Multidisciplinary on-site training teams and preceptorship experiences bridge the gap that may exist between knowledge and clinical practice. Health workers in highly stressful, resource-limited settings are the key to increasing access to PMTCT and pediatric HIV care services. Their willingness and commitment to take on these formidable challenges is a compelling motivation for the ongoing effort to develop creative, comprehensive training strategies and tools to meet the urgent need for training to scale up services.
REFERENCE LIST


Training and Clinical Mentorship to Support the Scale-Up of Pediatric HIV Care: Lessons Learned from Uganda

Edward Bitarakwate

Elizabeth Glaser Pediatric AIDS Foundation, Uganda

Despite the significant progress that has been achieved in Uganda in increasing access to combination antiretroviral therapy (ART), only about 9,200 of the 100,000 individuals receiving ART (9.2%) are children.\(^1\) This rate of treatment coverage falls short of the national pediatric treatment target of 15% of the total number of patients on ART. This rather slow scale-up of pediatric HIV care and treatment has been attributed to inadequate HIV diagnosis, poor access to care, and limited capacity to treat children. For instance, while HIV care is largely centered at referral health units, a majority of HIV-positive children seek care at lower-level health facilities. Another reason for the low proportion of pediatric patients in HIV care and treatment is the failure of health-care providers to systematically identify HIV-exposed or infected children.

Experiences in Uganda and other African countries show that even where basic resources for the provision of HIV care and treatment exist, providing health workers with formal didactic training alone does not significantly impact the total number of children who access care and treatment. A 2005 Ugandan national assessment highlighted limited health-worker skills as a key impediment to pediatric HIV care and treatment scale-up.\(^2\) Subsequent stakeholder meetings conducted by the Uganda Ministry of Health (MOH) produced recommendations in support of the decentralization of standardized basic training in pediatric HIV care and clinical mentorship in order to increase clinical staff capacity to offer pediatric HIV care.

The goal of the Ugandan clinical mentorship program was to build sustainable capacity for scaling up access to and improving the quality of pediatric HIV care and treatment. The specific objectives outlined to achieve this goal were (1) to enhance the application of classroom learning to patient care, (2) to support decentralized pediatric HIV service delivery and develop clinical expertise at lower-level health-care facilities, (3) to improve health-worker motivation by providing effective technical support, and (4) to maintain high clinical standards and practices through the provision of technical support to health workers. Key activities of the program included the creation of systems to support clinical mentorship, the recruitment and professional development of mentors, the completion of a needs assessment of participating programs, and the creation of an action plan, followed by the initiation of mentoring activities.
Monitoring and evaluation (M&E) activities were used to inform and improve the mentorship program, as well as to improve overall pediatric HIV care service delivery.

The principles and practices outlined in this chapter are based on the author’s experience with creating a clinical mentorship program for pediatric HIV care in Uganda.

**PRINCIPLES OF CLINICAL MENTORSHIP**

The World Health Organization (WHO) defines clinical mentorship as a system of practical training and consultation that fosters ongoing professional development to yield sustainable, high-quality clinical care outcomes. Mentoring should be seen as part of the continuum of education required to create competent health-care providers. The mentorship model used in Uganda is based on the existing hierarchy of supportive supervision within the district health services. Senior clinical and nursing staff based at regional hospitals and district health offices are targeted for enrollment as clinical mentors, who then offer practical training and consultation to health-care workers at lower-level health facilities. Through a process of training and retraining, these select groups of health workers progressively acquire HIV care and treatment expertise in aspects including, but not limited to, leadership and team building, training, M&E, and quality assurance (QA).

Focal persons within the regional HIV care and treatment team coordinate with and create linkages between the national- and district-level HIV care and treatment programs. Program activities designed by this team of clinical mentors form an integral part of the broader regional HIV-related work plans. Activity reports generated by the clinical mentorship team are then shared with the participating health facilities, the district health office, the MOH AIDS control program, and supporting partner organizations.

Figure 2 shows the technical hierarchy of ART services support in Uganda. Guiding policy at the national level allows for the organization of clinical mentorship at the regional level and its implementation at the district and health-center level.

The following considerations are crucial to the implementation of a sound clinical mentorship program.

**Planning and Coordination**

Key stakeholders must be involved in the development and adoption of a strategy for clinical mentorship within the host HIV care and treatment program.
A participatory approach at this initial stage builds ownership and commonality of purpose by incorporating views from a diverse range of interests, a key prerequisite for ensuring the successful implementation of national programs. In the Ugandan experience, stakeholder involvement was most successfully achieved under the auspices of the national AIDS control program through its pediatric ART subcommittee. A WHO regional working meeting on clinical mentoring held in Uganda provided significant incentive for the buy-in and launching of this process. A core group of organizations, including the Elizabeth Glaser Pediatric AIDS Foundation, the African Network for Care of Children Affected by AIDS (ANECCA), and the Pediatric Infectious Disease Clinic in Mulago then took the lead in planning, developing, and piloting a clinical mentorship program. This collaborative process among nongovernmental and governmental partners pooled the necessary resources required to initiate the pediatric HIV care and treatment mentorship program.

Central coordination of the mentorship program is necessary for promoting the adoption of new training approaches and formalizing their integration into existing health-service provision structures. By promoting clinical mentorship as a necessary component of pediatric HIV care and treatment scale-up, the MOH motivated and encouraged other development partners to buy in to this program. This central role also served as a pivotal mechanism for coordinating ongoing activities, sharing experiences, and continuously reviewing programming objectives to respond to emerging needs.

**Technical Support**

Technical expertise will be required at different levels during the development of a clinical mentorship program. At the national level, technical
Special expertise may be required to adapt existing M&E frameworks to include clinical mentorship activities. In a related process, health management information systems (HMIS) may need to be strengthened in order to effectively capture any gains in patient care outcomes resulting from clinical mentorship.

Long-distance technical resources and support could also be provided through telephone warm lines and Web-based discussion forums to enhance continuing medical education (CME) and real-time clinical problem solving at participating health facilities. The AIDS Treatment Information Center (ATIC), a referral network housed at the Infectious Diseases Institute at Mulago Hospital in Kampala, Uganda, utilizes the Internet and cellular phones to provide health workers with access to the latest medical information and advice to assist them with their treatment of patients. Through a toll-free phone service, contact visits, and the Internet, health workers are able to consult HIV experts in various aspects of patient management.

Human Resources Support

Clinical mentorship can only be provided where a minimum level of the targeted service is being offered. For example, clinical mentorship for HIV care can only be implemented at a health facility that is offering at least basic (or palliative) HIV care. In some instances, existing staffing levels at the participating health facility may not permit effective delivery of services. In such circumstances, it may be necessary to second clinicians, nurses, and laboratory staff to support either general or specialized HIV service delivery. Likewise, a given region may not have clinical staff with the basic qualifications for enrollment into the mentorship program. This would necessitate the recruitment or redeployment of additional personnel to initiate the mentorship program. Both these scenarios require the close support and cooperation of the local or regional
health authorities. Innovative approaches in which staff members are compensated for time contributed to clinical mentorship activities may attract regular short-term commitments.

Logistical Support
Once the mentorship program is developed, resources for national and regional roll-out should be mobilized. Development partners to the Ugandan national AIDS control program responded positively to a call to contribute resources to clinical mentorship programs in the country’s health districts. Start-up activities should be planned and provided for by the implementing organization. The assessment of programming needs at the district and health-facility level, the development of work plans, and the routine operation of clinical mentorship activities present significant logistic and financial requirements.

Where major resource gaps exist within the health-care system, the provision of essential commodities for pediatric HIV prevention, care, and treatment may need to be considered as part of overall support for clinical services delivery. Supplies of HIV test kits, materials for collecting dry blood-spot samples for DNA polymerase chain reaction (PCR) tests, cotrimoxazole for opportunistic infection prophylaxis, and antiretroviral drugs (ARVs) may need to be secured in order to ensure delivery of basic HIV services.

The development of regional health facilities into pediatric HIV learning sites, when feasible, should be considered. These relatively high-volume clinics can accommodate staff from lower-level health facilities during training attachments. Such training and exchange visits by health facility staff require financial and logistical support. For example, clinical mentor teams that are based at the regional level would require support for transport, communications, field allowances, office equipment, and training materials. The ability of the clinical mentors to conduct program activities, follow up on implementation recommendations at the participating health facilities, file reports, and undertake operations research requires significant logistical support for transportation, meetings, and other operating expenses.

ENSURING PROGRAM QUALITY
The following are some general guidelines for enhancing the quality of a clinical mentorship program.

Characteristics of a Good Mentorship Program
Mentoring programs should be well integrated within the existing service delivery structures to ensure their long-term sustainability. Long-term mentorship activities (i.e., lasting several weeks to several months) are generally more effective than short-exposure activities (i.e., lasting a few days per mentorship relationship). Built-in post-mentorship follow-up, with long-term, on-site supervision and/or backup by a competent health professional who is able to reinforce lessons taught during the initial mentorship exercises, often leads to better outcomes. Repeat visits by the same mentor are particularly reinforcing.3,6

A mentor’s familiarity with local issues and national and/or institutional HIV care and treatment guidelines and practice strengthens the program by shortening the mentor’s learning curve and period of adaptation. Mentoring activities carried out within the trainee’s usual working environment allow for more tailored advice and foster the adaptation of solutions to local conditions; this approach may be more effective than preceptorships at more sophisticated, higher-level facilities (i.e., centers of excellence). A balance between these two approaches is recommended in order to achieve the best results. Additionally, the mentoring of clinical teams has proven more effective
than the mentoring of individuals, who in turn are expected to influence their teams’ practices.3,6

There should be a well-defined process for coordination and communication between mentors assigned to the same site. Such a process can help mentors use experiences and lessons learned to collectively plan and/or refine their approach so that the mentoring program is specifically relevant to the mentoring site. Mentoring teams also must have the ability to relate clinical and process activities at health facilities to care and treatment outcomes. In this way, outcome data can be used to design or strengthen care interventions resulting in more favorable outcomes.

Characteristics of a Good Mentor
A good mentor should be at a professional level equal to or higher than that of the trainee in the same or a closely related field. The mentor’s practical clinical experience in pediatric HIV care and patterns of related comorbidities in the trainee’s (or similar) work setting should be extensive, and his or her knowledge base should be up-to-date. The mentor should also have proven experience in supervision, training, and team building, as well as an ability to work with people of diverse backgrounds and knowledge and skill levels. A good working knowledge of the trainee’s language as well as the language(s) used by the majority of clients further increases the effectiveness of the mentor.

In order to effectively plan for the training needs of prospective clinical mentors, it is necessary to assess their knowledge and skills for a given clinical service. In Uganda, a rapid survey was conducted through a self-administered, semistructured questionnaire. The rapid assessment explored mentors’ current levels of competence in the areas of clinical care, trainer skills, supervision, and clinical mentoring. This approach enabled program managers to identify critical aspects of the mentors’ technical and professional abilities that required development and/or strengthening. Upon completion of the assessment, short- and medium-term training plans can then be tailored to address specific gaps in mentors’ knowledge and skills.

LESSONS LEARNED: BUILDING A CLINICAL MENTORSHIP PROGRAM
The following discussion outlines the key considerations for building a quality clinical mentorship program. A list of required steps for program initiation is presented in Figure 3.

Ensuring a Sound Training Base
As a basic requirement, mentors must have sound knowledge and skills in a given field of clinical care. In the absence of a standardized national curriculum, there is likely to be limited coordination of training programs, making an objective evaluation of the mentors’ background training difficult. Based on the report *Rapid Assessment of Capacity for Pediatric HIV/AIDS ART Training,* the Uganda MOH mandated a working collaboration of key players in training, including ANECCA, the Elizabeth Glaser Pediatric AIDS Foundation, and the Pediatric Infectious Diseases Clinic / Baylor College of Medicine Children’s Foundation–Uganda. These partners were together charged with the planning and roll-out of the national training program in comprehensive pediatric HIV/AIDS care in Uganda.

In the first three months of the program, all prospective mentors participated in a course in advanced pediatric HIV care to ensure the same level of basic training. By enrolling the core group of clinical mentors from among a team of MOH HIV clinical care trainers, the mentorship program utilizes the experience of these persons to continually guide training improvement based on needs that are identified over time.

Training in advanced pediatric HIV care provides prospective clinical mentors with specialist
knowledge and skills for pediatric HIV care and treatment. Major areas covered include clinical treatment reviews and updates, practical clinical experience, clinic management (including patient flow), mentorship skills, and regional program development/planning. Additional advanced training in the form of regular clinical attachments to pediatric HIV centers of excellence ensures continuity of skills and knowledge acquisition for the clinical mentors. These attachments are also designed to provide mentorship to the regional clinical mentors by senior national-level HIV care experts, thereby ensuring the transfer of knowledge and skills to the district and regional levels.

An advanced training of trainers (TOT) workshop was developed to further enhance training skills among the participants. At the end of this course, participants develop and refine action plans for their respective regions. This approach serves to decentralize training capacity from the large cities,

Figure 3. Steps in the initiation of a clinical mentorship program

Step 1: Recruitment of a core team of mentors
Step 2: Pre-implementation site visit
- Meet with district health managers, facility administrators, staff looking after children (MCH, OPD, IPD), and staff providing HIV services. Introduce the objective of the visit (general). Invite staff to share what the health facility is doing in terms of HIV services delivery. Prompt about pediatric services specifically.
- Introduce the concept and objectives of clinical mentorship. Receive staff feedback and suggestions on modalities of implementation.
- Introduce the need for a rapid participatory “baseline” assessment to inform a facility-specific action plan (including provider training needs). Get a named facility representative to work with you—preferably one of the staff you will be mentoring.

Step 3: Rapid assessment
- Assess what HIV services are provided at this facility, by whom, and where (i.e., points of service).
- Assess access for children—entry points, mechanisms and volume of referrals, registration process, actual services provided, numbers of children in care, etc. (using a standardized tool).

Step 4: Analysis and action planning
Based on the findings of the rapid assessment, consider what can be done to increase and improve pediatric HIV care. This may include the following:
- Identification of children and families in need of services
- Timely diagnosis of HIV among children coming for other services
- Expansion of HIV services (care +/- treatment, referrals) currently offered for children and their families

Once these improvements have been determined, move forward:
- Set some simple targets.
- Define a clinical mentoring schedule to support the achievement of these targets.

Step 5: Initiation of mentoring activities
- Undertake initial introductory and planning visits with health unit management and care teams.
- Introduce mentorship tools.
- Institute monitoring and evaluation activities.
- Initiate quality-improvement mechanisms.
- Share best practices.
while the built-in follow-up mechanisms ensure that training activities translate into expanded and improved pediatric HIV service delivery.

**Policy and Strategy**

To ensure coordinated planning and implementation of mentorship activities, the roles and functions of the various levels of health service delivery must be understood. A clinical mentorship program should be designed to fit into a national strategy for HIV/AIDS control, including scale-up plans for HIV care and treatment services. The Uganda MOH national AIDS control program's pediatric ART committee prioritized the initiation of a mentorship program in order to directly increase access to quality pediatric HIV care. In addition, the MOH participated in the identification of the prospective regional mentors. This high degree of commitment at the national level enabled the integration of clinical mentorship activities into regional and district HIV/AIDS care programming.

**Human Resource Capacity Development**

A successful clinical mentorship program will be dependent on a skilled human resource base that includes the following components:

- Skilled, experienced, multidisciplinary team mentors
- Engaged and willing service providers to work with the mentoring team
- Consistent technical support for the mentor development program

This will require access to national HIV care centers of excellence and teaching institutions where senior pediatric HIV experts are found. Where local pediatric HIV care expertise is lacking, clinicians may need to be sourced from other countries. The mentors would also require periodic supervisory and monitoring visits from national-level program managers and pediatric HIV care experts. Additional technical resources might include resource materials (print, electronic, CME courses, etc.) and access to various forms of continued technical exchange.

**Logistics**

The clinical mentorship program should always work within the existing health system to avoid additional pressure on already overburdened public health services. However, additional logistics are needed to facilitate the movement of mentors to the various health facilities and the movement of clinical staff from lower-level health facilities to the regional referral hospitals for clinical training attachments. Mobile telephony could be provided as a practical means of efficient communication with and between different levels of health service delivery. Mentors should also be provided with training materials and job aids to establish and improve site-level systems to deliver pediatric HIV care and treatment.

**Monitoring and Evaluation / Quality Improvement**

An M&E framework and QA program are essential to ensure that the clinical mentorship program achieves its objectives. Ideally, these systems should be integrated with, and complementary to, existing M&E and QA systems within the national ART program.

The main goal of the M&E activities is to assess increased access and enhanced quality of pediatric HIV care services. In the Ugandan case, monitoring activities are scheduled as follows: monthly for health facility mentoring activities, quarterly for numbers of patients served, and semiannually for mentor development processes (e.g., training, individual evaluations). The focus of monitoring is on the numbers of individuals served and on qualitative aspects of the mentorship program (e.g., the establishment of a patient flow pattern that ensures the provision of adherence counseling
In Uganda, a collaborative effort between multiple development partners and the MOH has led to the development of a framework for a national clinical mentorship program as a part of efforts to deliver scaled-up prevention, treatment, and care infrastructure for children affected by HIV and AIDS. The Ugandan experience has shown that it is feasible to develop a clinical mentorship program based primarily on locally available human resources.

To date, 16 doctors from eight health regions within Uganda have been recruited into the mentorship program. This team of clinical mentors has participated both in training lower-level health providers on various aspects of pediatric HIV care and in the development and field testing of clinical mentorship tools. The national roll-out of a program for early identification of HIV-exposed and infected infants has been supported through the clinical mentorship program, and improvements have been noted in the quality of care offered to HIV-positive children.

The results of M&E activities can be used to inform and improve the mentorship program as well as overall pediatric HIV care service delivery. In this way, the clinical mentorship program provides an opportunity to strengthen existing national systems.
REFERENCE LIST


Developing National Training Materials for Prevention of Mother-to-Child Transmission of HIV: The Zimbabwe Experience

Agnes Mahomva, Anna Miller, and Rumbidzai Mugwagwa

PREVENTION OF MOTHER-TO-CHILD transmission of HIV (PMTCT)* is an important multidisciplinary public-health intervention. An effective national program will involve coordination among multiple programs (e.g., maternal and reproductive health, HIV testing and counseling, antiretroviral therapy (ART), immunization, nutrition, and other child survival initiatives) and various segments of the community (e.g., women, their male partners, infants, boys, girls, mothers-in-law, community-based organizations, etc.). Unfortunately, PMTCT has been implemented predominantly as a vertical program, with limited recognition of its multidisciplinary nature, and with minimal or no planned integration or links to other existing programs and the community. Appropriate training of PMTCT program implementers in several disciplines is therefore a key strategy that provides them with the necessary knowledge and skills for successful program roll-out. Development of materials for that training is a critical but complex undertaking. Although many generic PMTCT training materials have been developed to assist in the implementation of comprehensive PMTCT programs, use of such materials may be fraught with challenges.

LIMITATIONS OF INTERNATIONAL GENERIC AND LOCAL TRAINING MATERIALS

Existing international generic PMTCT training materials, such as those jointly produced by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), are evidence based, extremely detailed, and cover all the essential components of PMTCT. However, because of their generic nature, these materials contain few insights related to practical program implementation experiences unique to specific settings. Generic PMTCT training materials, by

*The term PMTCT appears throughout this chapter because it is a common term in the medical community and accurately describes the major physiological processes (in utero, intrapartum, or postpartum transmission via breastfeeding) that can cause children to acquire HIV infection. However, many community and advocacy groups use the term PPTCT (prevention of parent-to-child transmission) to avoid stigmatizing the mother and to emphasize the responsibilities of both the mother and her male partner. In fact, neither term accurately reflects the multidisciplinary nature of the combined interventions and support required to eliminate HIV infection in infants.
definition, cannot fully integrate specific training components from individual countries, including existing national policies and practices in the many established disciplines covered by PMTCT. These limitations compound existing challenges, such as the constantly evolving science relating to specific PMTCT interventions (e.g., antiretroviral drug use, infant-feeding practices to optimize HIV-free survival, etc.) and the multidisciplinary nature of its components. Thus, training materials must undergo frequent updates and cover the various disciplines that PMTCT encompasses. That means generic international training materials are often used only as reference materials, rather than as the basis for national training programs.

Adaptation of generic materials has been advocated for and shown to be possible in several countries. However, the process of adapting generic PMTCT training materials for practical use in specific settings has proved challenging. For the process to be feasible, program managers and implementers require training in adaptation methods. Adaptation experiences in Kenya have shown that while adaptation of WHO and CDC generic training materials was possible, an existing draft national curriculum was needed to hasten the adaptation process. In Ethiopia, adaptation of generic training materials was also found to be time consuming and required strong editorial and formatting assistance.

Both generic and locally specific training materials exist for most of the technical areas covered by PMTCT, such as ART and testing and counseling. However, the materials are often developed in many different formats, with similar information presented in different ways. In some cases, materials contain differing technical information and guidelines. The inconsistency, and in some cases redundancy, of training materials can result in individual health workers receiving several training sessions on the same information just presented differently. Consequently, learning and integration of information becomes difficult, and ultimately the delivery of holistic HIV prevention and care to women, their male partners, and their babies becomes problematic.

Because most PMTCT services are part of family and child health (FCH) services, existing national maternal and child health and reproductive health training materials should be used for PMTCT training sessions. The advantage of using existing local training materials is that they have been developed by the individual country, with country-specific health systems and program approaches in mind. Health workers are therefore already familiar with the materials and approaches. Given the relatively recent advent of PMTCT services, most existing training materials barely mention PMTCT and do not yet provide the detailed and comprehensive PMTCT content required for successful national program implementation and roll-out or comprehensive individual patient care. Thus, a lengthy process of revision and updating of existing materials, as well as the addition of materials that specifically focus on the integration of PMTCT with existing programs and health services, is necessary for successful PMTCT program scale-up.

This chapter describes Zimbabwe’s experiences in developing national PMTCT in-service and preservice training materials for facility- and community-based health workers. It also discusses the specific challenges associated with training materials development, summarized earlier, in the context of the Zimbabwe national health system.

**BACKGROUND**

Zimbabwe is situated in southern Africa and has a population of 11.6 million people. The country is divided into 10 health provinces and 60 health districts. The public health system is based on primary health-care services provided through rural health facilities, including primary care clinics and
district referral hospitals.\textsuperscript{5,6} Despite recent economic difficulties, Zimbabwe remains one of the more developed countries in sub-Saharan Africa, with an educated population and a well-developed transport and communication infrastructure.\textsuperscript{7}

The country’s health system has been greatly compromised by its declining economy. This has caused skilled health workers to leave the country in large numbers and has resulted in frequent stock-outs of drugs and other important commodities.\textsuperscript{8} Despite these challenges, the foundations of the national public health system have remained in place, including a district health system made up of primary health-care units and referral hospitals. The public health service is the lead provider of primary health care in the country. Nongovernmental organizations and other stakeholders also play an important role in supporting the system but do so only under the supervision and coordination of the Ministry of Health and Child Welfare (MoHCW). Zimbabwe’s health system has facilitated the introduction, implementation, strengthening, and roll-out of HIV/AIDS care interventions such as PMTCT.\textsuperscript{6}

Although the HIV prevalence in Zimbabwe has declined over recent years,\textsuperscript{9,10} the country continues to experience one of the world’s most severe HIV epidemics. At the end of 2007, HIV prevalence was estimated to be 15.6% among the adult population\textsuperscript{11} and 21.3% among women attending antenatal clinics (ANCs).\textsuperscript{12} Many initiatives and programs, such as the national PMTCT program, have been put in place in response to the scale of the epidemic.

\textbf{NATIONAL PMTCT PROGRAM ROLL-OUT}

Prevention of mother-to-child transmission of HIV has been identified as a priority intervention in the national fight against HIV/AIDS. The national PMTCT program was initiated as a pilot project between 1999 and 2001. National program roll-out started at the end of the pilot project period in 2001.\textsuperscript{6} By the end of 2005, the national program had expanded to 1,395 sites (approximately 98% of all health institutions in Zimbabwe). Roughly 70% of total reported births in the same year were to women attending ANCs where PMTCT services were available.\textsuperscript{13} These services were being offered as an integral part of ANC, delivery, and postnatal care services.

The MOHCW is the main provider of PMTCT services in Zimbabwe. However, many partners have collaborated with the MOHCW in providing PMTCT services at all levels. The MOHCW coordinates the participation of its partners through the national PMTCT Partnership Forum. Factors that contributed to the rapid roll-out of the national PMTCT program included the leadership of the MOHCW, the coordination of the national program, and the meaningful participation of local and international PMTCT technical partners in the national program roll-out activities, including production of standardized national training materials.\textsuperscript{11,13}

\textbf{THE ZIMBABWE NATIONAL PMTCT TRAINING PROGRAM}

The national PMTCT training program encompasses in-service and preservice training for facility- and community-based health workers (Figure 1, next page). During the early years of program roll-out (from 2001 to 2004), the main emphasis was on in-service training for facility-based health workers to establish health system readiness and provide a minimum level of service in as many facilities as possible, as quickly as possible. Community-based and preservice training were developed later, between 2004 and 2006.

The national PMTCT training program for in-service health workers is divided into two broad types of trainings: (1) general PMTCT training and (2) detailed trainings on infant feeding and rapid HIV tests. The five-day general PMTCT training is aimed primarily at midwives and all other nurses
and represents the cornerstone of training for the national PMTCT program. It covers all aspects of PMTCT, including an overview of HIV testing and counseling and infant-feeding counseling. Once all health workers at a facility have received the general training, that facility can register to begin providing PMTCT services, assuming all other logistics (e.g., laboratory and pharmacy supplies) are in place.\textsuperscript{14}

The widespread provision of general PMTCT training has been facilitated by a cascading training-of-trainers approach. The national training team is composed of key individuals from the MOHCW and implementing partners. First, these national PMTCT trainers are equipped with the knowledge and skills they need to train two provincial trainers from each province. Next, each provincial trainer trains two district trainers for each district in his or her province, and then the district trainers train health workers at the facility level with support from national and provincial trainers. An additional detailed six-day training on infant feeding and a three-day training on rapid HIV testing are provided by the national nutrition department and the national reference laboratory, respectively. These trainings are given to select nurses at registered PMTCT sites to ensure their capacity to perform rapid HIV tests and provide more specialized infant-feeding counseling for mothers living with HIV. In addition to employing the training-of-trainers model, the national in-service training program provides on-site training of mentors as well as on-site refresher training during supervisory visits and program review workshops.

DEVELOPMENT OF NATIONAL PMTCT TRAINING MATERIALS
The national PMTCT program expansion began in 2001, before standardized national training
materials were developed. In response to the need for standardized training materials, the MOCHW began developing comprehensive, national PMTCT materials for facility-based and community-based health workers; these materials were adapted for preservice and in-service training. The primary goal of the development process was to strike a balance between adaptation of existing materials (both local and generic international PMTCT training materials) and development of new materials. The steps of this process are outlined in Box 1.

Following are the steps taken in developing the national training materials.

1. **Hold a national consultation with provincial medical directorates (PMDs), program implementers, and key stakeholders.** At the end of the national PMTCT pilot project in May 2001, a consultation of PMDs and key PMTCT stakeholders was held on the roll-out of PMTCT. Participants were from all 10 provinces in Zimbabwe and represented various disciplines, such as health education, pediatrics, obstetrics, laboratory, nursing, drug control, epidemiology, nutrition, pharmacy, and health informatics. Local and international agencies in support of PMTCT in Zimbabwe were also represented. The main objectives of the consultation were to update participants on scientific advances in PMTCT and on the current situation regarding PMTCT policy and programming in Zimbabwe, and to obtain input from participants on strategies to support scale-up of the national PMTCT program. Key considerations highlighted during the consultation included (1) the evolving science relating to PMTCT programming and implications for care program roll-out activities such as training; (2) the need to recognize that provincial and district teams are the implementers of the national program; (3) the need for partners to actively support the national program; and (4) the need for the MOCHW to coordinate, take leadership, and empower the provincial and district teams to implement the national program. To assist implementers in carrying out the national strategy, a program plan and guidelines were developed, and tools, such as standardized training materials and monitoring and evaluation tools, were provided.15

2. **Define broad national PMTCT training requirements.** During the national consultation, detailed updates on the status of PMTCT programming in the country were provided by province- and district-level teams involved in the national PMTCT pilot program and general program expansion. Reports from the pilot sites noted

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**Box 1. Steps in the Zimbabwe National PMTCT Training Materials Development Process**

1. Consult with provincial medical directorates (PMDs), program implementers, and stakeholders on national PMTCT program roll-out strategies, including PMTCT training.
2. Define national PMTCT training requirements based on
   - PMTCT pilot project evaluation report,
   - PMD and stakeholder consultation report, and
   - initial program roll-out experiences and lessons learned.
3. Develop national PMTCT training matrix plan: who gets trained, on what, where, and for how long.
4. Develop in-service national PMTCT training materials for facility-based health workers with technical and financial partner support.
5. Review and update community-based health worker training material.
6. Develop preservice training curriculum “road map.”

*All steps led by the National PMTCT Unit of the Ministry of Health and Child Welfare, with support from partners through the PMTCT Partnership Forum.*
that only a few health workers at each site were trained to implement the program. Nevertheless, the health workers who had not received PMTCT training were carrying out PMTCT-related activities, such as providing infant-feeding demonstrations and group health education to mothers at ANCs.\textsuperscript{16} This was an important finding because it demonstrated that all health workers in ANCs where PMTCT was being implemented needed training. That need was confirmed by several provinces that had started rolling out PMTCT services after the official national PMTCT pilot project had been concluded.\textsuperscript{3,13,15,16} Early experiences from the provinces not only indicated the need for all health workers to be trained but also highlighted the need to adopt comprehensive implementation plans that included specific PMTCT training requirements for the various health-care cadres.

3. Define specific PMTCT training requirements. A PMTCT program training matrix was developed in collaboration with provincial and district teams, together with their technical partners. The matrix was a simple written table outlining the various staff groups and cadres to be trained and the training type, content, and duration for each group.\textsuperscript{14} The matrix also indicated essential resource materials needed for each type of training. Once developed, the matrix was used to guide national, provincial, and district teams in making their comprehensive PMTCT training plans and in mobilizing training resources. The tool was also useful for guiding the process of developing national PMTCT training materials.

4. Develop an in-service PMTCT training manual for facility-based health workers. The first national PMTCT training manual was developed in haste at the end of the national pilot project in 2001, after national program roll-out had already begun. As a result, the manual had numerous gaps that were discovered during the initial phase of program expansion.\textsuperscript{6} Gaps identified included lack of comprehensive content on links with other HIV/AIDS programs and inadequate consideration of the implications of existing FCH training materials. Identifying those gaps during program implementation led the district teams and their implementing partners to call for revision of the manual.

The MoHCW, as the main provider of PMTCT services, led the revision of the manual and the subsequent process of training material development. PMTCT implementers and the PMTCT Partnership Forum technical subcommittee, as well as specialists in various disciplines such as ART, contributed additional technical expertise. The development process concluded with the production of a trainer’s manual for an integrated approach to HIV/AIDS prevention, care, treatment, and follow-up for pregnant women, their babies, and their families. The new manual addressed shortcomings identified in the first manual and accompanying implementation protocols. It covered emerging issues such as the science of PMTCT and the implications of ART roll-out on PMTCT service delivery, while incorporating existing national public-health and primary health-care approaches. Training on family planning and infant-feeding counseling was strengthened and integrated with recently updated national policies on infant feeding, including clear recommendations on exclusive breastfeeding and HIV. A new module focused on integrating PMTCT with cross-cutting programs and services and was based on experience gained from the first phase of the national program expansion. In that module, integration, links, and referral systems were clearly described in detail and with accompanying flowcharts. The flowcharts were based on reviewed and updated charts from the original national PMTCT implementation protocols, aimed at ensuring appropriate patient flow and referral of individual women and infants for ongoing care.
Once the training manual was completed, it was reviewed to ensure that all information presented was evidence based and in line with current national policy and practice. Existing health worker training materials in FCH, HIV testing and counseling, and ART were used as reference materials during the review process. Other supporting documents included reports from provincial PMTCT program review meetings, which highlighted gaps and challenges in the first edition of the training manual; local PMTCT guidelines and policy documents (i.e., the national procedures and logistics manual on PMTCT and the national PMTCT implementation protocols); and current WHO guidelines and generic PMTCT training materials.

As the comprehensive training manual was being developed, the national PMTCT program had already expanded to multiple maternal and child health-care facilities. The new manual was therefore organized into eight freestanding modules (Box 2), with various sessions under each module. That organization enables trainers to use each module individually during refresher courses and mentor-training sessions or as part of a complete general PMTCT training course. In a complete general PMTCT training, all modules can be combined and taught during a five-day program.

The draft manual was pilot tested at a refresher training-of-trainer’s course and was well received by the participants. Gaps identified at that training enabled the national PMTCT team to appropriately finalize the new manual. At the time of this writing, the manual has been in use at the district and provincial levels for a few months and further evaluation regarding the success of the manual is forthcoming.

5. Develop in-service PMTCT training materials for community-based health workers. One of the strategies identified at the national consultation on PMTCT roll-out was the need to mobilize communities to ensure better program uptake. Community-based health workers, such as traditional midwives, community-based family planning commodities distributors, village health workers, and home-based caregivers, play an important role in community mobilization and community support for national PMTCT program roll-out. Those cadres are normally managed and supervised by the MOHCW, together with its supporting units, such as the Zimbabwe National Family Planning Council. Community nurses (who are among the facility-based health workers trained using the national PMTCT training manual) are responsible for organizing and providing training and supervision to the cadres.

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Box 2. Modules Contained in the Zimbabwe National PMTCT Training Manual

<table>
<thead>
<tr>
<th>Manual Title: Prevention of mother-to-child transmission of HIV in Zimbabwe: A trainer’s manual for the integrated approach to HIV and AIDS prevention, care, treatment, and follow-up for pregnant women, their babies, and their families</th>
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</thead>
<tbody>
<tr>
<td><strong>Modules:</strong></td>
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<tr>
<td>1. Overview of HIV and AIDS</td>
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<tr>
<td>2. HIV prevention in mothers, infants, and young children</td>
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<tr>
<td>3. HIV testing and counseling in PMTCT</td>
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<tr>
<td>4. Specific interventions for PMTCT (antiretroviral drugs and family planning)</td>
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<tr>
<td>5. Infant feeding in the context of HIV infection</td>
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<tr>
<td>6. Additional care and support in PMTCT for mothers, babies, and health workers</td>
</tr>
<tr>
<td>7. Practical integration of PMTCT, FCH, ART, and testing and counseling services in Zimbabwe</td>
</tr>
<tr>
<td>8. Practical monitoring and evaluation of PMTCT services in the integrated Zimbabwe HIV and AIDS program</td>
</tr>
</tbody>
</table>
in their districts. In 2004, existing MOHCW training materials for community-based health workers were reviewed and updated to include appropriate PMTCT content. That was done by a technical working group composed of several community health nurses and technical specialists and partners in PMTCT. Modules from the newly developed national PMTCT training manual were used as reference materials. Financial and technical support for revising and updating the training materials came from implementing partners through the national PMTCT Partnership Forum.

6. Develop a draft preservice training curriculum or “road map.” The national PMTCT program recognized the need to review and update the existing preservice training curriculum for counselors, nurses, and doctors to include PMTCT content. The introduction of primary care counselors into the MOHCW structure during the expansion of the national PMTCT program provided an opportunity to ensure that the preservice training curriculum for the new counseling cadre included relevant and comprehensive PMTCT content. The national PMTCT team, with its PMTCT Partnership Forum technical partners, participated in the development of the preservice training curriculum for the new cadre. Training modules from the newly developed national PMTCT training manual were used as reference material to ensure that PMTCT content was consistent with that being taught to other health workers. The development of this curriculum was led by the National HIV Testing and Counseling Partnership Forum, composed of various local and international organizations supporting the MOHCW on HIV testing and counseling.

Discussions about updating and revising the preservice training curriculum for doctors and nurses to include PMTCT took place at the inception of the national PMTCT program roll-out. In 2005 the University of Zimbabwe’s HIV Quality of Care Initiative convened a stakeholder workshop to propose and initiate the revision of the preservice curriculum for health-care cadres, especially medical and nursing care cadres.17,18 The main objective of the stakeholder workshop was to review the existing curriculum and suggest updates on HIV/AIDS programs, including PMTCT. Key participants included the MOHCW technical and program officers and the university’s HIV curriculum working group.

The workshop participants were divided into working groups according to their specialties. The working groups focused on three key areas: (1) defining the minimum curriculum content; (2) determining the delivery process by looking at how it should be taught, by whom, and with what resources; and (3) determining how to evaluate students to ensure that they had acquired the necessary skills and competencies.18 At the end of the workshop, HIV/AIDS content, including PMTCT, had been included in the draft revised preservice curriculum for nursing and medical schools.

OVERCOMING CHALLENGES IN DEVELOPING TRAINING MATERIALS FOR PMTCT

Introduction, integration, and expansion of national PMTCT services within existing health systems requires comprehensive and well-developed training materials for various health care cadres. The consultative process used by Zimbabwe in the development of its training materials was a major challenge, primarily because of the large amount of time needed to get partners to participate at every stage of the process. Despite these challenges, meaningful participation and buy-in by the partners was essential, because the success of the national program roll-out relied heavily on their support.

Developing a comprehensive PMTCT training manual that could be used by various health-care
The economic constraints faced by the national program, as well as the limited human capacity at the national level, presented further challenges for the materials development process. The national PMTCT unit relied heavily on the financial and technical support of its partners for all the development steps (Box 3). The national PMTCT Partnership Forum assisted in mobilizing the technical and financial support needed through its Training Technical Working Subcommittee.

**LESSONS LEARNED**

- When developing national training materials, it is important to adopt a holistic and comprehensive approach by looking at broad and specific national program training requirements, and by looking at both in-service and preservice materials. Although difficult, addressing preservice training is likely to reduce the future costs (including opportunity costs) of frequent in-service training.
- Development of PMTCT training materials should address the needs of both facility- and community-based health workers. The process should consider the cross-cutting nature of PMTCT by looking at existing training materials; the implications of other HIV/AIDS programs, national policies, and approaches; and current evidence-based information on PMTCT.
- A national training matrix that provides information on who to train and what information to
include in the training is an important tool. The matrix not only provides an outline of the specific training requirements for each health-care cadre but also demonstrates the link between training materials development and a comprehensive national training plan. Using a training matrix also helps to identify gaps where new training materials are required.

- Developing training materials for a national program that has the involvement of many partners requires wide consultation. A consultative process is critical to involving the partners in using the materials and aids they have helped to develop.

- Participation of partners throughout the entire process provides meaningful technical and financial support. This participation increases stakeholder involvement in the national program roll-out and strengthens government collaboration with and coordination of all stakeholders. It also fosters program ownership by provincial and district implementing teams.

- Deeper integration of vertical ART and PMTCT programs is now required to maximize care for women and minimize HIV transmission to infants (e.g., via the provision of opportunistic infections services and ART within ANC facilities). Integration takes time but can be spearheaded through a comprehensive process of training materials revision that brings together leaders, managers, and implementers from both programs.

- Large amounts of content can be put into modular form to increase flexibility, simplify refresher training, help programs manage large numbers of trainings for in-service workers, and ease updating of specific sections as science and practice evolve.

**CONCLUSION AND RECOMMENDATIONS**

The process of PMTCT training materials development should consider the multidisciplinary nature of PMTCT by looking at existing training materials, the implications of other HIV/AIDS and maternal and child health programs, national policies and approaches, and current evidence-based information on PMTCT. The process should be practical and reflect the status and experiences of the PMTCT and ART program roll-out, the existing national health systems, and the public and primary health-care approaches. Above all, it requires collaboration and cooperation between key stakeholders, program leaders, and implementers at all levels to facilitate integration and enable successful service provision for women, infants, and families.
REFERENCE LIST


14. MOHCW. Prevention of mother to child transmission of HIV programme: procedures...


17. HIV/AIDS Quality of Care Initiative, Clinical Epidemiology Resource and Training Centre (CERTC), University of Zimbabwe. Report of the workshop on integrating HIV and AIDS issues into pre-service medical and nursing curricula in Zimbabwe; April 20–22, 2006; Nyanga, Zimbabwe.

Expanding the Role of Nurses and Advanced Practice Nursing in HIV/AIDS Care

Suzanne Willard

Nurses are probably the best equipped to provide care to people living with HIV. The ability to develop a therapeutic relationship with the patient and to work with them over the long term is both the rewarding and draining part of working in HIV. With good medicines, there are more rewards than emotional drains.

—Carol Hutelmyer, RN, CRNP, advanced practice nurse with over 20 years’ experience working with people living with HIV (personal communication, October 2007)

The complexity of HIV disease management has necessitated greater provider collaboration and communication and a broader role for nurses in all aspects of patient care. While the expansion of all health-care provider roles and the evolution of their scopes of practice are inevitable in the context of HIV/AIDS, nurses are particularly well positioned to respond to the wide-ranging needs of people living with HIV. The demand for the expansion of nursing care driven by the increasing numbers of patients seeking care will continue to increase as HIV/AIDS programs are scaled up. For example, in South Africa it has been estimated that for every 500 people placed on antiretroviral therapy (ART), three extra nurses (one with advanced skills) and one extra pharmacist will be needed.1

The emergence of the HIV pandemic will surely be remembered as one of the critical points in history where nurses have made a significant contribution to public health. Nurses have many responsibilities in the clinical setting and many of these tasks can be shifted to non-nursing personnel. Task shifting is one strategy that provides opportunities for nurses to take a leadership role in addressing the pandemic. For instance, tasks such as attending on waiting areas, pulling patient files, and even checking vital signs need not be done by nurses (despite being common practice in many settings). Shifting these basic tasks to lower-level staff and training nurses in more advanced skills will permit them to focus on clinical care and the core components of nursing.

This chapter will outline the role of advanced practice nursing in HIV management and will discuss how the greater utilization of nurses overall can lead to improved outcomes.

INTRODUCTION TO ADVANCED PRACTICE NURSING

The health-care landscape in sub-Saharan Africa as well as other resource-limited settings has evolved significantly over the past decade. A particularly significant shift has been the renewed emphasis on the primary health-care model (with chronic care
as a key component) as opposed to the curative care model (i.e., treatment of acute conditions, such as malaria). The expansion of long-term care services for people living with HIV has brought with it the need for nurses to expand their role beyond the direct provision of care, to include the prescribing of medicines and the overall management of HIV/AIDS programs, including traditional training and the supervision of less skilled health-care workers.

Margretta Styles, a respected leader in the nursing profession, identified the four basic characteristics of advanced practice nursing as follows:

1. A specialized focus and population served
2. Expanded knowledge and skills
3. Complex clinical-practice challenges faced and clinical judgment required
4. Independent decision making

A nurse practitioner or advanced practice nurse is a registered nurse who has acquired the expert knowledge base, complex decision-making skills, and clinical competencies for expanded practice (see Box 1).

Many programs have proven that nurses can successfully provide high-quality HIV care services, including the prescribing of antiretroviral and other medicines. For example, in a study undertaken at 68 HIV care sites in the United States, Wilson and colleagues reported that nurse practitioners provided a similar quality of care to that of physician HIV experts, and a better quality of care than physician non-HIV experts.

An expanded role for nurses is not a new concept. Historically, nurses have often taken on additional responsibilities out of necessity, with little if any additional training or supervision, and nurses have always worked to meet the changing needs of their patients. Other practitioners also frequently take on expanded roles; midwives have long been recognized for their important role in maternal and child health, while clinical officers provide medical services in many settings where there is a shortage of physicians. In support of these expanding roles, the World Health Organization (WHO) has recently compiled recommendations and guidelines for task shifting that support an expanded role for nurses and other health facility staff in resource-limited settings.

The term nurse is in itself problematic, as it does not accurately describe an individual’s level of preparation; each country has differing guidelines for nurse preparation and educational programs, which can range from a one-year course to a three- or five-year program. Despite these differences, there are many nursing concepts that are common across all countries. At the most basic level, all nurses are trained to provide care and

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**Box 1. Core Competencies of the Advanced Practice Nurse**

- Able to integrate research, education, practice, and management
- Demonstrates a high degree of professional autonomy and independent practice
- Capable of managing his or her own caseload
- Able to perform advanced health assessments and in possession of decision-making and diagnostic reasoning skills
- Possesses advanced clinical skills
- Able to provide consultation to other health-care providers
- Able to plan, implement, and evaluate programs
- Recognized first point of contact for clients

*Source: International Council of Nurses and Advanced Practice Nursing Network.*

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support to patients through the course of their illness. Vocational nurses, practical nurses, enrolled nurses, and registered nurses have all received some level of training in this area. Some of the more complex tasks related to patient care fall within the scope of practice of the advanced practice nurse. As such, the advanced practice nurse must have advanced skills in health assessment, clinical decision making, and expanded diagnostic reasoning.

In many settings, allowing nurses to prescribe medications can improve clinical outcomes and enhance the patient experience. For example, many developed countries have successfully adopted practice frameworks that allow nurses who are working in the field, regardless of educational preparation, to prescribe medications within the context of the scope of nursing practice. In developing countries, nurses occasionally do prescribe medications, but this is often done informally on an ad hoc basis. Often this need arises and is addressed before the educational system steps in to provide greater guidance. It is therefore essential that the responsibilities, training, rights, and roles of nurses relating to prescribing activities be clearly defined.

In 2004, the International Council of Nurses (ICN) created a framework for the involvement of nurses in drug-prescribing activities (Table 1). These models can be adapted to a range of settings in which there is a need to expand the current role of nurses beyond the direct provision of care.

### IMPLEMENTATION OF ADVANCED PRACTICE NURSING

Countries that have successfully adopted the framework of advanced practice nursing have done so by addressing a number of key issues, including legal requirements, such as needed approvals by government agencies and medical associations; development

<table>
<thead>
<tr>
<th>Prescribing Model Type</th>
<th>Practice Description</th>
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<tbody>
<tr>
<td>Initial, independent, autonomous, or substitute prescribing</td>
<td>The practitioner is accountable for assessing the client; making a differential diagnosis; determining the appropriate medication, treatment, or appliance required to manage the client; and issuing the appropriate prescription.</td>
</tr>
<tr>
<td>Dependent, collaborative, semi-autonomous, complementary, or supplementary prescribing</td>
<td>The practitioner may prescribe as a dependent prescriber in collaboration with an independent prescriber, usually a medical practitioner, but without the need for direct supervision by the independent prescriber. The dependent prescriber is not usually responsible for the assessment and diagnosis of the client. This method is useful for issuing ongoing prescriptions after the initial prescription has been issued by the independent prescriber.</td>
</tr>
<tr>
<td>Group protocols or patient-group directions</td>
<td>The practitioner may supply and/or administer a named medicine in an identified clinical situation directly to groups of patients who may not be individually identified before presentation for treatment. It is not a form of prescribing.</td>
</tr>
<tr>
<td>Time and dose prescribing</td>
<td>The practitioner works within patient-specific protocols. Nurses are allowed to alter the time and dosage of particular medications. Again, this is not strictly defined as prescribing.</td>
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</table>

Source: Adapted from International Council of Nurses.
Guidelines issued by the U.S. Department of Health and Human Services (DHHS) now contain modified language that reflects the greater share of responsibilities being placed on nurses. For instance, the term health-care provider has largely replaced physician, acknowledging the role that nonphysician providers have in prescribing medications and in the provision of HIV care generally. WHO is also supporting various regional efforts aimed at developing policies that support the expansion of nursing roles and responsibilities; prescribing guidelines for nonphysician providers have been developed to assist in this effort. Médecins Sans Frontières (MSF) has also targeted nurses in its guidelines for drug management.7

Training and Education
The ICN recommends that advanced practice nurses receive a master’s-level education. However, of adequate training, supervision, and evaluation procedures; and the creation of effective referral systems for cases that lie outside the advanced practice nurses’ scope of practice6,9 (Box 2).

The ICN network for nurse practitioners and advanced practice nurses has recommended that countries interested in establishing a role for advanced practice nursing give attention to three key areas3:

1. Regulation—to monitor and protect individual practitioners and the general population
2. Professional training—to prepare nurses for higher-level practice
3. Ongoing professional and practical development—to assess and maintain the core competencies of advanced practice nursing

As highlighted earlier, WHO has begun to provide guidance for the task shifting now under way in many settings. Additionally, HIV treatment guidelines issued by the U.S. Department of Health and Human Services (DHHS) now contain modified language that reflects the greater share of responsibilities being placed on nurses. For instance, the term health-care provider has largely replaced physician, acknowledging the role that nonphysician providers have in prescribing medications and in the provision of HIV care generally. WHO is also supporting various regional efforts aimed at developing policies that support the expansion of nursing roles and responsibilities; prescribing guidelines for nonphysician providers have been developed to assist in this effort. Médecins Sans Frontières (MSF) has also targeted nurses in its guidelines for drug management.7

<table>
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<tr>
<th>Box 2. Laying the Groundwork for Advanced Practice Nursing</th>
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<tbody>
<tr>
<td>The implementation of advanced practice nursing requires that a variety of supportive systems be in place, including the following:</td>
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<tr>
<td><strong>Educational Support</strong></td>
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<tr>
<td>- Advanced level of nursing education (available either in-country or via accessible foreign institutions)</td>
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<tr>
<td>- Formal recognition at the national level of educational programs to prepare nurse practitioners, along with accreditation or approval of the advanced nursing role</td>
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<tr>
<td>- Formal system of licensure, registration, certification, and credentialing of advanced practice nurses</td>
</tr>
<tr>
<td><strong>Regulatory Support for Nursing Care</strong></td>
</tr>
<tr>
<td>- Right to diagnose</td>
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<tr>
<td>- Authority to prescribe medication</td>
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<tr>
<td>- Authority to prescribe treatment</td>
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<tr>
<td>- Authority to refer clients to other professionals</td>
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<tr>
<td>- Authority to admit patients to hospital</td>
</tr>
<tr>
<td>- Legislation to confer and protect the title “nurse practitioner” or “advanced practice nurse”</td>
</tr>
<tr>
<td>- Legislation or some other form of regulatory mechanism specific to advanced practice nurses</td>
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<tr>
<td>- Officially recognized titles for nurses working in advanced practice roles</td>
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*Source: Adapted from Affara and Schober.*
in light of the current rapid scale-up of HIV treatment programs in many countries, educational institutions should be encouraged to develop programs that can prepare highly trained nurses in the least possible amount of time, while still covering the essential elements of quality nursing care.

Multiple factors affect the quality and breadth of education in advanced practice nursing. Certificate programs are perhaps the quickest path to establishing a curriculum and preparing a group of qualified individuals. Academic institutions, due to their complex structures, are generally slow to change established approaches to nursing education. Thus, it is important for leaders of academic nursing programs to be actively involved in quickening the pace of progress. Going forward, it will be important for expanded roles for nurses to be included in formal nursing preparation. If this can be achieved, an advanced degree beyond basic nursing preparation will provide further credibility and support for such a role.

Students selected for participation in advanced degree programs should be highly motivated, and their length of time as a nurse should not be the sole criterion; although clinical experience is important, these skills can be learned while nurses prepare for their roles in advanced practice. Nursing faculty should also be motivated to support expanded roles for nurses. Faculty can be creative in their approach to developing new programs of study and collaborate when appropriate with physicians and clinical officers in imparting needed skills. Those wishing to initiate an advanced nursing program can also collaborate with other universities that have had prior experience instituting such programs. Examples of successful partnerships established for this purpose include the relationship between the University of California, San Francisco (UCSF) and the University of Tanzania, and between the International Training and Education Center on HIV (I-TECH), the University of Namibia, and the Ethiopia Nursing Council.

Physicians can provide content and guidance for areas of practice that have traditionally been outside the scope of nursing. Faculty should be encouraged to teach in multidisciplinary teams to encourage the sharing of information and broader skill development. There should also be strong linkages between classroom education and practical, on-site mentoring. Practical training sites that are supportive of the development of nurses should be identified for this purpose.

Recommended core content for advanced nursing training includes the following:

- Core concepts and philosophy of nursing, including where nurses fit within the healthcare system and treatment framework.
- Scientific knowledge base—a deep understanding of anatomy and physiology, pathophysiology, pharmacology, nutrition, and family and social systems. Prescribing as part of treatment practice is critical. A key module in pharmacology is the teaching of medications and the importance of drug interactions. It is also important to be able to understand and interpret laboratory values and to be able to use these values, such as CD4 lymphocyte counts, to monitor HIV disease. This will form the most complex part of a nurse’s work.
- Physical examination—the ability to perform thorough physical examinations and to identify common conditions.
- Role implementation—an understanding of the scope of advanced nursing practice in the context of HIV disease management.
- Common management concerns. HIV disease management is not limited to pharmacology; therefore, knowledge regarding stigma, disclosure, substance abuse, and prevention issues should be highlighted.
THE UCSF ASPIRE NURSE TRAINING PROGRAM
By Catherine Lyons, Project ASPIRE, University of California, San Francisco

The University of California, San Francisco (UCSF) Positive Health Program’s international training arm, ASPIRE (AIDS Services, Prevention, Intervention, Research and Education), has provided training for nurses in South Africa, Zambia, Tanzania, Kenya, and Côte d’Ivoire. The program is based on the belief that many nurses in resource-limited settings have the required skills to adequately evaluate patients. Much as the transition from acute care to chronic care has required a rearranging of how care is provided (e.g., the introduction of longitudinal medical records), the shift in nurses’ roles requires both didactic training and clinical mentoring; in many cases, just a refresher course on skills that have not been actively utilized is required.

The overarching goal of the ASPIRE program is to enable nurses to independently manage patients. Expected outcomes stemming from this increased responsibility may include the following:

- Shifting of tasks from more highly trained to lower-level cadres of health-care providers and lay staff
- Down shifting of patients from central hospitals to regional, district, and local health centers
- Improving patient flow and efficiency of care
- Making the best use of professional resources
- Empowering nurses to practice at their full capacity
- Developing nursing expertise and independence in the area of HIV/AIDS care
- Developing a cadre of nurse leaders, mentors, and trainers

The ASPIRE program’s training is divided into two parts: classroom review and on-site observation and mentorship. The components of training are as follows.

1. Classroom review (utilizing case discussions and role play) of the following:
   - Medication side effects, identification of severe reactions, and treatment of minor side effects
   - Understanding the natural history of the disease, including the relationship between CD4 lymphocyte counts and opportunistic infections
   - Specific opportunistic infections and presenting symptoms
   - How to do a systematic review of symptoms
   - Basic physical exam, including pertinent vital signs
   - When to do a more extensive exam

2. On-site observation and mentoring of nurses, including feedback and correction as needed (may require two to five initial observations and regular follow-up observations)
The implementation of any new professional role is enhanced when experienced practitioners mentor newly trained workers. Mentorship provides these new workers with an opportunity to expand their skills and competencies beyond the formal training period. It is expected that the first groups of advanced nursing graduates will provide leadership to subsequent graduates. Mentorship should be built into any training program from the beginning. Since there is a great demand for these new skills, time and space must be allotted to ensure that experienced nurses will have the time and resources needed to mentor new groups of trainees.

Training is essential to protect and expand the practice of nursing as well as to ensure quality of care. Since the establishment of sufficient numbers of formal academic nursing programs is not feasible in many countries, innovative methods should be employed to fill the need for nurse training. Certificate programs, mentoring, and distance education are but a few of the methods that can be considered to support nurses in their work. For instance, I-TECH has developed several HIV/AIDS-focused training programs for nurses and other health-care workers in developing countries. These programs include on-site didactic (classroom) training as well as printed manuals, CD-ROMS, and videos that can be used together or separately to support quality HIV care. While access to technology such as cell phones and computers is still a challenge in many settings, the use of technology to enhance both training and practice can be highly beneficial.

The advanced practice role requires the support of the entire health-care team in addition to that of academic institutions and policymakers. There also needs to be active collaboration with more experienced clinicians. For instance, nurses will routinely need to have access to more experienced clinicians who can help them problem solve difficult or complex cases. As part of this process, a referral system should be established that provides patients with the benefit of easy access to quality health care as well as access to more experienced clinician opinions if their health status warrants. This clinical “backup” will require the use of technology and transportation assistance to ensure a seamless care model.

It should be noted that it is generally unwise to wait until adequate resources (e.g., graduate education programs) are in place to provide advanced training; advanced nursing practice is already occurring due to patient demand and limited human resources, and in these instances immediate training support is needed to ensure quality of care. Along with additional training, evaluation must be provided. It must be responsive to the changing roles of providers and should be ongoing in order to ensure that desired outcomes are consistently being achieved.

Professional Role Development

Nursing is emotionally challenging and labor intensive. Chronic HIV care requires the long-term, hands-on involvement of the care provider, with many difficult decisions to be made along the way. In addition to the detection of physical signs and symptoms and assessment of risk, every patient encounter is also an opportunity for counseling about HIV disease, treatment, infant feeding, family planning, and safer sexual practices. Quality management of HIV encompasses all these activities and demands that nurses be creative and comprehensive in their approach to care.

As nursing roles expand, there is also a need to develop innovative models of care provision to accommodate these new roles. For example, a unique model of HIV health services has been developed in South Africa—outside the government system—that utilizes a team consisting of a nurse practitioner, a pharmacist, and a physician. The clinic is located in a storefront inside
EXPERIENCES AND CHALLENGES AMONG NURSES IN MALAWI
By Evelyn B. Chilemba, Kamuzu College of Nursing, University of Malawi

THE AIDS PANDEMIC POSES GREAT challenges for nurses working as primary caregivers in high-prevalence, resource-limited settings such as Malawi. These challenges are due to a number of factors, such as staff shortages, limited resources, weak referral systems, and inadequate bed capacity in existing health-care settings.11

Nurses as primary caregivers of people living with HIV must possess the requisite knowledge and advanced skills to provide a broad array of care and support, including counseling services (e.g., nutritional and psychological counseling), prevention services, clinical management of HIV and other sexually transmitted infections, and the provision of antiretroviral therapy. But even with the proper knowledge and skills, the quality and availability of services may still suffer due to care being delivered in a hurried and sometimes careless manner because of inadequate staff and/or facilities.

Most clients depend on nurses to support them in a variety of ways beyond the direct provision of care. As a source of psychosocial support, nurses are crucial to sustaining patients’ sense of hope and, consequently, their adherence to therapy. Most people living with HIV also suffer from other chronic conditions that require specialized attention and care. In Malawi, the most common HIV-related conditions are tuberculosis, pneumonia, meningitis, diarrhea, and Kaposi’s sarcoma. When clients are informed of their diagnoses with these and other HIV-related conditions, they are counseled on lifestyle changes that can help them maintain adequate health despite the chronic nature of their illnesses. Yet even when a client has accepted the reality of his or her HIV diagnosis, the individual may still harbor feelings of sadness or anger. These emotions, if left unaddressed, can have a detrimental effect on the patient’s adherence to treatment, since the client may not yet understand or appreciate the need to continue taking his or her medications. In some instances, clients have even committed suicide due to lack of adequate emotional support.

Medical wards in high-prevalence areas are often overcrowded with HIV-positive clients suffering from various HIV-related infections. These patients tend to stay in the hospital for a shorter time than is recommended due to the limited bed space and shortage of human and material resources. Premature discharge of these patients can lead to further complications—even the emergence of life-threatening complications.

The nurse’s role is to instill hope in clients living with HIV to help them gather the will to live positively.12 When clients first learn that they are HIV-positive, they will require a great deal of support to help them cope with personal dilemmas, stigma, and other challenges. Individuals diagnosed with HIV experience a range of emotional reactions such as fear, guilt, shame, and uncertainty.13 Yet the shortage of nurses in most public health facilities in Malawi has resulted in minimal interactions between nurses and their patients, limiting
nurses’ ability to provide needed support and encouragement. These interactions are also an important opportunity to provide information on HIV/AIDS, correct misconceptions, and raise patients’ levels of awareness about important issues related to their HIV-positive diagnoses and the services available to them.^

A study among women receiving prevention of mother-to-child transmission (PMTCT) services at a provincial hospital in Kenya found that most clients had received inadequate information during patient interviews and treatment visits and could not recall information communicated to them during counseling sessions.^

Other studies have found that patients may drop out of PMTCT programs due in part to inadequate counseling.^

These findings reinforce the importance of freeing up more time for nurses to provide much-needed psychological support before, during, and after the provision of critical services such as PMTCT.

In Malawi, nurses following up with clients via home visits have noticed that stigma and discrimination can arise as a result of these visits. Frequent caregiver visits to a patient’s home can cause neighbors to believe that someone living in the home is HIV-positive. As a result, some clients may move to a different location without informing the nurses. This abrupt discontinuation of the nurse-client relationship can endanger the client’s health while leading to feelings of discouragement or burnout on the part of the caregiver. To address this problem, nurses in Malawi are working together with clients to devise ways to protect client confidentiality. Strategies used by nurses to date include not wearing their hospital uniform during visits, having the hospital vehicle drop them far from the client’s home, and planning visits so they do not occur at fixed times.

a shopping center, providing a convenient, “one-stop-shopping” site for health-care services. For South African regulatory purposes, the nurse practitioner is considered an employee of the pharmacist, but it is expected that all members of the team will work as equal partners. In this model, the nurse practitioner provides assessment, diagnosis, treatment, and care while the pharmacist prescribes and dispenses medications. The off-site physician is available for referrals and assistance with emergencies or complicated cases. This model was developed to enable efficient operation despite the country’s restrictive regulatory environment with regard to nursing practice. The success of this program has led South African regulatory authorities to consider less stringent limitations on nursing practice so that quality HIV care can be made more accessible. Such steps will need to be taken in many countries where health-care regulations, while protective of patients, have not kept pace with ever-changing patient needs and health-care realities. For this reason, advocacy is a necessary component of any strategy to expand traditional nursing roles, so that regulations are modified to support these changes.

Evaluation
Evaluation is an essential component of nursing practice. Evaluation of the advanced practice nursing role should be based on (1) clinical outcomes, (2) integration within professional circles, and (3) acceptance by patients/communities.
Nurse participation in the actual hands-on provision of care as well as the evaluation of these efforts is important, as nurses have significant ties to the communities in which they serve. The evaluation of nurses’ impact on patient outcomes needs to take into account the social, economic, and political components of health. HIV is a social issue as well as a medical condition, and as such requires a greater understanding of and sensitivity to the patient experience on the part of the healthcare provider. Implementing advanced practice nursing in HIV care requires behavior change on the part of nurses and other health staff, as well as an understanding of the social and cultural complexities that can arise when a patient is identified as being HIV-positive. Areas of focus for evaluation activities include access to and availability of services, acceptance of expanded nursing roles among patients and health professionals, cost of care, and quality of care.

Evaluation findings are important to advance the acceptance of task shifting and other needed measures. In the United States, several studies have examined the acceptance of advanced roles for nurses.4,17 A common finding was that patients’ acceptance of nurses in advanced roles increases as they have more experience with nurses in such roles.

Further research is also needed to analyze the impact of expanded nursing roles on clinical outcomes. For example, Bolton-Moore and colleagues18 reviewed clinical outcomes among children on ART in primary healthcare settings in Zambia, where the majority of care providers were nurses and clinical officers. Clinical outcomes measured included patient survival, weight gain, CD4 lymphocyte counts, and hemoglobin responses. The nurses received advanced training in ART as well as on-site mentorship. The study demonstrated that with appropriate training and mentorship, ART programs that rely primarily on nurses and clinical officers can provide quality care while efficiently utilizing available human resources. More studies like this are needed to demonstrate the potential of advanced practice nurses in resource-limited settings with high HIV prevalence.

**CONCLUSION**

In summary, there are four domains that impact the feasibility of an expanded role for nurses. The first is knowledge—do nurses have the information needed to provide quality care? The second domain is the validation of the role—is there support from other health-care providers for this role, and are there regulatory agencies that need to be involved? The third domain lies in the competency and skills of the clinicians—are the competencies needed to begin any new role clearly defined and can they be measured? Finally, the fourth domain to consider is the environment—is there a place within the health-care system for this new role?

HIV/AIDS has challenged health-care systems around the world. The impacts on science, research, and clinical care have been enormous, and the virus will continue to change the way we approach the management of chronic disease. In this changing landscape, nurses need to be vocal advocates on behalf of their patients and their profession. Nurses who choose to take on the advanced practice role will need to understand the importance of their voice and have the courage to use it. HIV care has evolved from the ground up, with nursing at the core of this framework. Nursing provides what few other health disciplines can: skilled professionals with the willingness and desire to develop long-term, therapeutic relationships with their patients. Such a commitment can be rewarding as well as frustrating. Implementing advanced nursing practice in resource-limited settings will help lessen these frustrations by matching skills and responsibilities as well as providing tools to improve patient outcomes.
While some policymakers may see this new cadre of advanced practice nurses as a short- or long-term solution to physician shortages, the nursing profession has never promoted advanced practice nurses as substitutes for physicians. Rather, this expanded role has been offered as a way to address the service gap that currently exists. Research and other public-health evaluations should carefully examine the health policy and other considerations that arise as this new approach is rolled out.

Acceptance by patients and other health-care providers, such as physicians and pharmacists, of the advanced practice nursing role is also key to the strategy’s success. There is much debate as to whether HIV care is a specialty that should be in the hands of medical specialists only. However, in areas where resources are limited and where there is an overwhelmingly high prevalence of HIV and other life-threatening illnesses, treatment can no longer be left in the hands of a few.
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LABORATORY AND PHARMACY SERVICES
LABORATORY TESTING FOR HIV AND related opportunistic diseases plays a critical role in the effective implementation of prevention, care, and treatment programs with regard to disease screening, clinical diagnosis, staging of disease, therapeutic monitoring, blood safety, and surveillance. Because of this pivotal role, the overall goal of any laboratory program in a developing country should be to ensure sustainable, integrated laboratory capacity that can provide quality, rapid, accurate, affordable, and reliable diagnostic tests for the effective implementation of lifesaving treatment and prevention programs. However, because of a lack of access to reliable diagnostic testing and an acute shortage of trained staff, coupled with under-resourced laboratory infrastructure in developing countries, inconsistent diagnoses frequently lead to inadequate treatment, increased mortality, and inaccurate determination of the true burden and/or stage of the disease.¹

Since 2003, concerted efforts have been made to provide access to antiretroviral therapy (ART) to the approximately 40 million HIV-positive people residing in developing countries. These efforts include the United Nations–supported Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM); the World Health Organization (WHO) “3 by 5” initiative, which planned to provide ART to 3 million AIDS patients by 2005; and the U.S. President’s Emergency Program for AIDS Relief (PEPFAR), which has the goal of preventing 7 million new HIV infections, providing treatment to 2 million HIV-positive people living in targeted countries, and providing palliative care to 10 million HIV-positive people. Globally, the current state of laboratories in developing countries cannot support program needs. Indeed, the paucity of functional, quality laboratories—in terms of both human capacity and physical infrastructure—is uniform across most developing countries. Thus, from a public-health perspective, laboratory services must be significantly strengthened and expanded for these well-intentioned efforts to be successful. For laboratory services to be valuable in any program, they must be easily accessible and able to provide accurate and reliable results in a predictably quick turnaround time. The lack of laboratory services was highlighted in a survey conducted in 2000 by the WHO-sponsored African AIDS Vaccine Program (AAVP).² The survey revealed that, as of 2000, fewer than 10 countries in sub-Saharan Africa had the capability to perform...
HIV-1 RNA viral load or CD4 lymphocyte count testing. A similar survey performed by the WHO African Regional Office (AFRO) found out that although many countries were performing HIV serologic testing, only very few laboratories were enrolled in any form of quality control or external quality assessment (EQA) program.

In this chapter, we review the multiple challenges that hinder the smooth functioning of quality laboratory services in developing countries and argue that five key areas must be addressed in developing countries in order to develop sustainable public-health laboratories: (1) development of a national strategic plan that emphasizes the need for an integrated approach to disease diagnosis and monitoring—that is, a single laboratory should be able to provide diagnosis and monitoring for HIV/AIDS, TB, malaria, and opportunistic infections (OIs); (2) implementation of an effective tiered laboratory network for referrals; (3) ensuring better coordination of resources and partners in each country in order to avoid parallelism and to strengthen dialogue between research and service delivery laboratories; (4) advocacy for laboratory experts to be represented at all policy levels and during program design; and (5) establishment of a strong quality management system.

CHALLENGES IN PROVIDING RELIABLE LABORATORY SERVICES TO MEET PROGRAM GOALS

Finding and Training Laboratory Technicians and Managers

The systemic acute lack of qualified laboratory personnel is a major and severe constraint in implementing and scaling up HIV/AIDS prevention and care programs. In most developing countries, there is a clear correlation between the quality of trained staff and the relative distance from the capital city. National reference laboratories (NRLs) that are situated in the capital city tend to have more qualified staff than do regional or district-level laboratories. The severe lack of trained laboratory experts at the regional and district levels presents an additional layer of challenge in the rapid expansion and decentralization of prevention and care services to district health centers in areas where most of the population resides. To achieve rapid scale-up of services, the training of laboratory personnel is critical at all levels of the laboratory network.

Encouraging results have been reported by WHO AFRO. According to a survey conducted from 2003 to 2005, the number of laboratory staff trained annually in sub-Saharan Africa increased significantly at the district level. This increase suggests that countries are making substantial efforts to address the issue of the chronic lack of laboratory staff at the district level, in order to meet the huge demand for decentralized services. Training has also involved task shifting with nonlaboratory staff for some HIV laboratory testing services, such as rapid testing at the district level. In fact, nonlaboratory staff, if well trained, can task shift and perform less sophisticated laboratory testing at the district level, thereby allowing more qualified laboratory staff to focus on more sophisticated testing and the implementation of quality control and assurance programs. If appropriate standard operating procedures (SOPs) are established, nonlaboratory staff can be trained to properly and safely collect and handle samples, and either test them or ship them to regional and higher laboratories for complex analyses. The same WHO AFRO survey reported that the total number of nonlaboratory staff trained in HIV laboratory techniques increased from 387 in 2003 to 791 in 2005.

To address these staffing and training challenges, efforts are being directed to at least three areas: in-service training and the organization of
test-specific workshops to meet immediate needs, increasing preservice training that includes curriculum on the full spectrum of testing, and establishing a culture of effective quality management. Advocacy targeted toward universities and other training institutions is needed for effective incorporation of HIV-related content into laboratory curricula. Training must be accompanied by a strategy for recruitment and retention of staff in the public sector. In developing countries, considerable numbers of trained staff are currently being lost to the private sector and to developed countries. In addition, public sector health facilities should also ensure that trained staff members are not redeployed to other job functions where their newly acquired skills are not in use. Because the retention of well-trained laboratory staff is an integral part of total quality management programs, strengthening human resource capacity should be a major goal of building sustainable laboratory capacity.

As training programs are rolled out, it is important that each country develop a program for individual certification that establishes criteria for the successful completion of a standardized training program for both laboratory and nonlaboratory staff. Certification should evaluate trainees based on a written examination and a demonstration of competency in the relevant laboratory techniques. To maintain the integrity and quality of trainees, systems should be put in place for continued on-site monitoring of the competence of trained laboratory and nonlaboratory staff with respect to their ability to follow SOPs, including handing of samples, interpretation of results based on national protocols, and record keeping. Policies are also needed to deal with issues such as certification, training requirements, and necessary qualifications for personnel performing tests. This is especially important for HIV rapid testing and TB smear microscopy.

**Providing Reliable HIV Rapid Testing**

Reliable HIV testing is the cornerstone for meeting the health goals of prevention, care, and treatment programs in developing countries. To meet these health goals, millions of individuals must be tested for HIV infection, as knowing one’s status is critical to prevention. Since the early 1990s, several rapid tests have become available that detect HIV antibodies in 5 to 30 minutes and, when used correctly in the right algorithm, provide results that are as reliable as results obtained from using a combination of Enzyme-Linked ImmunoSorbent Assays (ELISAs) and Western blot (WB). These tests are less dependent on a cold chain, are easier to interpret, and do not require specialized laboratory personnel and equipment. Moreover, most materials needed to perform the tests are supplied in the test kit. Fairly recently, in response to the increasing need for HIV rapid testing, there has been a proliferation of new rapid tests produced by several companies from around the world. The number of commercially available rapid tests has increased at least fivefold, from an estimated 10 in 1995 to about 50 in 2005. Only 4 rapid tests have been approved by the U.S. Food and Drug Administration (FDA). Several rapid tests have been evaluated in Africa, and many tests have demonstrated sensitivity and specificity comparable to ELISA. However, there is a huge challenge in ensuring the quality and reliability of these new rapid tests as well as in ensuring lot-to-lot consistency. This requires a standardized and systematic assessment of the tests’ performance in order to determine their eligibility for use in programs. For this reason, providing appropriate guidelines and testing algorithms to ensure accurate rapid test results has been a priority for several institutions such as WHO and the U.S. Centers for Disease Control and Prevention (CDC). As a first step to ensure that only reliable rapid tests are used in PEPFAR programs, the CDC and the United States Agency for International
that have well-trained personnel and adequate procedures, and seldom in the peripheral laborato-
ries where their use is intended. New strategies and guidelines to ensure the quality of rapid testing are
needed to address these challenges.

Laboratory Clinical Monitoring
As ART programs continue to be scaled up in developing countries, CD4 lymphocyte count testing has
become critical in initiating and monitoring response to ART. The lack of access to laboratories capable of
performing CD4 count testing has led WHO to reccomend using clinical staging to decide whether or
not a patient should be initiated on ART. However, clinical staging does not always correspond to the
degree of immunosuppression. Several challenges account for the lack of wider use of CD4 cell counts,
even at central laboratories: (1) the high cost of flow cytometry, which is considered the reference method
of CD4 cell counting; (2) a lack of skilled laboratory staff; (3) the inability to maintain machines; (4) diffi-
culties in managing the supply of reagents; (5) a lack of reliable point-of-care and easy-to-use machines;
and (6) a lack of adequate quality assurance schemes to ensure reliable results. In order to address these
critical challenges, simplified non-flow-cytometric CD4 cell counting methods are being developed.

In each country, once rapid tests have been deployed, appropriate external quality assurance
measures are implemented. These consist of regular site visits, proficiency testing, and the retesting
of a small percentage of samples at reference or referral laboratories. However, having enough
trained personnel dedicated to site visits to review on-site testing where voluntary counseling and
testing (VCT), provider initiative testing, prevention of mother-to-child transmission (PMTCT),
and other programs are offered has been challenging in many countries. In addition, most countries
lack the capacity to develop a well-characterized panel for use in proficiency testing to monitor the
quality and performance of rapid tests at peripheral and district laboratories. The traditional practice
of retesting 5% to 10% of samples has not proven practical due to the large numbers of samples cur-
cently being tested. For instance, retesting 10% of two million samples in a given country can be very
taxing. In some settings, samples have been effec-
tively collected from district and peripheral labora-
tories and then retested. However, the results have
not been returned on time (or at all), thus prevent-
ing the tests from serving their intended purpose.
This is particularly crucial as many new rapid tests
are initially evaluated and approved in laboratories
Development (USAID) have developed a global panel of blood units that are being used to system-
atically evaluate the quality of rapid tests for use in all PEPFAR-supported countries. Second, the CDC
is working with WHO AFRO and other partners to implement postmarket surveillance to monitor
the performance of rapid tests once they are in use in the field and to evaluate lot-to-lot consistency.
This effort is aimed at ensuring that the quality and integrity of rapid tests are maintained at all times
as new lots of tests are released. Third, WHO, the
CDC, and USAID have developed a comprehen-
sive training package that provides guidance for
the deployment of HIV rapid tests in the field.

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ing the tests from serving their intended purpose.
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are initially evaluated and approved in laboratories
Whether viral load testing will become widely available in developing countries in the coming years depends on the cost and complexity of the test. The WHO 2006 guidelines state that viral load testing may have a role in identifying failure and indicating when to switch medications in some patients. In addition, WHO supports wider access to viral load testing at tertiary laboratories. To fully address the issue of viral load testing to support the roll-out of treatment programs, cheaper and simpler viral assays are urgently needed. Until then, most treatments in developing countries will continue to be based on an invalidated public-health approach, but a continued push to make these and other technologies accessible to developing countries is necessary.

Some key partners and a number of well-known AIDS clinicians have argued strongly for the inclusion of viral load testing in the treatment of HIV patients in developing countries. However, in their present format, viral load tests cannot be deployed on a large scale in developing countries, especially at point-of-care sites. These assays must be performed by technicians well trained in virologic testing methods and require that venous blood be obtained, processed, and transported while frozen to the testing laboratory, with a turnaround time of eight hours. They also require a steady supply of electricity and large amounts of distilled water to run equipment that is usually very costly.

There is a consensus in the field that a suitable point-of-care viral load test should require no more than a finger stick of blood, with a single cartridge for testing and capturing results. The test should not require specimen refrigeration and the equipment should be able to run on batteries, with a cost of less than US$500 to $1,000 per instrument and US$5 to $7 per test. Results should be provided within two hours, and a health worker in the field with limited training should
be able to administer the test. Other options include blood draws and stable transport to referral laboratories where testing would not require the current level of sample integrity.

In order to meet the above requirements, it is conceivable that the way forward could be to develop a semi-quantitative test that would indicate the presence of a significant viral load over a certain threshold based on the intensity of a single test line. With this in mind, Dineva and colleagues have developed a prototype test that is based on a dipstick approach, which seems to produce viral load results as efficient as the complex, expensive, and instrument-dependent standard assays. However, such prototype tests require extensive validation before they can be used for clinical monitoring of patients.

**Assays for Toxicity in ART**

One of the causes of treatment interruption and subsequent failure among patients receiving ART is the acute and long-term toxicity that many of the drugs can cause. The monitoring of patients on treatment for HIV must also include routine clinical chemistry and hematology tests. Unfortunately, this is also a problem for many health facilities in resource-constrained countries, as very few laboratories are equipped to perform these assays. Guidelines are needed to establish the minimum tests that are required for the proper monitoring of toxicities. Again, the ideal situation for peripheral clinics in resource-constrained settings would be a strip-based assay that would allow simultaneous measurement on one strip for all the necessary tests for ART toxicities monitoring. Such an assay would work on whole blood and be electricity independent. This would be conceptually easier than developing simple solutions for CD4 and viral load testing, as most of these assays already exist in various formats on strips or are amenable to such a format.

**Resistance Testing and ART Treatment Programs in Developing Countries**

Because of the high cost and complexity of the HIV-drug-resistance assays, most developing countries lack the capacity to perform reliable testing for drug resistance. For example, in sub-Saharan Africa, drug-resistance testing capacity exists in only a few countries, including Cameroon, Côte d'Ivoire, Ethiopia, Kenya, and Senegal. As a consequence, it was clear at the start of the recent scale-up of ART programs that resistance testing would not be included as part of the laboratory test for monitoring patients on ART. Instead, what was implemented was monitoring HIV drug resistance at the population level and developing approaches to reduce its emergence and spread.

When WHO launched the “3 by 5” initiative in 2005 to expand access to treatment in developing countries, many critics were concerned that the large-scale use of ART drugs would lead to the occurrence of a drug-resistant HIV epidemic if the antiretroviral (ARV) drugs were not used appropriately. The impact of drug resistance on treatment programs can be enormous, as the transmission of resistant strains can lead to the need to develop new anti-HIV drugs and result in increased direct and indirect health costs. Thus, drug-resistant HIV strains have been recognized as a serious threat to the efficacy of current and future HIV treatment, although it is not clear how rapidly resistant strains will develop.

In countries where ART drugs have been used for many years, the prevalence of resistance among treatment-naïve subjects in several studies varied from 5% to 30%. A study carried out in Boston in 1999 showed a prevalence of resistance mutations of 18% in treatment-naïve HIV-positive people. More recently, a study conducted in Nigeria suggested that up to 17% of drug-naïve individuals carry viruses harboring drug-resistance mutations. Data from several European countries indicate that 10% of untreated HIV-positive patients had a drug-resistant virus. In sub-Saharan
Africa, the prevalence of drug resistance in treated populations has been comparable to that reported in Europe and the United States.23-25

Several major HIV-related public-health issues are being addressed by WHO, including the level of resistance to ART among prevalent HIV strains, changes in HIV-drug-resistance prevalence over time in different areas, and how adherence-enhancing interventions can slow the emergence of resistant HIV strains.26 WHO and its partners have laid emphasis on understanding the key determinants of resistance, especially adherence to treatment and factors that undermine it, while identifying ways to minimize the occurrence, evolution, and spread of drug resistance and providing information to international and country-level policymakers. WHO and PEPFAR are actively involved in the development and implementation of surveillance systems at national and regional levels. These joint efforts aim to measure HIV-drug-resistance prevalence among newly diagnosed and treatment-naive subjects. Monitoring systems are also being developed and implemented to measure HIV-drug-resistance prevalence among those treated. As part of its support for PEPFAR and WHO, the CDC is currently helping several countries conduct their threshold surveys, including Côte d’Ivoire, Kenya, Malawi, Namibia, Nigeria, Swaziland, Tanzania, Uganda, and Zimbabwe. WHO is establishing and strengthening a global network of experts and laboratories involved in HIV resistance testing and supporting technology transfer in resource-limited settings.

Several ongoing public-private partnerships are also addressing the issue of drug resistance in developing countries. For instance, Virco, a European pharmaceutical company, is actively involved in developing easy-to-use drug-resistance assays that can be deployed in sub-Saharan Africa. This company is a key commercial partner in an exclusive public-private partnership called Affordable Resistance Test for Africa (ARTA), which will receive a grant from the Dutch Ministry of Development Cooperation for the purposes of HIV-drug-resistance technology transfer.

**Early Infant Diagnosis**

Although WHO estimates that approximately two million HIV-positive people are currently receiving ART in developing countries,27 relatively few infants have received ART. As of 2007, the United Nations Children’s Fund (UNICEF) estimates that the percentage of infected infants in need of ART but currently not receiving it varies from 0.4% in Congo to 18.3% in South Africa.28 Determining the HIV status of infants has proven to be one of the most challenging aspects of PMTCT programs in developing countries. Clinical diagnosis is limited to identifying HIV-positive infants with symptomatic and/or advanced-stage disease and has a low predictive value for ruling out HIV infection in children who are asymptomatic but immunocompromised and in need of PI prophylaxis.29 Infants of HIV-positive mothers acquire HIV antibodies transplacentally and test positive for the presence of antibodies regardless of their actual HIV status. This transplacental transfer of HIV antibodies makes laboratory diagnosis of HIV infection in infants very complex. However, as maternal antibodies decay over time, most uninfected infants become HIV antibody negative by 12 months, and all are negative by 18 months. Thus, before 18 months, virologic tests are the only reliable means of detecting the HIV infection status of infants.29 Nearly 50% of HIV-infected infants under the age of two die before they can be diagnosed and effectively treated.29

Because of the lack of virologic tests in developing countries, access to accurate and timely diagnosis of infants has been a great challenge to the scaling up of early lifesaving pediatric treatment. Virologic tests are expensive and require more sophisticated laboratory facilities. Ensuring the accuracy of these tests for purposes of quality control and assurance...
is also expensive. More importantly, laboratory technicians specializing in virologic or molecular diagnosis techniques are in short supply in many resource-limited countries. Adequately trained technicians may have high turnover rates, as they are often sought by researchers and by other countries struggling to expand their capabilities.

Other challenges also exist. Phlebotomy of young infants requires supplies and skilled staff that are often unavailable outside large cities. Transport difficulties and distances make it impossible for whole blood samples to reach high-level laboratories in time and in good enough condition for accurate testing. Because of difficulties in returning results quickly to distant clinical sites, staff and mothers may lose confidence in a test and thus reduce its acceptability, while allowing results to go unclaimed. Despite the challenges, however, recent success has been realized using dried blood spot (DBS) nucleic acid polymerase chain reaction (PCR) testing.

**HIV DNA PCR and p24 Testing**

WHO recommends using HIV DNA PCR testing to diagnose perinatal HIV infection in exposed infants at their first immunization visit at six weeks after delivery. Although several commercial and home-brew methods for DNA PCR testing exist worldwide, the Roche Amplicor HIV-1 DNA test, version 1.5, has been shown to be highly accurate in detecting the multitudes of HIV subtypes that circulate in Africa and is currently being used in many programs across the continent.\(^{30-32}\)

The ultrasensitive p24Ag assay has been used by some groups for early diagnosis of HIV in infants as an alternative to DNA PCR testing. This quantitative assay is based on simpler technology that does not require the detection of the viral genome. Although some studies have shown a sensitivity and specificity comparable to that of HIV DNA PCR, the assay is not yet widely used because more validated studies are needed on its performance in different settings with different subtypes. In a recent study, false-negative DBS p24 results were associated with subtype D; the performance of DBS PCR was 84% for DBS p24 testing, 79% for DBS DNA PCR testing, 85% for plasma p24 testing, and 100% for plasma RNA testing.\(^{33}\)

Easy-to-use point-of-care virologic technologies are needed to support early infant diagnosis in resource-poor countries.

**Improved Early Infant Diagnosis Due to DBS Use**

DBS use has facilitated access to virologic diagnosis of HIV. Once the blood spots are thoroughly dried and stored with desiccant, nucleic acids in DBSs can be stable for several months at ambient temperatures. This feature of DBSs makes them ideal for transporting specimens from remote rural sites to a central or regional testing laboratory, thus allowing the creation of laboratory networks for early infant diagnosis. Although specimen transport remains challenging, networks of DBS PCR testing laboratories have been established in several countries, some based on the use of volunteers to transport DBS specimens to the nearest PCR testing facility. For instance, a strong laboratory network for DBS DNA PCR testing has been set up in Kenya. In Nyanza Province in western Kenya, 140 DBS collecting sites transport about 500 to 800 samples per month to the CDC-Kenya Medical Research Institute (KEMRI) laboratory in Kisumu for testing. The turnaround time for the KEMRI laboratory to return results to the collection site is two weeks. Similarly, the KEMRI laboratories in Nairobi provide PCR testing support to 37 sites in Central Province, while the Walter Reed Laboratory in Kericho serves 18 sites in Rift Valley Province (C. Zeh et al, 2006, personal communication). In Namibia, DBS PCR testing has resulted in a significant increase in the number of children diagnosed and placed on ART. With the support of PEPFAR, DBS PCR testing has been expanded to several countries within the last three years (Figure 1).
Several challenges still exist with regard to DBS use for early infant diagnosis. As programs expand, one obstacle has been the procurement and distribution of supplies for DBS collection. To meet scale-up needs and ensure consistency, it would be useful to distribute kits containing all the necessary supplies to health facilities. The precise contents of each kit for use in infant diagnosis or quality control of HIV testing would need to be determined individually for each country. Another challenge is the variety of DBS formats, some of which do not work properly. For DBS PCR testing laboratory networks to be effective, the relevant health-care staff must receive specific training in the collection, labeling, drying, and packaging of blood spots to ensure the quality of specimens for virologic diagnosis. Upon receipt at the testing laboratory, specimens must be evaluated by an experienced technologist using SOPs for rejection of samples. If more than 2% of specimens are unsatisfactory, staff at the site should be retrained in collection procedures.

Note: The Caribbean not shown on map

Figure 1. Expanding HIV-1 DBS-based early infant diagnosis in PEPFAR countries
away with the need for drying racks and separating paper. Because of this variety, it is often difficult for country program managers to determine which formats are appropriate for use. Most countries are currently using the Schleicher and Schuell (S&S) 903 specimen collection paper (Whatman) for DBS collection. An acceptable alternative to S&S 903 paper is Whatman FTA paper. High-volume laboratories may encounter difficulties in testing DBS specimens because extracting DNA from a DBS is labor-intensive and prone to cross-contamination. Further work in automating DBS punching and DNA extraction rather than replicating workstations is needed when testing large volumes of specimens, but with perseverance these programs can be very successful. Approximately 100,000 infants have been tested in the past 12 months and referred for appropriate treatment.

Setting Up Appropriate Quality Assurance Programs and the Need for Laboratory Accreditation

As indicated above, HIV prevention, care, and treatment programs have expanded very rapidly. However, laboratory infrastructure is still lagging behind in terms of the critical components of a quality management system (QMS), which is essential to the improvement of overall laboratory diagnostic services and provides a blueprint for sustainable quality testing. The basic concepts of a QMS must be implemented at all levels of the laboratory pyramid, including quality assurance for the testing process: (1) the pre-analytic phase, which involves competency of personnel, test selection, patient/client preparation, test requisition, correct labeling, transport of specimens, and safety; (2) the analytic phase, which includes specimen processing and storage, reagent preparation, preventive maintenance, quality control, method verification, test performance, proficiency testing, and safety; and (3) the post-analytic phase, which includes reviewing results and quality control, reporting test results and interpretation, and record keeping. In many developing countries, none of these three phases is being properly implemented. To implement an effective QMS, the country must have a laboratory policy that defines the needs and importance of accurate laboratory results. This remains a major limitation and is a gap that must be bridged as programs are scaled up in most developing countries.

In order to ensure that the current increase in resources leads to a significant improvement in laboratory services, standards-based strategies must be adopted in developing countries. This can best be achieved by making laboratory accreditation a critical element of the national laboratory policy and strategy. In sub-Saharan Africa, for example, the few laboratories in Ethiopia, Kenya, and Uganda that are accredited all use external bodies for accreditation and are supported mostly by externally funded research institutions. A standards-based strategy must include the continuing competency of testing personnel, quality management principles, routine audits of laboratory performance, and the customization of international standards that are applicable in-country. Each country could develop strategies and policies for accreditation of laboratories at all levels of the health system and create linkages with regional accreditation bodies that already exist or that could be set up and given the mandate to design regional accreditation schemes. Regional accreditation bodies could be set up along the lines of the existing regional economic communities in Africa, such as the East African Community (EAC), the Economic Community of West African States (ECOWAS), the Economic Community of Central African States (ECCAS), and the Southern African Development Community (SADC).
SANAS is recognized by the South African government as the sole national accreditation body giving formal recognition to laboratories. It is also recognized by the International Organization for Standardization (ISO), the international standard-setting body composed of representatives from various national standards organizations.

As an independent institution, SANAS is capable of evaluating laboratories with regard to their compliance with relevant international and national standards and assessing their competence to perform the tasks defined in their scope of duties. The accredited institutions’ tests, inspection reports, and certificates are recognized by other countries whose national accreditation bodies have reached mutual recognition agreements with SANAS. SANAS is currently represented on the major committees in the accreditation field and also participates in the assessments of other national and regional accreditation bodies. These linkages provide assurance that the rules applied to the SANAS-accredited system are as rigorous as those applied to other accredited organizations around the world. Because most countries in Africa cannot currently afford their own independent accreditation systems, a regional approach, such as the recently adopted WHO AFRO laboratory accreditation scheme, is likely the best strategy. In parallel, with international support, each country is assisted by implementation partners to strengthen its own accreditation body. In brief, laboratory accreditation should form the backbone of sustainable quality management systems.

Supply Management and Equipment Maintenance

In developing countries, it has been a challenge to ensure consistent supply and provision of laboratory commodities to meet the demand created by the rapid scale-up of programs. The timely availability of essential equipment, supplies, and reagents is critical to ensure the overall quality of laboratory testing and avoid disruptions in patient care. A system for the dependable and sustainable acquisition of high-quality reagents and supplies is urgently needed. When PEPFAR was created, USAID established a supply chain management system (SCMS) in order to standardize the procurement and distribution of laboratory commodities to support all PEPFAR countries. Moreover, WHO, the World Bank, GFATM, PEPFAR, the Bill & Melinda Gates Foundation, various countries’ ministries of health, and other stakeholders are working to build consensus on the best way to standardize laboratory commodities across programs and laboratory networks. Standardization of laboratory commodities offers a unique opportunity to coordinate the maintenance of equipment, bulk purchases, training on common instrumentation, and contract services mechanisms. Special attention must be paid to training service maintenance engineers in order to provide a network of biomedical engineers at all levels of the laboratory system. Critical to this aspect is the development of a national laboratory strategic plan that specifies the policies that govern laboratories at each level of a tiered system.
Laboratory Diagnosis of TB and OIs

TB accounts for about two million deaths each year, most of which occur in developing countries and are associated with HIV coinfection. Accurate laboratory diagnosis of TB is a challenge in developing countries for several reasons: a lack of trained personnel, inappropriate laboratory working environments, weak or nonexistent external quality assurance measures, a lack of referral systems for patient samples, a limited number of state-of-the-art laboratories to culture and perform drug susceptibility testing, and the creation of stand-alone silo laboratories. In fact, there are only two WHO supranational laboratories in Africa (one in South Africa and the other in Algeria). TB is the most common OI in HIV-positive people, and in some developing countries up to 40% of TB patients are living with HIV. Therefore, the need for accurate diagnosis of TB has become critical, especially as ART is being scaled up. Reports have shown that up to 40% of TB patients who are HIV-positive have smear-negative results. Moreover, in view of recent reports of extremely drug-resistant TB in South Africa, there has been an increased emphasis on strengthening laboratory capacity to diagnose TB in HIV-positive patients and on TB culture. Paradoxically, TB laboratories are some of the most neglected and understaffed laboratories in developing countries. However, some major programs such as PEPFAR have placed substantial emphasis on strengthening laboratory capacity to perform TB diagnosis in the context of HIV/AIDS care and treatment. As part of this PEPFAR effort, a regional integrated training laboratory center for HIV, OIs, and TB has been established by PEPFAR in Johannesburg in partnership with the leadership of the South African National Institute of Communicable Diseases (NICD). The NICD training facility will provide hands-on training for laboratory experts in all aspects of TB diagnostics, including smear microscopy, setting up EQA programs, specimen transportation, culture, and drug susceptibility testing. Moreover, this facility will provide integrated laboratory training to meet the needs of HIV, TB, malaria, and OI prevention, care, and treatment programs. Similar PEPFAR partnerships are being developed in other parts of sub-Saharan Africa. Challenges not specific to developing countries, but certainly more acute in resource-limited settings, remain for the diagnosis of TB in infants and young children, largely due to the difficulty of obtaining good sputum specimens from this age group.

Laboratory Information and Management Systems

As programs scale up rapidly, the implementation of laboratory information and management system (LIMS) technologies has become another major challenge. A LIMS is an integral part of a QMS and includes developing simple-to-use systems that allow for the tracking of samples at collection sites during testing and during delivery of the final results to the patients, and the archiving of leftover specimens. All of the above processes may occur in the same local laboratory, or it may be necessary for specimens to be transported across the laboratory pyramid in a network system to a reference laboratory for testing. Regardless of what approach is used, a well-defined laboratory system is needed to ensure proper specimen handling and efficient results reporting.

Because of the difficulties in implementing electronic software at all levels of the laboratory network, standardized, paper-based systems are needed at different levels of the laboratory pyramid in developing countries. In practice, source documents are too often handwritten pieces of paper or books that are sometimes retranscribed several times before reaching a patient or the clinical personnel providing care. This process creates many opportunities for error and resultant losses. In addition, accurate compilation of data for laboratory organization (such as assessment of needs) and for programmatic purposes is difficult.
Modern LIMS technologies have the potential to significantly improve data sharing across tiered laboratory networks in developing countries and to provide timely results at point-of-care facilities. Such technologies should be coordinated and supported—from the national public-health laboratory network to the peripheral laboratories. If such systems are implemented, they will not only improve the quality of clinical laboratory diagnosis but will strengthen the capability to provide epidemic alert and response by recording and analyzing essential laboratory data, maintaining and sharing the data in the laboratory network system in a standardized format, and facilitating frequent exchanges of information and surveillance data with other laboratories within the network and between countries. It will also facilitate a timely flow of information in the laboratory network, which will help inform policy- and decision-making authorities.

In the absence of a LIMS, a computerized system for the management of data, with entry performed directly from source documents, is highly desirable.

**Infrastructure**

In many developing countries, health facilities and laboratories in particular have significant infrastructural challenges. It is common to see facilities with minimal physical infrastructure, with even the physical building being inadequate for the needs of the laboratory. Moreover, laboratories, when they exist, are often in a degraded state. Significant investment in laboratory infrastructure development is desirable in these situations. This requires a concerted effort by government and external donors, preferably within a strategic plan. The chronic lack of clean running water and a stable power supply is an additional challenge that must be tackled while establishing adequate laboratory services and strengthening laboratory networks. Current infrastructure in most facilities also does not allow the development of adequate biosafety procedures in the laboratory and the health facility in general. The lack of proper waste management systems is a crucial problem encountered in many health facilities, where laboratory waste is often disposed of inappropriately, exposing patients, health workers, and the community at large to possibly dangerous infectious waste.

**Laboratory Automation**

Related to data management, it is also important to pay particular attention to the role of automated instruments in laboratory practices. Although the initial cost is high, these instruments often offer considerable reagent savings and allow laboratories to perform a much larger number of tests more reliably. As noted before, this is a more efficient and cost-effective approach than multiplying the number of workstations. The integration of these instruments in a LIMS is easier and increases the reliability of results by reducing human error, both in the performance of the assay and in the transcription of results. Unfortunately, equipment costs, maintenance issues, and operational problems limit the number of laboratories where these systems are feasible. Linking together LIMSs with regional laboratory automated systems enhances the quality of testing.

**The Way Forward for the Development of Sustainable and Quality Laboratory Capacity**

**Strengthening Sustainable Laboratory Health Systems through National Strategic Plans with Integration of Diseases in Mind**

We believe that to achieve the goal of sustainable laboratory infrastructure and services in developing countries, a well-thought-out and implementable national laboratory strategic plan is indispensable. A well-developed laboratory strategic plan should consider integrating the laboratory work required for at least the three major epidemic diseases: HIV/AIDS,
TB, and malaria, such that a laboratory at every layer of the health system can provide timely support for the accurate and reliable diagnosis, monitoring, and surveillance of these diseases, as well as a central national public-health reference laboratory.

Each strategic laboratory plan should address the specific situation of the country and the needs that must be met in order to support health programs and promote in-country capacity building. The plan would provide a platform for coordinating the efforts of all implementing partners and create a framework for advocacy and partnerships at the country level. Such a plan should be based on an integrated approach to laboratory infrastructure development that comprehensively tackles major diseases of public-health importance, such as TB, HIV/AIDS, and malaria. In addition, the plan should be based on a tiered laboratory network, with a strong role for a functional national public-health reference laboratory that is well linked to regional and district laboratory systems, so as to provide effective referral services. The plan should, however, make the effort to take into account and integrate the existing facilities that have been developed prior to the drafting of the plan, so as not to waste resources and the opportunities provided by these facilities. As outlined in Figure 2, the essential elements of an adequate national strategic

Figure 2. Cross-cutting elements for strengthening integrated tiered laboratory systems for HIV, malaria, and TB
labatory plan for an integrated, tiered network
include, but are not limited to, the following:
1. **Integration of laboratory needs for TB, HIV, OIs, and malaria, including diagnosis, treatment, and prevention.** Emphasis should be placed on strengthening laboratory health-care systems that can be used to respond to major infectious diseases of public-health importance. In fact, the current major drivers of disease burden in developing countries are HIV, TB, and malaria; therefore, laboratory capacity developed to address these diseases could invariably be used to fight other disease outbreaks. This approach would shift emphasis away from developing disease-specific laboratories (which are very often difficult to sustain due to a lack of adequate human resources) in favor of an integrated, tiered approach. Such an integrated approach would also allow for cross-training of laboratory staff and provide a unifying approach for EQA and task shifting.

2. **Definition of training needs and retention approaches.** This should include a well-laid plan for training, with strategic imperatives on preservice, service, and laboratory management adapted for the different laboratory system tiers. Retention strategies should include innovative approaches to improve laboratory-based jobs.

3. **Standards and policies for quality of laboratory services.** These include guidelines for certification and accreditation of laboratory personnel and services that address issues such as who is allowed to perform testing and at what level of laboratory tests should be performed, as well as guidelines on new technologies and their use in programs.

4. **Issues surrounding supply chain management.** These include standardization of laboratory commodities and equipment, as well as problems related to the cold chain and maintenance of equipment.

5. **Issues relating to laboratory safety and security.**

6. **A clear framework for working with all funding partners to avoid duplication and parallelism of efforts.**

### Developing Laboratory Capacity through Tiered Laboratory Network Systems

Strengthening tiered laboratory networks in developing countries is critical to meet program goals. HIV laboratory services should be integrated into general laboratory services (see Figure 3), which is not currently the case in many countries. Often HIV laboratories are either physically separated from routine laboratory services and/or use separate equipment and reagents.

### Developing Sustainable Laboratory Capacity by Leveraging Effective Partnerships and Coordination

Since 2002, multiple institutions and bilateral and multilateral programs have continued to provide generous funding to support programs and laboratory services in developing countries. However, generosity may be a burden if it is not well coordinated and managed by capable leadership. In most African countries, it is common for the World Bank, WHO, PEPFAR, the Clinton Foundation, GFATM, and private companies to work with the ministries of health to support laboratory capacity strengthening. If well managed through a national strategic laboratory plan and with coordination at the level of the funding bodies, this support can significantly strengthen laboratory capacity in a sustainable way.

Public-private partnerships could be established between funding bodies and private companies so as to allow them to develop low-cost, accurate, and rapid diagnostic tests that can be used at point-of-care sites to provide same-day results to patients. By eliminating the need for patients to make
multiple clinic visits, such tests would significantly improve the ability of patients to be monitored.

An example of leveraging resources is the effective partnership PEPFAR has established through the CDC Global AIDS Program together with four large not-for-profit medical societies that pursue exclusively educational, scientific, and charitable activities: the Association of Public Health Laboratories (APHL), the American Society for Clinical Pathology (ASCP), the American Society for Microbiology (ASM), and the Clinical and Laboratory Standards Institute (CLSI).

APHL provides consultations by senior laboratory professionals who direct or supervise public-health laboratories in the United States. The team members typically have 15 to 20 years of experience in quality laboratory system practice. APHL has the longest-standing laboratory cooperative agreement and is active in Angola, Botswana, Côte d’Ivoire, the Democratic Republic of the Congo, Ethiopia, Haiti, Kenya, Madagascar, Malawi, Mozambique, Namibia, Rwanda, Tanzania, Vietnam, and Zimbabwe. The association has taken on a variety of responsibilities and roles in these countries, but its primary efforts have been in national strategic planning, improvement of the infrastructure for laboratory referral networks, laboratory management training, and laboratory information systems. APHL has established links between state public-health laboratories and in-country services and fostered the training of senior staff as well as the development of local public-health laboratory associations. It has provided regional and country-specific management training to senior laboratory personnel in Ethiopia, Kenya, Namibia, and Zimbabwe, with an emphasis on quality systems management practices.

ASCP, which has a membership of more than 129,000 laboratory professionals, is active in Ethiopia, Guyana, Kenya, Lesotho, Swaziland, and Tanzania. It has also been requested to support in-service training activities in Nigeria and Rwanda. The primary focus of its support to countries has been in-service training in clinical hematology and chemistry. The organization has led in the development of a training-of-trainers (TOT) approach.
TIERED LABORATORY NETWORK SYSTEMS: THE EXAMPLE OF RWANDA

RwandA is often cited as an example of a country in Africa with a fairly developed tiered laboratory network system. In collaboration with foreign partners, the government of Rwanda has developed a network of laboratories across health systems in the country for the detection and confirmation of diseases of public-health importance such as HIV, TB, malaria, and other major outbreaks such as cholera. The national laboratory network system ensures that there is a pyramidal structure with a top-down and bottom-up approach. Thus, the NRL and the five university hospital laboratories constitute the first level of laboratory services, the district and private hospitals make up the second level of laboratories, and the third level of laboratories are those at the health centers (the bottom of the pyramid). At each level, there is a defined package of requirements, needs, and capabilities, accompanied by specific SOPs and testing abilities (Table 1). For instance, the NRL assumes responsibility for developing standards and coordinating laboratory activities for the different levels. To standardize the services offered at different levels of laboratories inside the national laboratory network, the NRL has established guidelines that define biomedical laboratory standards related to construction and basic supply requirements (e.g., equipment, reagents, and consumables) at each level of the laboratory pyramid (Table 2). The NRL also performs in-service training for laboratory technicians within the national laboratory network. These training activities are strongly supported by partners. The quality control and quality assurance activities are very well established at the NRL and cut across diseases. Because laboratory capacity for HIV/AIDS, TB, and malaria testing has been strengthened at the NRL and central level, the laboratory is presently armed to support the investigation of other outbreaks in coordination with other district laboratories. To ensure the quality of laboratory testing for HIV, TB, and other diseases, reports are submitted by the district and hospital laboratories to the NRL. Supervision and feedback are provided using a checklist, as applicable to the different levels. The NRL has an elaborate quality assurance program that includes, but is not limited to, HIV serology rapid testing, DNA PCR testing for early infant diagnosis, CD4 counts, and TB and malaria smears. As multiple partners such as GFATM, the World Bank, PEPFAR, and others continue to assist the country, consideration should be given to strengthening the following gaps: the shortage of skilled staff to perform specialized laboratory tests, the need for an improved laboratory information system, the need for creative ways to ensure proper sample referral, inadequate communication facilities, power outages, supply chain management and distribution of reagents and laboratory equipment, and disposal of laboratory waste.
### Table 1. Example of Testing in a Tiered Laboratory System

<table>
<thead>
<tr>
<th>Test</th>
<th>General Hospitals</th>
<th>Rural Hospitals</th>
<th>PMTCT-Only Sites (PMTCT mini-labs)</th>
<th>VCT-Only Sites (VCT mini-labs)</th>
<th>TB/DOTS Sites (TB mini-labs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV serology</td>
<td>Rapid tests as per national algorithm</td>
<td>Rapid tests as per national algorithm</td>
<td>Rapid tests as per national algorithm</td>
<td>Rapid tests as per national algorithm</td>
<td>Rapid tests as per national algorithm</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>CyFlow SL3</td>
<td>CyFlow FL1</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
</tr>
<tr>
<td>PCR/DBS for infant diagnosis</td>
<td>Refer DBS to reference laboratory</td>
<td>Collect samples on-site; transport DBS to GH lab</td>
<td>Collect samples on-site; transport DBS to GH lab</td>
<td>Collect samples on-site; transport DBS to GH lab</td>
<td>Collect samples on-site; transport DBS to GH lab</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Vitros DT 250</td>
<td>Vitros DT 60 II</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
</tr>
<tr>
<td>Hematology</td>
<td>Sysmex KX21 (3 diff)</td>
<td>Sysmex KX21 (3 diff)</td>
<td>On-site HemoCue (Hb estimation only)</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
</tr>
<tr>
<td>TB</td>
<td>Microscopy</td>
<td>Microscopy</td>
<td>Refer patients to HIV clinics at GH or RH or to local DOTS site</td>
<td>Refer patients to HIV clinics at GH or RH or to local DOTS site</td>
<td>Microscopy with AFB</td>
</tr>
<tr>
<td>Syphilis</td>
<td>TPHA, RPR</td>
<td>TPHA, RPR</td>
<td>TPHA, RPR</td>
<td>Refer patients to HIV and/or STI clinics at GH or RH</td>
<td>Refer patients to HIV and/or STI clinics at GH or RH</td>
</tr>
<tr>
<td>OI diagnosis</td>
<td>Microscopy and serology</td>
<td>Microscopy</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
</tr>
<tr>
<td>Parasitology</td>
<td>Microscopy, malaria smear</td>
<td>Microscopy, malaria smear</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Test strip and reader</td>
<td>Strip</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
<td>Refer patients to HIV clinics at GH or RH</td>
</tr>
<tr>
<td>Pregnancy tests</td>
<td>Rapid hCG tests</td>
<td>Rapid hCG tests</td>
<td>Rapid hCG tests</td>
<td>Rapid hCG tests</td>
<td>Refer HIV-positive women to clinics at GH or RH</td>
</tr>
</tbody>
</table>

AFB = acid-fast bacilli; DBS = dried blood spot; DOTS = directly observed therapy, short course; GH = general hospital; Hb = hemoglobin; hCG = human chorionic gonadotropin; OI = opportunistic infection; PCR = polymerase chain reaction; PMTCT = prevention of mother-to-child transmission; RH = rural hospital; RPR = rapid plasma reagin; STI = sexually transmitted infection; TPHA = Treponema pallidum hemagglutination assay; VCT = voluntary counseling and testing.

*Source:* Adapted with permission from the International Center for AIDS Care and Treatment Programs (ICAP), Columbia University, New York.
### Table 2. Examples of Standardization of Laboratory Testing Carried Out at Different Levels of the Laboratory Network in Rwanda

<table>
<thead>
<tr>
<th>Test</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral Laboratories</strong></td>
<td></td>
</tr>
<tr>
<td>Rapid HIV test kits</td>
<td>First Response, Determine, UniGold, Capillus algorithm</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Manual method (hemoglobinometer) and QBC in some large health centers</td>
</tr>
<tr>
<td>TB light microscopy</td>
<td>Kynioun</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>Generic latex with controls</td>
</tr>
<tr>
<td>Total lymphocyte count</td>
<td>Manual hemacytometer / stained differential count</td>
</tr>
<tr>
<td>Malaria / hemoparasite smear / microscopy</td>
<td>Giemsa and Field’s stain to be stocked</td>
</tr>
<tr>
<td>UA dipstick for albumin and glucose</td>
<td>Generic procurement</td>
</tr>
<tr>
<td>Stool / urine microscopy</td>
<td>Manual method</td>
</tr>
<tr>
<td>General “wet preparation” microscopy</td>
<td>Manual method</td>
</tr>
<tr>
<td>Syphilis test</td>
<td>RPR or VDRL methodology</td>
</tr>
<tr>
<td><strong>Intermediate Levels + All Peripheral Tests</strong></td>
<td></td>
</tr>
<tr>
<td>Full blood count</td>
<td>Automated using QBC or Beckman Coulter 5 diff and/or Sysmex (CHK, CHUB, etc.)</td>
</tr>
<tr>
<td>Liver, renal, and pancreas function tests</td>
<td>ALT, creatinine, amylase, TBD by country</td>
</tr>
<tr>
<td>Diagnosis of bacterial, fungal, and parasitic infections</td>
<td>Stool/rectal C&amp;S, urine C&amp;S, blood C&amp;S, pus/wound C&amp;S, aspirate/liquid C&amp;S, cryptococcus (India ink), toxoplasmosis serological tests at referral hospitals (CHUB, CHK, King Faycal, etc.)</td>
</tr>
<tr>
<td>CSF microscopy, including cell count, Gram stain, etc.—critical for diagnosing meningitis</td>
<td>Microscopy</td>
</tr>
<tr>
<td>CD4 test</td>
<td>FACSCount using CD4/CD3 single BD reagent</td>
</tr>
<tr>
<td><strong>Central Level (NRL Kigali)</strong></td>
<td></td>
</tr>
<tr>
<td>Viral load</td>
<td>Amplicor real-time PCR machine</td>
</tr>
<tr>
<td>DNA PCR (EID)</td>
<td>Amplicor HIV DNA (DUO)</td>
</tr>
<tr>
<td>CD4 test</td>
<td>FACSCalibur Tritest using TruCount tubes</td>
</tr>
<tr>
<td>Chemistry tests</td>
<td>Cholesterol, triglycerides, glucose, electrolytes, total protein, urea nitrogen, amylase (Cobas Integra – Roche)</td>
</tr>
<tr>
<td>Diagnosis of opportunistic infections</td>
<td>Automated systems</td>
</tr>
<tr>
<td>Hematology, WBC</td>
<td>Beckman Coulter 5 diff</td>
</tr>
<tr>
<td>HIV-drug-resistance testing</td>
<td>ABI 3100 avant</td>
</tr>
<tr>
<td>TB</td>
<td>Solid culture, DST for treatment-failure patients</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; culture and staining; CSF = cerebrospinal fluid; DST = drug susceptibility testing; NRL = National Reference Laboratory; PCR = polymerase chain reaction; RPR = rapid plasma reagin; TBD = to be determined; UA = urinary albumin; VDRL = venereal disease research laboratory; WBC = white blood cell
to expanding these services from the federal to district levels in Ethiopia, Kenya, and Tanzania. In Lesotho and Swaziland, it has been integrally involved in strategic planning for public-health laboratory services. In Ethiopia, it is partnering with Joint Commission International to establish national standards for laboratory accreditation.

ASM is the oldest and largest single life science organization in the world and the largest publisher of peer-reviewed professional journals. Consultants are chosen for their technical and cultural expertise from among the society’s more than 43,000 active members worldwide. The partners are currently providing technical assistance in the following areas: laboratory networks, laboratory information systems, accreditation, pre- and in-service training, general microbiology, development of protocols, laboratory management, chemistry and hematology, and quality assurance. ASM is actively supporting programs in Côte d’Ivoire, Kenya, Mozambique, Namibia, Nigeria, Zambia, and Zimbabwe. Its primary focus to date has centered on the enhancement of services for TB and other OIs. In this capacity, the organization is working closely with the ministries of health, WHO, and in-country implementing partners. Its activities include in-service training and infrastructure support for basic microscopy, TB culture and resistance testing, and assistance to countries in strategic planning for laboratory services. In Zimbabwe, ASM is also working with the ministry of health to standardize clinical microbiology protocols on a national scale and expand quality assurance measures at all levels. Work in Kenya, Namibia, and Zambia was initiated during the first year of the cooperative agreement, and activities in Côte d’Ivoire, Mozambique, Nigeria, and Zimbabwe were initiated this year.

CLSI, which writes and distributes guidelines for best practices in the field of medical laboratory testing, is the convener of the ISO’s 52-national-member committee on medical laboratory standards. CLSI has been active in Tanzania and Zimbabwe and has recently started to work in Ethiopia and Nigeria. CLSI is working with countries to align national practices with the ISO’s international standards for laboratory accreditation. In this capacity, the organization is participating in workshops to develop SOPs and train laboratory staff in the documentation of these procedures to be maintained in laboratories. It will continue these activities in both Ethiopia and Nigeria. CLSI is also working with ASCP and Joint Commission International to promote clinical laboratory accreditation by developing a stepwise approach for aligning laboratory standards with ISO guidelines at all service levels in resource-poor settings. This effort is focused on identifying specific steps that can be taken in training, record keeping, specimen handling, and laboratory management at each service tier that will facilitate progress toward accreditation and establish national norms.

Collaborations are also in place with WHO Geneva, WHO AFRO, and the Clinton Foundation. These strong partnerships have led to joint laboratory guidance, including the following:

- Guidelines for Appropriate Evaluations of HIV Testing Technologies in Africa
- Guidelines for Using HIV Testing Technologies in Surveillance
- Guidelines for Assuring the Accuracy and Reliability of HIV Rapid Testing
- Manual for the Laboratory Identification and Antimicrobial Susceptibility Testing of Bacterial Pathogens of Public Health Importance in the Developing World
- A comprehensive training package for HIV rapid testing

PEPFAR also maintains close collaboration with the Clinton Foundation and WHO AFRO to develop guidance on facility-based laboratory management and safe laboratory practices.
Advocacy for Laboratory Experts in Policymaking and Program Planning

Strengthening laboratory medicine in developing countries must be seen as an integral and critical step toward improving overall health-care systems. To achieve this goal, laboratory leaders should be trained and laboratory departments should be created within the ministries of health in developing countries and supported with defined budgets. Strong leadership within the ministries of health will ensure that laboratories do not remain an afterthought in the process of strengthening health systems. Another area that needs much attention is greater laboratory involvement early in the planning stage of program design. Often, laboratory input is sought only after program managers’ planning is quite advanced or near the execution of activities. In addition, due to the complexity and specificity of laboratory activities, infrastructure development, equipment installation, training, and initiation of operations generally require more time than many other aspects of a program. This usually leaves the laboratory lagging behind other components of the program and limits its ability to provide useful insights and contributions.

CONCLUSION

With increased resources to fight HIV/AIDS and related diseases, laboratories in developing countries are now faced with an opportunity. We can collectively take advantage of the increased resources currently available for global health to expand programs and strengthen laboratory services. A coordinated approach using a national strategic laboratory plan could provide a vehicle for meeting this goal, which would contribute significantly to the development of overall health systems. While directly facilitating the prevention, care, and treatment of HIV disease, better-quality laboratories that are developed to support the roll-out of HIV/AIDS programs can also be important in the fight against other emerging or reemerging infectious diseases and would provide future capacity to support clinical trials for HIV/AIDS, TB, and malaria programs. The increase in resources may present a challenge if efforts are not coordinated, resulting in the emergence of parallel laboratory systems that may lead to the collapse of fragile national laboratory systems and undermine the goal of sustainability. Moreover, if the quality of laboratory services is not improved as quickly as possible, program managers may not see the usefulness of laboratory testing in the overall arsenal of global health protection measures. The key to achieving a sustainable laboratory-strengthening effort is for each country to develop a national laboratory plan that integrates the testing required for the prevention and treatment of all diseases of major public-health importance. Such a national plan will help donors and implementing partners identify where and how to support the ministry of health’s laboratory goals.
REFERENCE LIST


LABORATORY INITIATIVES THAT support the prevention and treatment of HIV and associated opportunistic infections are a critical component of any successful national response. Despite this fact, laboratory activities are generally not assigned the same priority as clinical site development.1 Historically, little emphasis or investment has been put forth for laboratory capacity development2-4 and the importance of laboratory diagnosis is often underestimated by clinicians and other decision makers. For instance, numerous examples can be found in the literature where the clinical diagnosis for a common infectious disease is not sufficiently sensitive or specific.5 More recently, organizations such as the Centers for Disease Control and Prevention (CDC), under the Global AIDS Program (GAP), have assisted resource-limited countries in developing laboratory capacity and infrastructure.6 Yet these improvement efforts are complicated by the fact that laboratories in Africa are increasingly being used to support internationally initiated clinical research trials for HIV prevention and vaccine development.7

Although substantial variation exists within and between countries, the overriding feature of laboratory programs in sub-Saharan Africa is a general lack of resources, including funding, facilities, equipment, and skilled staff.12 Due to the significant differences in laboratory capacity among different countries and between regions within a single country, a universal laboratory solution is not feasible; approaches need to be tailored to the region and the local disease epidemiology.8,9

Few laboratory services within African countries are coordinated under a single regulatory authority. One exception is South Africa, where the National Health Laboratory Service (NHLS)4 coordinates all laboratory activities within the public sector and the South African National Accreditation System (SANAS)5 has been appointed to ensure certification of laboratories according to internationally and nationally accepted “good laboratory practice” standards. Unlike countries such as the United States, where clinical testing is conducted in highly regulated environments according to Clinical Laboratory Improvement Amendments (CLIA) guidelines7

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(using only assays approved by the Food and Drug Administration [FDA]), clinical testing in developing countries is often unregulated. Additional challenges arise from the fact that many laboratories within the African region are established by external funding agencies, often with little coordination between different funding organizations. This results in significant duplication in a region where consolidation of resources may be far more practical.

This chapter presents the accumulated experiences of a core laboratory support group established in Johannesburg, South Africa, to assist laboratories in embarking on HIV treatment initiatives, the evaluation of HIV vaccine candidates (funded by the International AIDS Vaccine Initiative [IAVI]), and clinical research efforts (such as those sponsored by the Bill & Melinda Gates Foundation, CDC, and the Microbicide Development Program). This support group has provided input for the development of laboratory quality systems in Rwanda, Kenya, Botswana, Malawi, Zambia, Uganda, and Tanzania, with approximately 45 centers being supported from the group’s base in Johannesburg. Activities conducted to date have included site assessments, delivery of specific laboratory training programs, design of laboratory space, facilitation of equipment procurement, provision of external quality assurance (EQA) programs, cross-validation studies, method validation, and reviews of relevant standard operating procedures (SOPs). The detailed approach used by the group to set up one or more laboratories is depicted in Figure 1.

ASSAY SELECTION

The repertoire of tests that may be needed in the course of implementing an HIV clinical program can include a combination of the following:

1. HIV diagnosis for infants and adults,
2. Safety testing in the form of chemistry and hematology,
3. CD4 testing for treatment initiation and monitoring,
4. Hepatitis B screening,
5. Viral load testing (considered optional in many programs),
6. Reference testing (e.g., genotyping, which is used for resistance surveillance in developing countries), and
7. Diagnosis of opportunistic infections (with an emphasis on TB diagnosis). 

(Note: A discussion on the development of laboratories for specialized clinical trials, such as vaccine trials, can be found in a 2007 publication by IAVI.)

Ongoing research and development (R&D) needs to be fostered to ensure that laboratory assays to support HIV prevention and treatment initiatives are made affordable and accessible. Such R&D includes novel assay and instrument design, as well as the development of innovative, more affordable diagnostic algorithms and improvements in specimen collection and transport.

SITE NEEDS ASSESSMENT

Site visits are essential to gain an understanding of the region and clinical environment in which the laboratory program will be implemented. At the first visit, the scope of the project is determined (i.e., whether one or more laboratories are needed to serve the needs of a given area). The needs assessment should include a thorough evaluation of population demographics, the local prevalence of HIV and/or other important diseases, and the geography of the local terrain. The political environment, local health-care hierarchy, and mandates of funding agencies also need to be carefully considered. Assessment of the individual laboratory should include a detailed inventory of existing facilities, equipment, technical skills, supplier networks, safety concerns, and waste disposal facilities. Power and

*CLIA guidelines are available at http://www.fda.gov/cdrh/clia.
Figure 1. Proposed approach to the establishment of a new laboratory / laboratory service in African settings
water supplies should also be investigated, since they are frequently erratic in these regions. It is important to assess the current laboratory workload to ensure that any additional sample referral will not overload the existing capacity.

Close consultation with local clinicians is required to determine the repertoire of tests that will be used to support the clinical program. At this stage it is also vital to determine required turnaround times for assays, as this will have an impact on service design. The anticipated rate of patient recruitment into treatment and prevention programs needs to be determined as well, since the workflow design and analyzer selection are entirely related to the volume of tests required. Ongoing laboratory-clinic communication is fundamental to maintaining the overall quality of laboratory services.

**COMMUNICATION STRATEGY**

It is important to establish appropriate lines of communication for the duration of the implementation process; failure to do so early on can derail a project very quickly. Regular communication with the implementing laboratory, whether through face-to-face visits, conference calls or e-mails, should be maintained to ensure the continued momentum of the process. A detailed project implementation plan with defined milestones agreed upon by all stakeholders is also essential to keep everyone’s expectations in alignment. The challenges presented by communication difficulties should not be underestimated, as information technology (IT) infrastructure can be lacking in several areas. Cultural and language differences between local staff and visiting trainers are equally significant and can influence site laboratory staff receptiveness to planning and training activities. For instance, while English is generally accepted as the common language for such activities, the English language competency of the laboratory staff should be assessed prior to the initiation of training.

**BUDGET DEVELOPMENT**

All budgets should be well researched; this may require the assistance of organizations that specialize in project management or local individuals with the appropriate experience. The budget should make allowances for required capital equipment such as analyzers and centrifuges, facility management (e.g., furniture and equipment, facility rentals), staffing costs, ongoing maintenance of major and minor equipment, reagents and consumables, costs of internal and external quality assurance, and courier and sample collection costs. The cost of a test is often calculated based on reagent costs alone. However, all expenses should be taken into account and final test costs per reportable result should be calculated based on cumulative total expenses in order for laboratory servicing to be sustainable. This cumulative total should include the cost of labor for specimen collection, sample analysis, data entry, and reporting. In addition, direct material costs should include reagents, consumables, controls, and calibrators. Fixed costs that are incurred regardless of whether or not a test is processed (e.g., rent, equipment maintenance, quality assurance, and management) should also be factored into the cost per test. A simplified template for test costing is presented in Table 1.

**STAFF RESOURCES**

Professional staff shortages are commonplace in African countries, and skilled laboratory technical personnel are no exception. For instance, the World Health Organization (WHO) has estimated that countries in sub-Saharan Africa would have to increase their workforce by 140% to achieve adequate health coverage. A published survey in Ghana conducted in 205 laboratories revealed that only one-quarter of staff had professional qualifications. Staff turnover rates are often extremely high, with many staff succumbing to HIV infection themselves or leaving the country for better wages
Many of the international guidelines for GLP are intentionally vague and thus not easily translated into practice. Courses need to be designed to focus on basic, practical implementation issues (e.g., implementation of audit trails, development of SoPs, maintenance logs, temperature monitoring, etc.) through the use of working examples. Observations of numerous training courses in the region indicate that many sites are beginning to transfer the skills attained during training to other centers in their region, a very encouraging development. Training of trainers (ToT) workshops may also be useful for the training of senior staff so that they can then conduct their own regional training programs.

<table>
<thead>
<tr>
<th>Table 1. Sample Laboratory Test Costing Template</th>
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<tr>
<td>1. Specimen collection costs</td>
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<td>2. Equipment/depreciation</td>
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<td>= Total cost</td>
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<tr>
<td>6. Laboratory overhead (% of Total cost)</td>
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<tr>
<td>Total cost per reportable result</td>
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The need for laboratory management skills is often overlooked. Once a defined laboratory hierarchy is established, the overall laboratory manager and deputy may need training or refresher courses in laboratory management skills. In addition to all of the principles of GLP, this instruction needs to include practical assistance regarding human resource management, budgeting, procurement, stock control, negotiation skills, and the development of an internal audit process to ensure long-term sustainability of the facility. The identification and appropriate training of a specific quality manager (or individual responsible for quality of testing) and safety officer is of key importance.

Further needs include technical training on how to conduct the assays that have been selected (e.g., serology, CD4 count, hematology, biochemistry, polymerase chain reaction [PCR] for infant diagnosis, and viral load monitoring). After technical proficiency has been established, more advanced training is generally required to ensure that the subtleties involved in monitoring aspects of quality assurance and troubleshooting are understood for each assay. An approach that combines the use of on- and off-site training for each assay works quite well.

Training of clinical personnel at the associated clinical sites should not be overlooked. Topics that may need to be covered include the interpretation of laboratory assays and proper sample collection, particularly if there are specialized requirements such as the collection of dried blood spots for infant diagnosis or plasma for HIV viral load assays requiring specialized centrifugation and transport. If sites are conducting rapid testing, such as HIV diagnosis or B-HCG (beta human chorionic gonadotropin) tests to exclude pregnancy, on-site training is vital, as are mechanisms to ensure the ongoing maintenance of quality and proficiency by clinic staff. This may involve sending a percentage of samples (usually 5% to 10%) to a reference laboratory for confirmatory testing. A regular process in which witness testing of clinic staff is conducted by trained technical staff is also useful to ensure that assays are conducted accurately and safely.

**EQUIPMENT**

Assay and equipment selection is typically determined by the volume of samples to be processed and available budgets. It is advisable to select equipment from a supplier that has a strong local presence and who can guarantee fast turnaround times for servicing, maintenance, and equipment repairs. Feasibility of implementation for any new assay needs to be considered, including (1) the level of technical skill required to conduct the assay; (2) sample collection, transport, and storage needs; (3) the required turnaround time; and (4) workflow and space requirements (particularly for PCR or culture work). Water and power supply for analyzers should be considered very carefully when determining the placement of instrumentation within the laboratory itself. It is prudent to install a generator backup and an uninterrupted power supply (UPS) for all instruments, as electrical power cuts are a common occurrence.

**SPECIFIC ASSAYS**

**HIV Diagnosis**

Most developing countries use rapid HIV tests either singly or in combination for the diagnosis of HIV in adults. These are generally conducted at the clinic as part of a larger voluntary counseling and testing (VCT) process, and their use has facilitated a dramatic increase in access to care in many regions. These assays are by and large easy
to implement; lists of proven and reliable assays are available from WHO and CDC. Limited local validation of new assays is advisable prior to implementation and is of particular relevance in settings where less common HIV subtypes are present. Ongoing surveillance of assay performance is also recommended. Collating data on rapid HIV tests can be challenging due to problematic record keeping in many remote clinics, with few sites having data management systems in place to monitor the number of assays and their performance.

As discussed previously, monitoring of quality is an essential part of any laboratory testing program, and it is advisable that at least 5% of samples are retested in a reference laboratory. This can be easily achieved using dried blood spots to reduce the time needed for sample collection and to avoid sample transport restrictions. A recent study in South Africa evaluating the performance of rapid tests for malaria in the Limpopo province demonstrated the need for improved quality assurance and end-user training. GLP needs to be extended to the clinic operations as well, with factors such as temperature monitoring for kit storage and equipment maintenance factored into daily work practices.

Early infant diagnosis of HIV is particularly complex, since passive transfer of maternal antibodies complicates the use of antibody-based assays. However, recent work has suggested that rapid antibody assays could be used for the screening of HIV exposure in infants, and most groups recognize the need for virological assays for early infant diagnosis. These assays can be in the form of DNA-based PCR assays; quantitative RNA assays; or heat-denatured, ultrasensitive p24 antigen quantitation. It should be noted that nucleic acid–based testing strategies require significant technical skill and dedicated workspace to prevent contamination.

**Hematology**

Hemoglobin is an important independent predictor of outcomes in the setting of HIV. Since many antiretroviral drugs are bone marrow suppressive, ongoing monitoring of hemoglobin is an important component of any treatment program. The selection of hematology equipment is fairly simple and is largely volume driven. In low-volume primary health-care clinics where only a hemoglobin value is requested by clinicians, instrumentation such as the HemoCue system can be easily implemented. As volumes increase and the need for automation arises, there are a variety of analyzers that are suitable for both low- and high-volume ranges.

**Chemistry**

Many HIV-care programs will include a limited repertoire of biochemistry parameters, such as alanine transaminase (ALT) levels. The selection of appropriate analyzers is once again volume driven, but is particularly challenging for the medium-volume, small-repertoire range of instruments. There are sufficient point-of-care (POC) options for low-volume, decentralized testing, as well as high-volume, large-repertoire instruments.

**METHOD VALIDATION**

Method validation is critical prior to implementation of a new method or instrument. A full validation is needed when a new method or instrument is implemented for the first time. However, a full validation process may not be feasible at all sites due to costs or lack of technical or statistical skills. A

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b For more information, visit http://www.hemocue.com.
partial validation process may be considered when transferring a previously validated method into a new laboratory site. The approach to method comparison can be divided into four distinct phases: (1) obtaining background literature and understanding theoretical principles and performance specifications, (2) design and analysis, (3) compilation of a report, and (4) ongoing monitoring of performance. Several international guidelines and reference documents are available for consultation during the validation process and include the CLIA guidelines (CLIA 88 final rule-2003); NCCLS (now referred to as CLSI [Clinical and Laboratory Standards Institute]) EP9A2, EP5A2, and EP17A4; and the College of American Pathologists (CAP) general checklist. There is much debate as to what constitutes an appropriate method validation process for a new assay or method. This issue has been discussed extensively within organizations such as WHO, CDC, and, more recently, the Forum for Collaborative HIV Research. There is some agreement that the components of an appropriate method-validation process should include the following determinations: (1) precision—within run and between run; (2) accuracy; (3) evaluation of quality controls and reference material; and (4) reportable linear range, linearity, and sensitivity. The validation process should be followed up by a multisite comparison, longitudinal evaluation of patients, and participation in EQA programs to assess ongoing performance.

EXTERNAL QUALITY ASSESSMENT PROGRAMS

Dramatic improvements in overall laboratory performance have been demonstrated in countries or within programs utilizing proficiency testing programs. It has also been established that many EQA programs are too infrequent (i.e., conducted quarterly) to ensure adequate monitoring of performance and that if a problem is identified, testing will continue for several months before a corrective action is implemented. Access to international EQA schemes is limited in Africa, mainly due to the high costs of participation and courier service. Logistical difficulties related to the delivery of EQA samples, including poor courier networks and inefficient customs departments, also make access to EQA challenging. For these reasons, and because of limited resources and fear of reprisal, EQA schemes remain largely underutilized in many African laboratories.

Several EQA programs are, however, available and their selection by a laboratory will depend on the parameters being evaluated, the distribution network of the particular program, the frequency of shipment, and associated costs. The following are well-recognized international providers: CAP (U.S.-based, CLIA certified), United Kingdom National External Quality Assessment Service (UKNEQAS), Royal College of Pathologists of Australasia (RCPA), and Quality Assurance Systems International (QASI). Other programs that are available to assist laboratories within the African region include those provided by WHO, CDC, National Institutes of Health (NIH; offering virology quality assessment [VQA] and immunology quality assessment [IQA]), and the South African NHLS-managed African Regional External Quality Assessment Scheme (AFREQAS). The AFREQAS CD4 proficiency program was initially based on a collaboration between WHO, the NHLS,
and QASI in 2002 for the purposes of establishing monitoring of CD4 testing in the region. The program now runs independently and has facilitated the development of several national EQA programs under the umbrella of the AFREQAS. The program has also been instrumental in facilitating knowledge transfer and providing technical advice and support to ensure that appropriate corrective action is taken when failure occurs in participating laboratories. To date, 35 successful trials have been delivered, with more than 500 sites participating from 20 different countries in the Africa region. Overall performance within the program has been very good, confirming that high standards of laboratory testing can be achieved in many remote African settings.30,31

In the area of HIV diagnostics, HIV serology EQA programs have been extended to include the clinical sites at which the bulk of HIV testing (using rapid tests) takes place. Electronic submission of results has proven to be reliable, ensuring rapid return of results and allowing for immediate corrective action. However, in non-grant-funded sites, communication is often difficult and requires dedicated follow-up and repeated communication by telephone or fax to encourage participants to submit results. Once a relationship is established between the coordinators and participants, compliance for results submission can improve.

LABORATORY SAFETY
Safety issues are generally not given adequate attention in laboratories in Africa, where staff are at great risk of exposure to HIV and hepatitis.32 The working conditions for TB diagnosis are generally substandard in many developing countries and significant resources need to be allocated to ensure that the risk of laboratory-acquired TB is greatly reduced.33 Other serious safety concerns that have been highlighted in the region include lack of access to appropriate waste disposal facilities, such as incinerators, and the absence of provisions for the administration of HIV postexposure prophylaxis (PEP) to staff members.

COURIER AND TRANSPORT SYSTEMS
Transport collection systems in most African countries are generally poorly developed and the absence of transport often severely limits access to testing. This is exacerbated by the requirements of some commonly used HIV diagnostic and monitoring methods, such as viral load and CD4 testing, which require a cold chain or processing within a specified time frame. Some of these issues for CD4 testing have been alleviated through the use of fixatives34 or the development of innovative flow cytometric assay approaches, such as panleucogated CD4 testing, which facilitates delayed testing for up to five days.35,36 The use of dried blood spots37 or other collection devices, such as the SampleTanker, facilitates delayed centralized nucleic acid testing.

CONCLUSION
Experience has shown that even relatively rural laboratory sites can support the implementation of basic antiretroviral programs as long as sufficient investments are made in training and regional support. Willing participation at training courses and high participation rates in EQA programs30 demonstrate that laboratory personnel in the African region recognize the need to attain—and sustain—quality laboratory services. African laboratory professionals have shown that they are willing and able to embrace the latest technologies and apply and or modify them as needed to suit local needs.31 Sustainable laboratory practices based on proven technologies modified to suit local conditions are an essential component of the HIV/AIDS response.
**REFERENCE LIST**


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Managing Medicines and Supplies for HIV/AIDS Program Scale-Up

Helena Walkowiak and Douglas Keene

As countries move to rapidly scale up comprehensive HIV/AIDS programs, it is critical that the adequate and continuous availability of diagnostics, medicines, and other pharmaceuticals be ensured at the point of service. If HIV test kits are unavailable, opportunities to offer testing are missed. Stock-outs or irrational use of antiretroviral medicines (ARVs) can result in treatment interruptions that can quickly lead to treatment failure and the development of drug resistance. The success of these programs is also largely dependent on the capability of the health-care team to promote the proper use of ARVs and other products. Inappropriate use can increase the risk of toxicity of HIV/AIDS-related medicines and, in addition, can waste costly laboratory tests and medicines. Despite many improvements, the limited availability of ARVs and HIV test kits continues to be reported as a major constraint to scaling up programs.¹⁻³

A wide range of medicines and other pharmaceutical products are needed to support implementation of a comprehensive package of HIV/AIDS services for treatment, care, and prevention (see Box 1). While a single health facility may not carry all needed products, clients should be able to access products that are unavailable at their local facility through a referral process. Some services require new products, while others need large-scale increases in quantities of existing medicines and supplies. These requirements change as new technologies or formulations become available and as practices or patient needs change. In addition, some products are complex to manage, requiring cool or refrigerated storage and careful tracking of short shelf lives to minimize wastage.

Box 1. Pharmaceuticals Needed to Support Comprehensive HIV/AIDS Programs

- Medicines:
  - Medicines to treat HIV infections (antiretrovirals)
  - Medicines to prevent and treat opportunistic infections (OIs)
  - Medicines for palliative and supportive care
  - Medicines to prevent and treat sexually transmitted infections (STIs)
  - Medicines to treat HIV-related cancers
- Diagnostic test kits for HIV, STIs, and OIs
- Laboratory reagents, supplies, and equipment:
  - To monitor the progression of HIV infection
  - To identify adverse drug reactions
- Medical equipment and supplies
The World Health Organization (WHO) estimates that at the end of 2006, only 28% of people in need of antiretroviral therapy (ART) in all low- and middle-income countries were receiving it and that steep increases in the rate of scale-up will be needed to achieve universal access to treatment by 2010.4 As countries move to decentralize ART services to the primary health-care level, the pharmaceutical management system must meet the challenge of delivering supplies to more service delivery points, across different sectors, and for an increasing number of clients. In many countries, procurement and distribution systems are struggling to keep up with this rapid expansion, and even systems that are working well will be challenged to support the level of scale-up that is to come.4

This chapter provides practical guidance on addressing some of the major challenges related to the management of medicines and other supplies being faced by HIV/AIDS programs in resource-limited settings. Successful approaches and lessons learned for building the capacity of pharmacy and supply services to support scale-up are shared.

APPROACHES TO STRENGTHENING SYSTEMS FOR GOING TO SCALE

As countries plan to scale up their HIV/AIDS programs, a key consideration is whether to integrate the supply of HIV/AIDS-related pharmaceuticals into an existing supply system or, alternatively, to establish one or more vertical or parallel systems. In a vertical supply system, all or some of the functions of the pharmaceutical management cycle (described below) are carried out separately for each program. Limitations to using parallel systems to supply HIV/AIDS programs include the wide range of products needed, the level of expansion to be achieved, and the shortage of skilled pharmaceutical management staff.

In many countries, governments are working with partners to rationalize multiple vertical supply systems and to foster service integration. Most pharmaceutical management systems have some strengths to build upon. A rapid assessment can help clarify what these strengths are and help identify which strategies are needed to build capacity where it is lacking. By prioritizing interventions, facilities can begin implementing new HIV/AIDS programs while working to strengthen existing pharmaceutical management systems for the longer term. Integrating pharmacy and supply services into existing systems allows capacity-building costs to be shared across programs. Integration also ultimately improves pharmaceutical management for other programs, since most improvements are system-based rather than disease-specific. In addition, integrated systems are better equipped to support scale-up, due to the fact that service provision, such as ARV dispensing, does not depend on the availability of a specific member of the pharmacy staff.

THE PHARMACEUTICAL MANAGEMENT SYSTEM

Managing pharmaceuticals in any setting (public or private) and at any level (local or national) follows a well-recognized framework that includes a cycle of selection, procurement, distribution, and use (see Figure 1). Management support functions hold the cycle together, and it is supported by policies, laws and regulations. As problems in any part of the cycle can disrupt the whole pharmaceutical management system, it is important that assessments of existing capacity consider all components of the framework.

SELECTION

The successful scale-up of ART programs depends on good selection practices. Selection involves reviewing HIV-related health problems, developing standard guidelines, and deciding which medicines, diagnostics, and supplies will
Figure 1. Pharmaceutical management framework

be available at each level of the health system. Good selection practices include the rational selection of the most effective and economical treatments or tests for a specific setting, performed through an inclusive and transparent process and underpinned by a plan for implementation. The benefits of standardization for selected testing and treatment protocols include more predictable demand for products, which allows for more accurate quantification; fewer products to procure and store; and lower prices due to bulk purchasing. However, ART selection is complicated by the need for multiple regimens to cover different indications and populations. Lack of clarity about regimen choices and multiple formulation options can confuse prescribers and complicate quantification. Rapidly changing scientific information on effectiveness, adverse effects, or resistance patterns, and the availability of new medicines or formulations, makes it difficult to keep ART guidelines current. However, if guidelines are perceived to be outdated or not based on scientific evidence, prescribers are less likely to follow them.

Points to Remember for a Successful Approach

Comprehensive and detailed guidelines help standardize practices and improve quantification accuracy. Although most countries have developed national guidelines for their HIV/AIDS interventions, program and procurement staff can encounter difficulties in implementing these recommendations. This is particularly true when the clients are children. Programs are better able to quantify needs and standardize procedures for prescribing and dispensing when ART guidelines specify the following:

- First- and second-line regimens, with recommendations for managing toxicity and treatment failure
- Regimens for individuals coinfected with TB and other chronic diseases, as well as for pregnant women and all age groups of children
- Regimens for postexposure prophylaxis (PEP) in both adults and children
- Guidance on managing the ART-experienced patient
- Recommendations for laboratory monitoring
- Recommendations for diagnosis and treatment of opportunistic infections (OIs) for both adults and children
- For children, a range of products to suit all ages, preferred formulations for weight and age, and weight-based dosing recommendations for available products (WHO has developed generic dosing tables for countries to adapt for this purpose.5)

An inclusive and transparent development process facilitates implementation of and adherence to guidelines. The inclusion of service providers and national pharmaceutical management staff in selection committees enables them to contribute to developing guidelines that are easier to put into practice. In addition, participation by representatives of the essential medicines committee can facilitate the addition of products to the lists that guide procurement. Including a wider range of constituencies (organizations or groups) can, in general, help build the credibility and acceptance of guidelines.

Updating guidelines requires planning and adequate budgeting. Regular updates to HIV/AIDS guidelines are necessary but can be costly. The process of planning and securing adequate funding in advance of any changes is very important. For instance, training materials, standard operating procedures (SOPs), supply management forms, and reporting and recording forms may all need to be updated. The launch of the new guidelines also needs to be synchronized with supply management, as it takes time to quantify, procure, and
Data from facilities. Changing needs for ARV regimens as patients experience toxicity or treatment failure can also be hard to forecast. Similarly, estimating requirements for new medicines as guidelines change or new formulations, such as fixed-dose combinations (FDCs), become available can be complex. Further complicating the process are lengthy procurement procedures and long supply pipelines that can delay the introduction of new products.

### Points to Remember for a Successful Approach

A national committee to coordinate procurement and distribution can optimize the purchasing power of multiple partners and improve the efficiency of pharmaceutical management. To improve the coordination of procurement, financing, and distribution activities, some governments have established national-level committees to support HIV/AIDS program expansion. The committee serves as a forum for planning collaborative action to strengthen the pharmaceutical management system. Although procurement managers are responsible for most activities, the committee enables them to work together with policy and program staff to map out current and anticipated service delivery points and targets. This collaborative process should lead to the development of a comprehensive procurement and distribution plan that includes an accurate estimate of resource needs. The committee can also work with the team tasked with quantification to review the quality of data collected and develop assumptions about future needs. It is also crucial that the procurement and distribution plan be updated regularly to ensure that procurement planning, program implementation, and disbursements of funds are synchronized.

Simple tools and training can improve quantification and data collection at the facility level. The provision of simple tools to assist facility-level

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**PROCUREMENT**

Pharmaceutical procurement consists of quantifying product needs, selecting procurement methods and suppliers, establishing and monitoring contract terms, and ensuring the quality of the medicines and other pharmaceuticals. Quality should never be compromised by pricing concerns or any other factor. In many countries, the complexity of procuring products for HIV/AIDS programs is challenging already weak procurement systems. The increased number of global and local partners, funding sources, and procurement mechanisms has complicated procurement planning, occasionally resulting in duplicative procurements and stock-outs. These complications are compounded by the fact that different funding sources can have different procurement cycles and requirements, resulting in complex record keeping, more orders to generate and track, and multiple brands of the same product.

Quantifying needs for ART programs that are scaling up is particularly challenging. The pace of program expansion often fluctuates over time, and enrollment may periodically slow down when the capacity to deliver services has reached its limit. Staff tasked with quantifying needs at the national level are often handicapped by the lack of reliable data from facilities. Changing needs for ARV regimens as patients experience toxicity or treatment failure can also be hard to forecast. Similarly, estimating requirements for new medicines as guidelines change or new formulations, such as fixed-dose combinations (FDCs), become available can be complex. Further complicating the process are lengthy procurement procedures and long supply pipelines that can delay the introduction of new products.
CASE STUDY 1: THE COORDINATED PROCUREMENT AND DISTRIBUTION SYSTEM FOR ANTIRETROVIRALS IN RWANDA

THE GOVERNMENT OF RWANDA has established the Coordinated Procurement and Distribution System (CPDS) to coordinate ARV procurement and distribution efforts among the government, donors, national institutions, and international organizations. The President’s Emergency Plan for AIDS Relief (PEPFAR), through the U.S. Agency for International Development (USAID), committed funds to the Rational Pharmaceutical Management Plus (RPM Plus) Program to support this coordination process. The CPDS had its beginnings in 2005, when the government coordinated the first national quantification and pooled procurement of ARVs. In 2006, a governance framework that describes CPDS objectives and functioning principles and the roles of its members, developed by consensus with all national and international stakeholders, was approved by the Ministry of Health. The CPDS has two primary components:

- A Resource Management Committee, chaired by the permanent secretary of the Ministry of Health and responsible for political, strategic, and financing decisions
- Technical committees responsible for procurement, quantification, distribution, and monitoring functions

The two components are linked by a coordinator who provides technical advice to the permanent secretary and coordinates the technical committees.

The coordination activities of the CPDS have simplified ART management and lowered costs by harmonizing formulations and brands, reducing wastage, and decreasing the number of purchase orders. Furthermore, to support its coordination efforts, the CPDS has accelerated efforts to strengthen the pharmaceutical sector. Pharmaceutical procedures and tools have been standardized, and pharmacy staff have been trained in pharmaceutical management.


staff in data collection and quantification of ARV and other product needs, coupled with training to improve staff quantification skills, can reduce stock-outs and the need for emergency orders. For district and frontline facilities that are scaling up ART, a modified consumption-based method of quantification is simpler to use than a morbidity-based method. From initial experiences, the consumption-based method appears to be sufficiently accurate, provided that consumption records are reliable, procurement periods do not exceed three months, and the pipeline is full. Data collection tools developed in collaboration with facility staff who actually use the data to quantify needs can improve the quality of the data collected and subsequently submitted to the national level.

Contracts should allow procurement to be flexible and responsive to fluctuations in scaling up. Procurement contracts should include staggered deliveries and allow adjustments to be made
to order quantities in case scale-up goes faster or slower than expected.

**DISTRIBUTION**

Distribution includes clearing customs, stock control, storage management, and delivery to depots and service delivery points. The drive to scale up access to HIV/AIDS programs is exposing weaknesses in the distribution systems of many resource-limited countries. Public-sector supply systems, especially in African countries, are struggling to manage hugely increased volumes of medicines, diagnostics, and other pharmaceuticals. Faith-based and other nongovernmental organizations (NGOs) that supply their own facilities are unlikely, even with expanded capacities, to be able to fill the gap as countries take their programs to scale. Multiple funding streams and parallel procurement systems result in multiple shipments needing to be cleared through customs. In most countries, this is a complex and time-consuming process.

The high value and short shelf life of some HIV/AIDS pharmaceuticals, coupled with frequently changing guidelines and the ongoing introduction of new formulations and technologies, puts pressure on supply managers to keep pipeline stock to a minimum while avoiding stock-outs. This is especially true for ARVs. Because scale-up is unpredictable and patients’ needs can change, interventions such as ART require frequent deliveries to a constantly increasing number of service delivery points.

**Points to Remember for a Successful Approach**

Multifaceted strategies and long-term investments are needed to build the capacity of supply systems for going to scale. Countries are exploring a number of options to strengthen national distribution systems in order to support rapid scale-up, including collaboration with faith-based NGOs and the harnessing of resources within the private sector. Some programs use a combination of distribution mechanisms to increase responsiveness. For example, they may use existing public-sector transport for routine orders and lease private vehicles or use express mail for emergency orders. Additional investments may be needed to improve the security, capacity, and integrity of storage sites at all levels, and to lease or purchase vehicles.

Strengthening inventory management will require resources for training as well as tools to help track commodities and monitor usage at central and site levels. Additional human resource needs may include an individual to coordinate distribution at the national level, and staff time for data collection and supervision. Where systems are integrated, efforts and resources expended to support HIV/AIDS program scale-up can strengthen the supply and distribution of all essential medicines.

Introducing flexibilities to make distribution systems more responsive can help avoid stock-outs, minimize wastage, and facilitate the introduction of new products and formulations. Strategies that can make distribution systems more flexible and responsive to users include increasing the frequency of deliveries, collecting and redistributing excess or short-dated stock, and processing nonroutine orders in a timely manner. Organizing the distribution system so as to limit the number of levels where stock is held can serve to minimize pipeline stock. Such an approach will vary depending on the local context. Some countries have centralized storage at the national level and use a relay system to move supplies to regional and district levels, while others, especially geographically large countries, have decentralized storage to one or more levels in the health-care system. In order to work well, a central management unit should be responsible for coordinating
The availability of pharmaceuticals alone does not ensure access to quality care. Medicines must be properly prescribed and dispensed and clients must use them correctly. For the patient, irrational prescribing and dispensing and poor adherence to ARVs and other anti-infectives can lead to treatment failure and the development of drug resistance. Pharmacy staff play a key role in promoting rational use, and the importance of dispensing activities is frequently underestimated. Very often, pharmacies are understaffed, labels and appropriate packaging are unavailable, and staff lack distribution, communicating with facility staff and program managers to update distribution plans and reallocate supplies based on uptake, and maintaining a robust information system that feeds data on consumption or requirements back to the central unit.

At new sites, allocating “ceilings” for new ART patients can facilitate distribution planning. Allocating monthly targets or ceilings for new patients can assist with distribution planning, especially in the early phases of scale-up, when facilities lack data and experience to calculate requirements accurately.

CASE STUDY 2: STRENGTHENING DISTRIBUTION SYSTEMS TO IMPROVE GEOGRAPHICAL ACCESS TO ANTIRETROVIRALS IN ETHIOPIA

As Ethiopia rolls out ART services, the challenges for distribution include the vast size of the country, the lack of all-weather roads to some facilities, ambient temperatures in certain regions that frequently exceed 30 degrees Celsius, and inadequate storage infrastructure at new sites. To deliver quality ARVs when and where they are needed, the Ministry of Health’s Pharmaceutical Supply and Logistics Department (PSLD) is working closely with PHARMID (the partly government-owned pharmaceutical company) and partners funded by PEPFAR, including the RPM Plus Program, to ensure that efforts are well coordinated. The distribution system for ARVs purchased with grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) has been integrated with the system used for PEPFAR-funded ARVs to increase efficiency. A distribution plan is developed quarterly; allocations are based on national “road map” targets and adjusted for uptake figures reported by sites. To minimize pipeline stock, ARV medicines are relayed out to PHARMID regional stores and directly on to facilities, which keep just one month of buffer stock. Regional pharmacy staff assist with responding to nonroutine orders and redistributing excess stock. A combination of transport mechanisms, including air, land, and courier services, is used according to the geographical context and the urgency of the order. Facility storage areas are being renovated and staff are being trained on the importance of proper storage of ARVs, including routine temperature monitoring of storage areas.

Source: Management Sciences for Health / RPM Plus Ethiopia office.

USE OF PHARMACEUTICALS

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the basic skills and access to current information necessary to properly counsel patients and advise prescribers.

ART adherence has received much attention, and many clinics and pharmacies collect substantial amounts of data. However, validated measurement tools for monitoring adherence in resource-limited settings are few,\textsuperscript{11} definitions of adherence and defaulting vary, and approaches to improving adherence are not always consistent.\textsuperscript{12} Dispensing medicines for children presents a set of additional challenges. For instance, calculating doses can be complex. Formulations that require the cutting of tablets or the accurate measurement of three different medicines make the delivery of counseling messages to the caregivers of young patients more complex.

**Points to Remember for a Successful Approach**

**Pharmacy staff can play a key role in promoting and monitoring ART adherence.** Studies in the developed world have found that support from pharmacists can positively affect adherence\textsuperscript{13} and that clinical pharmacists appear to have a strong impact on promoting positive clinical outcomes in patients starting ART, particularly in economically disadvantaged areas.\textsuperscript{14} In resource-limited settings, the contributions of traditional pharmacy activities (e.g., checking prescriptions, labeling medicines, and providing medication counseling) in facilitating ART adherence are increasingly being recognized. These responsibilities are also expanding to include adherence monitoring and identification of defaulting patients.

As programs scale up, it becomes more challenging to maintain the quality of pharmaceutical care. Resources can be stretched thin as patient numbers increase and ART dispensing is decentralized to facilities that lack trained pharmacy staff. Delineating health-provider roles in adherence counseling to eliminate unnecessary duplication of efforts can increase efficiency at the pharmacy. Furthermore, validated methods to monitor adherence can enable pharmacy staff to target interventions appropriately. Appropriately adapted SOPs that detail dispensing, adherence counseling, and monitoring processes, and job aids such as medication counseling checklists, can help maintain the quality of pharmacy practices. User-friendly information on ARV medicines, side effects, and interactions can also assist pharmacy staff in communicating key messages to their patients.

**Special efforts should be made to enable pharmacy staff to support ART rollout for children.** Pharmacy staff play an important role in checking ART prescriptions and doses for children, and in providing counseling to their caregivers. When information is lacking or nurse counselors are unavailable, health providers often rely on pharmacy staff to fill the gap. In addition to training in pediatric ART, pharmacy staff may also need to improve their math skills to be able to correctly calculate doses of medicines and quantities to dispense. Information on regimens and dosing recommendations, as well as advice for caregivers on special challenges, should be readily available. In addition, dispensing supplies such as labels, tablet cutters, and measuring devices should be provided. Colored tape can be helpful to distinguish similar-looking bottles of liquid formulations.

**Strengthening dispensing and medication counseling practices for ART programs can improve pharmaceutical care for all patients.** Where ART dispensing is integrated into existing systems and work schedules, staff can often adapt their training in ART medication counseling to improve the quality of counseling for other programs, particularly for patients on chronic treatments, such as for hypertension or diabetes.\textsuperscript{15}
FROM THE GROUND UP: LAYING A STRONG FOUNDATION

The registration process for new products can be lengthy, in some cases taking a year or longer, which can impede the introduction of new HIV/AIDS-related medicines or formulations, such as FDCs for children. The time taken to review dossiers and conduct site visits and the submission of incomplete dossiers by manufacturers may all contribute to these delays.

Points to Remember for a Successful Approach
Fast-track registration and recognition of efficacy and safety evaluations by another medicine regulatory authority can facilitate the introduction of new products.

POLICIES, LAWS, AND REGULATIONS
The pharmaceutical management framework includes all policies, laws, and regulations that impact the availability and use of medicines and other pharmaceuticals. This discussion focuses on one aspect of this framework, pharmaceutical registration. Pharmaceutical registration is the licensing or market authorization of a product based on evidence of efficacy, safety, and quality. The requirements and processes for registering products vary from country to country but will usually involve submission of a scientific dossier and, in some instances, a site visit. In developing countries, previously validated tools, namely, self-report, visual analogue scale, pill identification test, and pill count. The tool was tested at two hospital pharmacies over a 14-month period. The median time of five minutes to administer the tool was deemed acceptable for routine use, and the internal consistency was sufficiently strong to recommend piloting the tool in all provinces. In May 2007, the Comprehensive HIV and AIDS Care, Management and Treatment Plan National-Provincial Working Group agreed to implement the adherence assessment tool in all provinces, and RPM Plus was requested to develop a similar tool for use with children. The intent is to then adapt these tools for other chronic diseases.


CASE STUDY 3: DEVELOPING A TOOL FOR MONITORING ANTIRETROVIRAL THERAPY ADHERENCE IN SOUTH AFRICAN CLINICS

In South Africa, the RPM Plus Program, with funding from USAID, is assisting the national and provincial (Eastern Cape) HIV and AIDS directorates and partners to identify a simple, non-electronic medication adherence assessment tool that can be used by pharmacy staff and other providers at busy ART clinics. An initial literature search revealed that numerous instruments were available; however, no studies described their routine use in resource-limited settings. Given that a 2003 WHO report concluded that no gold standard for measuring adherence existed and recommended a multi-method approach, RPM Plus developed a multi-method adherence assessment tool based on

IN SOUTH AFRICA, THE RPM PLUS Program, with funding from USAID, is assisting the national and provincial (Eastern Cape) HIV and AIDS directorates and partners to identify a simple, non-electronic medication adherence assessment tool that can be used by pharmacy staff and other providers at busy ART clinics. An initial literature search revealed that numerous instruments were available; however, no studies described their routine use in resource-limited settings. Given that a 2003 WHO report concluded that no gold standard for measuring adherence existed and recommended a multi-method approach, RPM Plus developed a multi-method adherence assessment tool based on...
of new products for HIV/AIDS programs. Establishing a fast-track mechanism that prioritizes the evaluation and processing of registration applications for specific categories of pharmaceuticals, such as ARVs, is one strategy to expedite registration. Some countries recognize the efficacy and safety evaluations of other medicine regulatory authorities (e.g., countries participating in the International Conference on Harmonization [ICH]) to accelerate the registration process. Strategies to capacitate the regulatory authority to conduct dossier evaluations and manage the workload may include establishing a medicine registration database, staff training, implementing SOPs, and developing a database to manage the dossier review process.

As registration can be one of the longest and most difficult steps in updating guidelines, program managers should begin working with manufacturers early on to initiate the process of registering products.

MANAGEMENT SUPPORT: FINANCING

Funding for HIV/AIDS programs has increased significantly through large-scale initiatives such as the Global Fund, PEPFAR, and other donor initiatives. For many developing countries, achieving the exponential increases needed to take their programs to scale will depend on their success in securing external sources of funding. This funding is crucial not only for procurement, but also for the establishment of efficient pharmaceutical management systems that will function for years to come. The process for developing proposals, costing requirements, and gathering supporting information can be complex; delays in disbursement of Global Fund grants are common and may arise due to difficulties in developing procurement and supply management (PSM) plans, or in getting them approved. As discussed earlier, the large number of pharmaceuticals needed for comprehensive HIV/AIDS programming may require joint planning and budgeting between partners and different government departments.

Points to Remember for a Successful Approach

Developing a multiyear financing strategy as part of an overall HIV/AIDS plan and establishing a mechanism to coordinate proposal development and donor inputs facilitates resource planning. Programs should prepare multiyear forecasts of medicine needs to inform resource mobilization efforts. These forecasts should incorporate product procurement fees and shipping and importing costs into the budget. Financial resources for building the capacity of the pharmaceutical management system at both the facility and national level, including costs for technical assistance, should also be considered. Joint planning and budgeting with other government departments and programs can maximize efficiency in procurement and capacity-building activities. Moreover, donors may be more willing to invest in system strengthening if they know that activities will be cofunded from other sources.

Begin the process of developing PSM plans early to avoid delays in disbursement of Global Fund grants. Difficulties are most often encountered during the collection and verification of data to support the PSM plan, the forecasting of needs, and the development and budgeting of strategies to strengthen pharmaceutical management systems. Requests for technical assistance to help prepare the plan can take time to process. Having a mechanism in place to coordinate procurement, particularly quantification, and capacity-building efforts can facilitate the development of the PSM plan.
Furthermore, a well-functioning PMIS can help managers secure resources for scaling up their programs (see Case Study 4). Building on existing forms, reports, and procedures helps keep costs down and can facilitate acceptance by users. Where multiple supply systems exist with separate information systems, countries will need a strategy for working with stakeholders to standardize data collection tools and reporting requirements to facilitate integration. Improvements to the PMIS are often incremental; transitions are made from manual systems to interim computerized tools to complete software systems as tools become available and patient numbers grow. Changes are made at each step to support new responsibilities or to overcome emerging challenges as programs scale up. Ongoing funding will be needed to develop and maintain the PMIS, and budgets should include costs for printing forms, updating tools, and training, as well as staff time to collect, report, and monitor data quality.

Pharmacy staff need tools, including simple software, to help them collect, analyze, and report data. The data complexity, especially for pediatric ART, the growing number of patients, and the wide range of products can make manual methods of maintaining records and retrieving data more and more difficult to use. As programs outgrow manual tools and pharmacy staff expand pharmaceutical care activities (e.g., adherence monitoring), managers may need to plan and budget for the implementation of user-friendly computerized tools to facilitate record keeping and analysis. Similarly, procurement and distribution staff will need tools to track HIV/AIDS pharmaceuticals by program and funding source as they move through the supply chain. Accuracy in data collection is always a paramount consideration, and poor data-collection practices may not necessarily be improved by computerization. It is important to computerize at appropriate levels to achieve the right mix of

**Points to Remember for a Successful Approach**

A long-term strategy and investment to establish a well-functioning PMIS is essential to support HIV/AIDS programs as they scale up. Efforts to strengthen PMIS systems can take time but ultimately can improve the effectiveness of all pharmaceutical management functions. These benefits can extend to the management of other essential medicines in cases where programs are integrated.
HE FIRST IN-COUNTRY ASSESSMENT by the Global Fund required Swaziland to implement a reliable patient-monitoring and ARV-tracking system before the Global Fund would authorize funds of about US$7 million to purchase ARVs to support expansion of the national HIV/AIDS program. In January 2006, the Ministry of Health and Social Welfare, with assistance from the RPM Plus Program funded by USAID, began strengthening ARV supply management systems at all levels in the country by installing an integrated, computerized pharmaceutical management software—RxSolution—that supports the management of orders, receipts, issues, stocks, and dispensing of medicines at ART facilities.

By the end of July 2006, 11 hospitals and health centers were using RxSolution, and the ordering, inventory management, distribution, and dispensing of ARVs was fully computerized. In addition, system users were generating routine management reports to monitor stock levels and consumption trends, patient loads, and prescribing practices, and submitting them to national- and facility-level managers. By February 2007, no ARV stock-outs had been reported, and in May 2007, the local funding agent recommended that the funding restriction be lifted and that the patient monitoring system be integrated into RxSolution.


computer and manual systems and to provide the necessary training and support.

**MANAGEMENT SUPPORT: MONITORING AND EVALUATION**

Monitoring and evaluation provide the integral link between planning for scale-up and implementation. The challenge for many countries lies in sustaining the quality of pharmacy services as operations expand. With this expansion, managers need to monitor the performance of the pharmaceutical management system without overburdening staff with reporting requirements. Operations research can help identify important lessons on how best to strengthen pharmacy systems for scaling up HIV/AIDS interventions in a way that improves services for all health-care programs. Most importantly, programs are often required to demonstrate results to support new proposals or justify requests for ongoing funding. Pharmacovigilance systems for monitoring adverse events for newly introduced medicines such as ARVs, and for monitoring the quality of products in the marketplace, are commonly weak in developing countries.
Points to Remember for a Successful Approach

Regularly monitoring a few key pharmaceutical management indicators can help managers detect problems early and address them promptly. Pharmacy managers at both central and facility levels should identify a small set of well-defined indicators and ensure that the PMIS routinely collects data to generate and report these indicators. Indicators are useful for evaluating the impact of an intervention designed to address a pharmaceutical management problem and are essential for demonstrating results to donors.

Existing mechanisms for monitoring and evaluation should be used where possible. To minimize the monitoring workload, checklists used for self-monitoring by the pharmacy staff or by supervisors can be adapted to add selected HIV/AIDS program parameters. Similarly, selected HIV/AIDS medicines can be included in the tracer medicine list used by supervisors to track the performance of the essential medicine supply systems. Integrated monitoring systems also enable managers to promptly identify negative effects of HIV/AIDS scale-up on other programs. Efforts to strengthen pharmacovigilance and quality surveillance for HIV/AIDS medicines can be an opportunity to strengthen or develop national systems where none exist.

**MANAGEMENT SUPPORT: ORGANIZING SYSTEMS AND SUPPORTING PHARMACY STAFF FOR GOING TO SCALE**

The benefits of establishing mechanisms at the central level to coordinate procurement and capacity-building activities have been discussed. Likewise, good communication and coordination at the facility level are essential for successful supply management in order to support program introduction and scale-up. Technical and programmatic pharmaceutical management issues will need to be addressed as operations expand. Likewise, the pharmacy will need to set up linkages with other service providers to deliver services effectively, for example, to manage referrals to other departments within the facility or to follow up with patients who are late in collecting their ARV medicines.

The availability of HIV/AIDS-related medicines is dependent upon the leadership, planning, and management capabilities of pharmacy staff as well as their ability to forecast, order, distribute, and monitor pharmaceuticals effectively. However, pharmacists are in short supply in many developing countries, especially in the public sector and rural areas. Other staff must learn new skills and take on new roles where severe shortages of pharmacists exist so that pharmacists can focus on essential oversight activities. Training and retaining pharmacy workers as programs expand to include new interventions and practices is vital for the long-term success of HIV/AIDS initiatives. Training approaches that use one-time intensive sessions to transfer large amounts of information rarely lead to lasting improvements in practice and are even less useful where staff turnover is high.

Points to Remember for a Successful Approach

A facility-level committee, such as an ART team, that plans and reviews progress in scale-up can anticipate pharmaceutical management constraints and address problems promptly as they emerge. The ART team can also help the pharmacy staff quantify needs by identifying potential changes in guidelines or prescribing practices and developing projections for expansion. The role of the various staff in providing medication counseling can also be reviewed to identify gaps in the information being provided to patients and unnecessary duplication of efforts.
CASE STUDY 5: TRANSITIONING THE MANAGEMENT OF ANTIRETROVIRALS AND RELATED PHARMACEUTICALS IN LAOS

The Lao People’s Democratic Republic has been providing services for the diagnosis, care, and treatment of people living with HIV since 2001, with the financial and technical support of Médecins Sans Frontières (MSF). As of September 2007, 663 patients, including 44 children, were receiving ARVs in two outpatient sites.

MSF will continue its support through September 2008, when the Lao Ministry of Health (MOH) will take over responsibility for managing the ART program through the Center for HIV/AIDS/STI, which has to date primarily provided policy and technical guidance. Support for the ART program will be provided through Round 6 funding from the Global Fund.

This transition requires careful planning, since the MOH has not been responsible for the process of quantification, procurement, importation, and distribution of ARVs and other pharmaceuticals, nor the overall management of the program. Furthermore, the provision of medicines in Laos is fragmented, and essential programs are largely donor driven. MSF has implemented manual and electronic systems to track data for patient care and the management of medicines, and supported personnel dedicated to data entry and monitoring and supervision. The MOH plans to expand ART access to five sites within two years, and for three of these sites, implementation of ART will be a new undertaking. MSF has begun planning this transition together with the MOH. It is anticipated that this will be a collaborative process with partners to develop a comprehensive transition plan, evaluate technical assistance needs to support its implementation, and identify human and other resources needed.

Source: Médecins Sans Frontières Switzerland / Laos office and Management Sciences for Health / RPM Plus.

The pharmacy may need to establish linkages for a variety of tasks:
- Managing referrals to and from other facilities
- Following up on patients who are late in collecting ARVs
- Reporting adverse drug reactions
- Providing pharmaceutical support to sites without a pharmacist
- Informing patients about other services at the facility or in the community

Partnerships can enable governments to quickly fill priority vacancies in the public pharmaceutical sector and gradually absorb new personnel. By basing human resource interventions on existing government systems, donors and technical assistance partners can facilitate their eventual integration. In Namibia, PEPFAR committed funds through USAID to support additional pharmacy positions. The Management Sciences RPM Plus Program worked with the Ministry of Health and Social Services to develop a mechanism to hire pharmacists and assistants for priority positions. These positions were aligned with ministry priorities, job descriptions were made commensurate with the public sector, remunerations were set in accordance with government policies, and
ministry staff were involved in selection and supervision. After two years, 18 of 28 pharmacy staff recruited by RPM Plus to support ART scale-up had been absorbed into the government system.21

Pharmacists need training, tools, and a supervisory structure in order to be able to provide technical oversight to facilities without a pharmacist. Pharmacists need good leadership, management, and communication skills to mentor and assist staff to resolve problems and improve services. Support can include assisting staff to quantify needs and calculate storage requirements for program scale-up, implementing SOPs, and assisting teams in conducting rational-medicine-use reviews.

To achieve capacity-building goals for pharmaceutical management, countries need a national training strategy that synchronizes needs for trained pharmacy staff with scale-up goals and incorporates strategies to prepare health-care staff to take on new roles. Performance improvement strategies, such as the monitoring, training, and planning (MTP) approach,22 that empower pharmacy staff to achieve and sustain improvements in the workplace can be an effective alternative to traditional training approaches.

MANAGING REAGENTS, SUPPLIES, AND EQUIPMENT FOR THE LABORATORY: SPECIAL CONSIDERATIONS

In this section, some of the issues that are specific to managing laboratory reagents, supplies, and equipment for HIV/AIDS programs are briefly discussed. Other chapters in this section discuss laboratory diagnostics and patient monitoring at greater length. Interventions to strengthen supply management at the laboratory are usually developed as part of a national laboratory strategy by the ministry of health and national public health laboratory in collaboration with partners, such as the Centers for Disease Control and Prevention (CDC). To be effective, efforts to improve the availability and management of laboratory commodities must complement and support the efforts and inputs of the CDC and other partners who work with governments to build laboratory capacity in developing countries and provide assistance in obtaining equipment, reagents, and other critical supplies. A lack of functioning equipment and interruptions in the supply of laboratory reagents are common to HIV/AIDS programs in many developing countries. Laboratory commodity management systems are invariably weak due to years of underinvestment and neglect. Although funding for reagents, equipment, and supplies has increased substantially in some countries in recent years, laboratory management systems in general will require substantial strengthening in order to leverage and absorb these additional investments. The lack of standardization of laboratory supplies and equipment makes procurement and quantification difficult, and many countries do not yet have a dedicated budget for laboratories. Many laboratory tests are used for other programs in addition to HIV/AIDS, which further complicates quantification and budgeting but does favor integration over parallel supply systems. At the facility level, the pressure of the existing workload is already taxing laboratory staff, equipment, and systems. Laboratory staff typically lack the necessary training, management support, financial allocations, and tools to manage supplies effectively.

Points to Remember for a Successful Approach

Strengthening supply management at the laboratory requires time and a stepwise approach. Laboratory assessments usually reveal numerous commodity management problems and may require some operations to be set up from scratch. Focusing initial activities on the most critical and essential tests needed to support HIV/AIDS
programs, in addition to prioritizing interventions, enables implementers to establish working systems sooner and to gradually expand them to include a wider range of products and services.

Including management staff in commodity management training for laboratory staff enables them to support and ensure efficient use of the laboratory. Strategies to improve the performance of the laboratory commodity management system at the facility level are generally more effective when management and laboratory staff work together to solve problems. This is particularly true for problems related to procurement.

Priority interventions should include strengthening of inventory management at the facility level. Training facility staff in good storage practices and basic inventory management (e.g., introducing stock cards, reorganizing the storeroom, removing obsolete equipment and expired stock) is an essential first step.

A consultative process is needed to standardize laboratory testing requirements for HIV/AIDS programs. The tests and equipment that will be available at each level of health facility should be agreed upon as part of an overall national strategic plan. Although the process can take time, this step is critical to enable procurement staff to quantify needs and develop a procurement and distribution plan. Once agreement is reached, implementation can take time as products work their way through the pipeline. A decision will also need to be made on whether to keep or discard nonstandard equipment currently in use. At the facility level, clinical algorithms for laboratory monitoring should be standardized, and adherence to these standards should be monitored.

Selection and specifications of laboratory equipment should consider the needs of infants and children, where appropriate. For example, laboratory equipment may need to have the capacity to analyze small-volume samples, and CD4 technologies that provide percentage readings may be required.

Where usage data are not available and quantification is based on standard protocols and projected client visits, requirements for quality control, calibration of equipment, training, and wastage will need to be incorporated. If the reagents are used for non-HIV/AIDS purposes, estimates will need to incorporate other uses to avoid stock-outs. Establishing a system to collect consumption data is a priority, particularly at laboratories that serve many sites and a large number of external clients. In such cases, using projected client visits to estimate reagent and supply needs can be especially problematic.
REFERENCES


THIS CHAPTER DESCRIBES THE OVERALL approach to supply chain management for HIV/AIDS commodities in resource-limited settings that was developed by the USAID | DELIVER PROJECT and implemented by John Snow Inc. Since 2000, this approach has been employed in more than 10 countries affected by the HIV pandemic. The challenges and lessons learned in the management of supply chains for HIV/AIDS commodities, as discussed in this chapter, have led to the development of a set of technical strategies and resources that, when tailored to the needs of individual countries and programs, are critical to successful implementation and scale-up of HIV/AIDS programs. The country examples presented in this chapter illustrate specific supply chain interventions that have contributed to strengthening health systems, building human resource capacity, and enhancing the coordination of stakeholder funding, procurement, and technical assistance in supply chain management. These interventions have ultimately resulted in greater reliability and security in the supply of antiretroviral (ARV) drugs, HIV test kits, and HIV-related laboratory commodities for country programs and have helped ensure the continuous availability of these products for the people who need them, when and where they need them.

CHALLENGES IN MANAGING HIV/AIDS SUPPLY CHAINS

While efficient and effective supply chains are needed to support all health service delivery efforts, achieving such supply chains is significantly more challenging and important to consider for HIV/AIDS programs. For example, the success of many HIV/AIDS programs depends on access to the latest HIV/AIDS diagnostic and treatment technologies. As new, more effective and cost-efficient drugs and diagnostics become available, incorporation of these new products into national supply chains can be slowed by bureaucratic registration procedures due to the rigid or cumbersome regulatory environments in many countries.

Supply shortages as a result of budget shortfalls are a common challenge. Budgeting for and procurement of drug commodities in many resource-limited settings are based on available funding rather than on an understanding or rational estimate of actual need. When the supply does not meet the demand, programs are forced to ration the distribution of supplies to the end users—in this
case, people living with HIV and service providers who depend on a reliable supply of medicines, laboratory supplies, and other commodities to maintain their level of health and provide quality services.

Additionally, human resource capacity and skills in supply chain management need strengthening at all levels and across all supply chain functions. Activities critical to a well-functioning supply chain include linking product selection decisions to patient needs and to policies that ensure quality of care, and then reflecting those decisions in the quantification of commodity needs; basing financing and procurement decisions on an established quantification methodology; improving in-country inventory management of HIV/AIDS commodities; and implementing logistics management information systems that inform and drive all supply chain management activities and decisions.

And finally, the fact that procurement planning and procedures are not coordinated with other key supply chain functions, such as financing, quantification, and inventory management, is one of the most common challenges facing HIV/AIDS programs. Coordination efforts are further complicated by the existence of multiple funding sources, procurement mechanisms, and in-country distribution systems.

THE LOGISTICS CYCLE

Logistics refers to the series of activities, resources, people, and information needed to move products through the supply chain to the final customers or end users. The following diagram of the logistics cycle (Figure 1) depicts the key logistics management activities required to operate and maintain a supply chain for health commodities.

As indicated in the diagram, all these activities are interrelated and interdependent. They are all critical for a supply chain to function effectively and efficiently and to be able to ensure an uninterrupted supply of quality products to the end users.

Serving customers is at the top, as customer service is the ultimate goal of the supply chain. For HIV/AIDS programs, the ultimate customer is the person living with or affected by HIV/AIDS.

Based on the ultimate customers’ needs, the next step in the logistics cycle is product selection: choosing which products are appropriate for a service delivery program to meet customers’ needs at a particular point in time. Once the list of products has been determined in compliance with national standard treatment guidelines (STGs), these products should be included on the government’s National Essential Medicines List (NEML) and registered for importation by national drug authorities.

Once specific products have been selected, the next step is quantification of commodity requirements in both the short and the long term. Not only should the quantification include the quantities of commodities needed to serve customers, but it should also include a procurement plan outlining the quantities needed to manage and maintain appropriate stock levels in the country’s supply pipeline.

Based on the quantification of commodity requirements, the financing needed for procurement is determined, funding gaps are identified, and the allocation of available resources or the mobilization of needed resources is undertaken.

After products are procured and shipped, they are cleared through customs and subjected to inspection and quality control checks. Once the products are in the country, inventory management, which includes both transport and storage at perhaps several levels, becomes critical for efficient and effective management of the in-country supply pipeline. Eventually, the products must reach the service delivery point, which might be a fixed health facility, a laboratory, a field-worker’s distribution bag, or a mobile unit.

Finally, the products are dispensed to customers or users, including patients (in the case of ARVs) and laboratory technicians (in the case
of laboratory commodities), and the process repeats itself.

It is important to note that this entire cycle is information driven. Without a functioning logistics management information system (LMIS, depicted at the center of the cycle in Figure 1) to provide data to support decision making for each logistics management activity, the supply chain will not be able to function effectively or efficiently. In addition to an LMIS, other resources, mainly financial and human resources, are needed in order to keep the supply chain functioning.

Finally, quality monitoring mechanisms—of products, services, and system performance—as an overarching activity, must be in place throughout the cycle to track system performance, the impact of interventions, and progress toward the desired outcome of continuous product availability.

Each of these elements will be discussed in greater detail in the sections that follow. In addition, the challenges and lessons learned for each will be described.

**Product Selection**

Product selection is a critical first step in logistics management. The purpose is to select the most effective and cost-efficient commodities to support the goals of the program. When selecting commodities, a number of factors must be taken into consideration, including the following:

- Efficacy and safety
- Product cost and available financing for commodity procurement
- Product storage requirements (such as cold chain), adequate storage space, and conditions to maintain product quality
• Skill level of the personnel using or dispensing the products and any training-related requirements
• Ease of use of the commodity
• Packaging of the products to facilitate distribution
• Shelf life
• Compatibility with existing instrumentation (for lab supplies)

In addition, the product’s registration status with local regulatory bodies needs to be considered. Once registered, selected products must be included in standard treatment protocols and guidelines to ensure their rational use in country programs.

Challenges and Lessons Learned regarding Product Selection

The product selection process can be very complex and time consuming. The following are common challenges and suggested approaches to product selection for ARV drugs, HIV tests, and laboratory supplies.

**ARV Drugs**

The committees involved in updating NEMLS and developing STGs should consult the World Health Organization (WHO) recommendations when selecting ARV treatment regimens that are appropriate for their particular countries as a first step. The WHO publication *Scaling Up ART in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach* provides guidance for countries to facilitate the proper management and scale-up of antiretroviral therapy (ART). In the guidelines, WHO proposes a public health approach geared toward universal access, standardization, and simplification of ARV drug regimens to support implementation of treatment programs in resource-limited settings and to ensure that treatment programs using ARV drugs are based on scientific evidence. The goal is to avoid the use of substandard treatment protocols and to reduce the potential for the emergence of drug-resistant virus strains. In making the product selection decisions, policymakers should also consider key supply chain factors such as formulations, shelf life, cold chain requirements, and packaging, to ensure that commodities can be used successfully at all levels of the health system. The ARV drugs, regimens, formulations, and packaging selected will all affect forecasting, procurement, storage, and distribution.

ART program managers and product selection committees may need to review and update the ARV drugs on a NEML and in STGs frequently to stay in line with the growing body of evidence and experience as treatment is expanded in multiple resource-limited settings. Once updates to STGs and NEMLs have been made, policymakers should consider procurement lead times to ensure the availability of ARV drugs at the time of implementation.

**HIV Tests and Laboratory Commodities**

Deliberate strategies designed to streamline the provision of the many laboratory tests required to support a comprehensive HIV/AIDS program can improve the efficiency, quality, and affordability of testing for the service provider. Test menus, techniques, and equipment used in each country or program are an important consideration when selecting products for procurement. The number of testing platforms used for each test should be reduced in an effort to move toward a laboratory system that makes use of standard equipment across comparable facilities and levels in the health system (i.e., district or regional-level facilities).

Standardization of laboratory procedures and equipment—and thus supplies—can help countries and/or programs better allocate the limited resources available for laboratory services as well as provide the basis for external quality control. Standardization involves defining test menus,
techniques, operating procedures, and equipment for each type of test, for each level of the system, to be applied across all laboratories. The standardization of laboratory procedures and equipment streamlines the quantity and type of laboratory equipment and commodities that are required in countries. Standardization therefore greatly simplifies product selection and allows countries to better allocate limited resources.

Quantification
Once the products have been selected, countries or programs must quantify product needs. Quantification is a critical logistics management activity that links the quantities of product being used and patient needs on the ground to financing and procurement decisions. The quantification results can then be used to better inform manufacturer production decisions.

Quantification relies upon accurate, up-to-date information on
• service provision and consumption/use of commodities,
• stock levels throughout the in-country supply pipeline,
• funding sources and amounts for commodity procurement, and
• national policies and program expansion plans.

Quantification of health commodities involves estimating the quantities and the costs of products required to meet customer demand and maintain adequate stock levels in the supply pipeline. The quantification process takes into account the service delivery capacity, supply pipeline requirements, and resources available for procurement.

Quantification consists of five distinct steps (Figure 2): forecasting product consumption or use; estimating program requirements; calculating the costs for procuring the requirements; adjusting the final quantities to procure according to the amount of funding available (if needed); and developing a supply plan that includes shipment schedules, quantities, funding sources, and suppliers.

Ideally, the quantification exercise should be conducted by a group of key stakeholders including program managers, procurement specialists, and service providers (e.g., pharmacists, clinicians, laboratory technicians) on an annual basis and should be coordinated with government and donor budget cycles. The key benefits of quantification are outlined in Box 1.

The results of quantification may be used to calculate specific order quantities and plan shipment schedules for short-term procurement planning and for medium- to long-term program planning and resource mobilization efforts.

Challenges and Lessons Learned regarding Quantification
The following are lessons learned from DELIVER’s experience in conducting HIV/AIDS quantifications in more than 10 countries. These lessons have since been incorporated into the project’s approach to quantification.

Adequate time, funding, and human resources with appropriate skills to conduct the quantification exercise should be planned and budgeted for. The quantification exercise itself is time and resource intensive. Thus, the success of a quantification exercise is directly related to the extent to which appropriate resources have been deployed to conduct the exercise.

Quantifications should become more evidence-based over time, as the availability and quality of data improve through the strengthening of the LMIS. Data on HIV/AIDS services and product supply are limited and, when available, are often unreliable or insufficient for use in quantifying product requirements. Thus, current quantification exercises are based on informed assumptions as opposed to being based upon past logistics data.
Quantification requires a consultative process with multiple stakeholders and implementers to inform the assumptions about the selection, forecasting, and procurement of HIV/AIDS products. Quantification capacity is limited at the country and program levels, and communication and coordination are typically lacking among key stakeholders and implementers (i.e., policymakers, program managers, service providers, funding sources, procurement agents, and suppliers) on issues related to the selection, forecasting, and procurement of HIV/AIDS commodity needs.

Convening one or more consultative stakeholder meetings throughout the quantification process is recommended to clarify and review the data sources, assumptions, and methodologies used, and to reach consensus on commodity requirements and funding needs. STGs and testing protocols may be inconsistent, may need revision, or may not have been widely disseminated to providers. Consultative stakeholder meetings can be a critical step both toward gaining consensus on guidelines and protocols and toward obtaining buy-in for the results of the quantification process from in-country stakeholders. The meetings
can also serve to facilitate resource mobilization, clarify expectations, and promote collaboration and coordination, especially in the event of disruptions in commodity supply that may affect the availability of products for customers at service delivery points.

The quantification should be based on realistic program plans and on available financing. Program targets may not take into account the service delivery structure’s capacity to increase enrollment of new patients and to continue monitoring existing patients on ART or the supply chain’s capacity to finance, procure, and manage greater volumes of HIV/AIDS commodities. Since multiple sources of funding, procurement mechanisms, and distribution channels are used for HIV/AIDS commodities, quantification and procurement often occur when funding becomes available. This prevents such activities from occurring as part of program planning, when they could be useful for identifying commodity needs and mobilizing resources for procurement in a timely fashion. Performing quantification and procurement only when funding becomes available often leads to stock-outs and expensive emergency procurements.

The results of the quantification should be used to determine specific order quantities and shipment schedules for short-term procurement planning on the basis of available funding. Due to a lack of forecasting data in Zambia, consultation with providers experienced in the provision of first-line ART informed the estimated demand for ART and the breakdown of patients by type of regimen. Because assumptions were informed by providers’ experience, the forecast for first-line ARV drugs was relatively accurate. However, because the program was relatively new, the providers’ experience with second-line treatment was limited. Thus, the assumptions about second-line treatment were less informed by experience and were based largely on expectations, leading to an overestimate in forecasted consumption of second-line ARV drugs. Procurement planning was based on these assumptions—weak as they were—because of the lack of any kind of data. As a result of careful monitoring of consumption, the next second-line drug shipment—scheduled to arrive six months after the quantification and procurement planning exercise—was postponed, thereby preventing a large quantity of expensive second-line ARV drugs from expiring in the warehouse.

The results of the quantification should also be used for medium- and long-term program planning and for resource mobilization for ART. Program managers must prepare medium-term forecasts to be able to coordinate funding and procurement among multiple donors and to ensure uninterrupted supplies of ARV drugs.

The quantification should be reviewed and updated at least every six months, and supply

<table>
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<th>Box 1. The Benefits of Quantification</th>
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<td>■ Assures product selection according to standard treatment guidelines (STGs) and regulatory requirements (e.g., ensures that selected products comply with STGs, are registered in-country, and meet quality assurance standards)</td>
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<td>■ Informs decisions on quantities, costs, and timing of procurements</td>
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<td>■ Facilitates mobilization and allocation of financial resources for procurement (e.g., helps identify and address funding gaps)</td>
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<tr>
<td>■ Enhances timely procurement and shipment delivery planning (e.g., helps coordinate quantities and timing of commodity shipments with existing stock levels to ensure continuous/uninterrupted supply)</td>
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<td>■ Serves as an advocacy tool for supply chain improvements</td>
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Source: USAID | DELIVER PROJECT.
plans should be adjusted accordingly. Program expansion often does not occur as rapidly as expected. Program targets may not take into account either the service delivery structure’s capacity to increase HIV/AIDS testing and treatment rates or the supply chain’s capacity to finance, procure, and manage greater volumes of HIV/AIDS products. Additionally, program targets for increasing HIV testing may not be linked to program targets for increasing ART patient enrollment.

The emphasis in procurement should be on developing supplier relationships that allow for frequent shipments of relatively small quantities of newly manufactured HIV/AIDS products. When possible, the purchasing contract should allow for accelerating or delaying the delivery of products to the program in response to the actual consumption of those products.

The shipment schedule for all HIV/AIDS products must reflect the lead time and shelf life of each product, as well as the current storage and distribution capacity of the program. For example, products with a short shelf life and cold-chain storage requirements may have to be manufactured and shipped to a country at more frequent intervals than products that have a longer shelf life and can be stored at room temperature. The in-country pipeline for those items would need to be shorter and would need to be delivered to service delivery points more frequently. Products with significantly shorter shelf lives, such as HIV test kits, should be distributed from the central level straight to the service delivery points with no intervening layers of storage, handling, or paperwork. All other technical factors being equal, preference in selection should be given to those products that meet efficacy and safety requirements, do not require cold storage, and have longer shelf lives.

Other lessons learned in quantification specific to laboratory commodities include the following:

- Standard operating procedures (SOPs) for testing services are often lacking. Laboratories tend to individually develop their own SOPs, based on personnel experience, resulting in inconsistent techniques and procedures across laboratories at the same level.
- Testing techniques and laboratory procedures are often dictated by the availability of supplies rather than by standard protocols.
- Implementation of a standard system can pose significant challenges since it requires the training of all laboratory personnel in the recommended testing techniques. As a result, many countries are experiencing situations in which they have functioning machines that are not being used in compliance with the recommended SOPs, again leading to inconsistent use of reagents.
- Program targets may not take into account actual testing capacity and/or supply chain capacity to finance, procure, and manage greater volumes of laboratory supplies.

In the absence of logistics data, the most appropriate methodology for quantifying laboratory supplies seems to be service statistics using the number of each test performed over a period of time (with the exception of general laboratory consumables and durables, which require assumptions on usage data in consultation with laboratory personnel).

Prior to quantifying laboratory supplies, a standardization exercise should be conducted to either develop or confirm and update test menus, techniques, testing procedures, and equipment for each level of the health system. For example, in both Kenya and Uganda, DELIVER was tasked with quantifying laboratory supplies. However, quantification was not possible without first implementing a standardization process for the laboratory system. In each country, stakeholders, in partnership with DELIVER, standardized test menus and techniques; this led to a consensual agreement of
the required reagents and consumables needed for each test and to the subsequent reduction, by roughly 60% to 75%, in the number of different commodities requiring management.3

The standardization process should always be a consultative workshop with representatives from all programs and levels that provide testing services, as well as donors and all key players in the provision of laboratory services. The consultative nature of this process is a critical step toward transferring ownership of the results to in-country stakeholders. These meetings can also help mobilize resources, set expectations, and promote collaboration and coordination, especially if delays in commodity availability occur.

Procurement and Supply Planning
The procurement of HIV/AIDS commodities is a complicated process that varies according to the source of funding for procurement, the recipients, and the regulations that are in place in the host country. The global scale-up of HIV/AIDS treatment and care has increased the availability and accessibility of these services, as well as the required commodities. In many countries, the scale-up has also increased the complexity of the procurement environment and processes due to the increased number of players and steps involved. Thus, it is critical that the procurement process be a well-conceived, transparent process that is both influenced by and accessible to all stakeholders involved in HIV/AIDS commodity procurement.

Supply planning is a critical step in ensuring that products are continuously available in the program. The supply plan provides information on the quantities of drugs to be procured, including their costs and the proposed shipment schedules. This ensures that the commodity stock is managed between the desired inventory control levels. In planning procurement, the program takes into consideration the user requirements as determined during the forecast, the stock on hand in the in-country pipeline, supplier lead times, and the buffer stock needed to ensure an uninterrupted supply in the event of an unexpected increase in demand or shipment delay.

Challenges and Lessons Learned regarding Procurement and Supply Planning
Regardless of how well organized, planned, and managed the procurement process is, unexpected delays are inevitable. The following lessons address specific challenges encountered during the procurement of HIV/AIDS commodities.7

Start the procurement and preprocurement process early so that unexpected delays in the procurement and importation of commodities do not undermine program goals. Each recipient country has unique requirements and regulations and, although general steps in the procurement process may be learned, understood, and improved over time, each country’s procurement process and players are unique. For example, delays can be incurred during a preprocurement step, such as quantification, when a program’s STGs or testing algorithms are in flux or are not finalized; such protocols must be completed before needs can be quantified. Programs that have complete and updated quantifications can engage in procurement planning as soon as funds are available for procurement. Planning should establish a clear timeline for the procurement process up to the date the product is required in-country.

Build flexibility into the supply plan, including the shipment delivery schedules, to minimize product wastage and to ensure that manufacturers can continue to meet global demand. Many HIV/AIDS programs are relatively new or rapidly expanding, which makes forecasts less reliable than for stable programs. To make procurement more reliable, there should be built-in flexibility, such as smaller, more-frequent shipments for
IN 2005 IN NIGERIA, THERE WERE four funding sources for ARVs. Just one funding source, the President’s Emergency Plan for AIDS Relief (PEPFAR), had several implementing organizations, each of which partnered with different organizations that were responsible for different functions of the supply chain. Each funding source had different reporting requirements and different procurement restrictions (e.g., the ability to purchase only from manufacturers that are approved by the U.S. Food and Drug Administration [FDA] or are prequalified by WHO). Procedures for the multiple distribution channels or supply chains were not harmonized, with delivery and pickup systems operating side by side, and different formulas required for calculating orders. Often facilities were receiving commodities from multiple sources. In the case of ARVs, the components of a single regimen came from two different supply chains and were available in multiple brands. Service providers were often required to maintain separate records for each supply chain or implementing agency, and they had to collect some drugs and wait for others to be delivered.

As illustrated in Figure 3, having multiple sources of funding and various agencies involved in HIV/AIDS commodity procurement and program implementation complicates HIV/AIDS service provision, and this complexity ripples throughout the supply chain. This complexity influences the effectiveness of a supply chain in several ways. First, the need for coordination is heightened—from standardizing treatment guidelines to distribution and reporting. In Nigeria, standard treatment guidelines for ART varied by implementing partner. National ARV drug quantification was further complicated by the fact that the drugs included in first- or second-line treatment regimens differed across implementing partners, making it difficult to aggregate requirements. This difference, in turn, complicated the coordination of financing and procurement, because national quantification is critical to ensuring that sufficient funding is available for all patients across implementing agencies, and that procurement plans can be developed to ensure that all the ARVs within a regimen or all the tests within a testing algorithm are available simultaneously.

In response to these challenges, a central coordinating body was proposed at the Federal Ministry of Health (FMoH) to facilitate resource mobilization and coordinate procurement and delivery of HIV/AIDS commodities from multiple partners and sources of supply. This helped ensure a continuous supply of quality HIV/AIDS commodities to the federally supported testing sites.
Figure 3. Funding sources, procurement, and distribution of ARV drugs in Nigeria

Source: USAID | DELIVER PROJECT.
products for new programs. Planning for smaller, more-frequent shipments enables programs to avoid bringing in more commodities when programs are overstocked. Conversely, quantities can be added to existing planned shipments to prevent additional costly emergency shipments if product uptake is much higher than expected. However, as programs expand it is important to keep in mind that phasing procurement across several suppliers can add up to several shipments. Therefore, regular monitoring and clear and consistent updates by the procurement agent are critical to enabling programs to stay on track and to navigate the confusion generated by multiple shipments.

**Effective coordination through the sharing of information between partners involved in funding, procuring, and quantifying national needs and/or program needs is essential.** Coordination between in-country partners engaged in separate procurement processes can help ensure product availability and provide flexibility in responding to commodity shortfalls or delays. Effective coordination of all partners involved in procurement or in supply chain management for HIV/AIDS commodities in a country is challenging but can result in significant benefits for the program and for all partners. Many programs receive funding for procurement from multiple sources, and procurement is often conducted through various mechanisms, all of which may have different lead times. Thus, it is important that partners regularly share information on their procurement activities, including quantities of commodities being procured and their delivery schedules. Furthermore, effective coordination among all partners builds a sense of shared responsibility for ensuring continuous product availability and for resolving stock shortages or imbalances when these situations arise.

**Designate a primary contact for each organization or office to ensure clear and streamlined communication.** Developing and maintaining procedures for regular and clear communication among all partners involved in the procurement process can help clarify individual partners’ plans and activities. In order to ensure timely product availability, detailed information on procurement plans must be collected from and shared among all partners involved in the procurement of HIV/AIDS commodities.

This coordination can be achieved by engaging in the following practices:

- Establish clear procedures about regularity and mechanisms of communication.
- Designate individuals to serve as focal points for sharing information and for responding to queries within each organization or office, so that information exchange is not duplicative or contradictory.
- Design standard templates for collecting and sharing information.
- Ensure that all partners are regularly informed about issues that arise, including shipping changes, clearance delays, quality issues, payment requirements, and so on.
- Establish relationships with manufacturers by sharing commodity forecasts in order to minimize global commodity shortages and maximize product availability for recipient countries through strengthened relationships.

**Forecast information is valuable to manufacturers that are experiencing the strain of unpredictable, increasing global demand for HIV/AIDS commodities.** Country- and commodity-specific forecasts enable manufacturers to prepare accurate production projections. Reducing the number of global shortages and product availability crises also benefits recipient countries, donors, and organizations that are committed to ensuring continuous availability of HIV/AIDS commodities.

**Limiting procured items to already-registered products, without exploring options, could**
unnecessarily undermine program goals. Therefore, explore alternative mechanisms for ensuring that unregistered products can be legally imported into recipient countries.

Before a product is eliminated from procurement because of lack of registration, alternatives for obtaining registration should be explored, including mechanisms for fast-tracking registration and for receiving temporary authorization from the national drug regulatory authority of the recipient country to import a nonregistered product. Develop a map of the clearance process to define procedures and assign responsibilities at the country level for all steps in the process.

Defining responsibilities in-country for monitoring shipments, payments, and clearance processes will reduce lead time and potentially lengthy delays, especially if communication procedures are well established. Products can be delayed at numerous points in the process, and understanding the potential obstacles at each stage can help with preventive maintenance. Some obvious but critical steps in obtaining needed information can cause lengthy delays if they are not performed in a timely manner. These include identifying the consignee information and sharing this information with suppliers, determining the length of the customs clearance process, and identifying regulations that govern acceptable remaining shelf lives on imported products. Ensuring that the people responsible for procurement are updated on all issues that arise throughout the process has been a critical factor in resolving bottlenecks. Thus, when follow-up with the procurement agent and manufacturers is required, it can be done instantly.

Developing a stepwise approach to procurement can help multiple partners clearly understand and navigate the process, thereby reducing delays caused by miscommunication. Multiple sources of funding and multiple agencies involved in procurement and implementation complicate management of the program and of HIV/AIDS service provision, and this complexity can carry over into the supply chain. For example, in Nigeria, due to the extensive testing needs of such a large population, there are eight unique funding sources, eight different implementing agencies, and eight different procurement agents involved in the financing, procurement, and distribution of HIV tests. As a result, several different parallel systems have created an environment that, at the national level, makes it extremely difficult for managers to confidently determine whether there are adequate products to meet customers’ needs. Without a clearly defined stepwise approach to procurement, as well as other supply chain functions, the national program is at a heightened risk of delays and stock imbalances due to miscommunication.

Recommendations for Managing HIV/AIDS Supply Chains

A logistics system that manages any health commodity, including ARVs, HIV tests, and laboratory supplies, must have the infrastructure to manage and move commodities to support the supply chain as a whole. The purpose of supply chain management is to ensure a dependable, regular supply of quality commodities at service delivery points.

A well-functioning logistics system is critical to the success of all health programs. Without quality products available for the people who need them, when and where they need them, services cannot be provided.

Specifically, four key supply chain management activities are critical to the success of any supply chain: (1) the inventory control system (ICS), (2) the LMIS, (3) storage, and (4) distribution. These four areas of supply chain management require special consideration when managing ARVs, HIV tests, and HIV-related laboratory reagents and consumables.
While it is highly desirable for all supply systems to be as effective and as efficient as possible, the need for effectiveness and efficiency is even more important when managing ARVs, HIV tests, and laboratory supplies. The specific characteristics of these HIV/AIDS products influence how they are managed and require special adjustments to the supply chain. The particular characteristics of the products and how they are used influence the design of the ICS and LMIS and the storage and distribution networks.

Special characteristics of ARV drugs, HIV tests, and laboratory supplies include the following:\(^\text{10}\):

- Short shelf lives that can range from 6 to 24 months for HIV tests
- High prices, including a significant jump in price when moving from first-line ART to second-line treatment regimens
- Cool storage requirements for some products
- Treatment and testing protocols that require multiple products from multiple sources to be available simultaneously to provide a service
- Dynamic technology for products, leading to constantly evolving treatment and testing protocols
- Higher levels of accountability, including special reporting or other documentation requirements from either donors or manufacturers
- Greater potential for redistribution of products from one facility to another
- Limited number of sites authorized to use the products
- Limited possibility for substitution in the case of stock-outs

**INVENTORY CONTROL SYSTEMS**

Every supply chain must have a clearly defined ICS that informs the commodity manager when to order or issue products and the quantity of products to order or issue, and that helps maintain appropriate stock levels of all products to avoid shortages and oversupplies. The continuous supply of quality ARV drugs and HIV tests can only be guaranteed through the selection, design, and proper implementation of an appropriate ICS.

A number of strategies or ICSs can be adopted to manage commodities of any kind. Some of these, such as a rationing system, are more appropriate in situations in which the products being managed, or the financial resources available to purchase the products being managed, are uncertain. In a traditional rationing system, supplies are allocated based on some set of chosen criteria, for instance, to serve a certain proportion of the poorest clients, to treat a certain proportion of the priority disease burden in the region, or to ensure that a certain product accounts for no more than a certain proportion of the available budget. However, ARV drugs and HIV tests are expected to be in full supply for the desired target number of patients, at least in the short term. To be able to maintain a full supply of products effectively, a maximum-minimum ICS is recommended. Within a maximum-minimum ICS, maximum and minimum inventory levels are set based upon past product consumption. This protects the system from potential stock imbalances by managing the risk of expiries due to overstocks, and by minimizing the need for costly emergency orders due to inadequate stocks. All maximum-minimum ICSs allow resupply decisions based on need and take into account established levels of safety stock; the difference between them determines the point at which an order is placed and which products are ordered.

**Challenges and Lessons Learned regarding ICSs**

The experience of the USAID | DELIVER PROJECT in designing and implementing supply chains for HIV/AIDS and laboratory commodities highlights a few key considerations for ICSs in these contexts.\(^\text{11}\)
Ensure that the length of the supply pipeline accommodates the shelf life of products. The length of the supply pipeline must accommodate the relatively short shelf lives of ARV drugs and HIV tests, which average between 6 and 36 months. Adopting a strategy that affects one element of the supply chain will have an impact on other system elements, and the operation of the supply chain will be adversely affected if any one element is not strong enough to perform under the new requirement. Strategies for minimizing the length of the supply pipeline are listed below and must be selected based on the in-country situation and resources.

- **Utilize as few levels as possible in the supply chain.** This is the single most effective and most common strategy for ensuring relatively shorter in-country pipelines. Although this results in storage and distribution savings, this approach requires more resources for transportation at all levels.

- **Shorten the order interval at one or more levels.** Although this will reduce the pipeline length by reducing the maximum stock level, it will require more frequent reporting and ordering, which may place a burden on service providers to report more frequently and require more frequent transportation (e.g., monthly pickup/delivery instead of quarterly).

- **Reduce the lead time.** Overall pipeline length can be reduced by decreasing the amount of time it takes to fill and process orders and deliver products to the receiving facility. Of course, this increases pressure on personnel and transportation resources. Automation of data collection, reporting, analysis, and order processing can also help to reduce lead times.

- **Maintain lower levels of safety stock.** Safety stock is kept primarily because of uncertainty about the system’s ability to provide routine service. If uncertainty can be reduced—for instance, if suppliers consistently provide timely delivery, if customs clearance formalities are reduced or eliminated, or if communications and transportation within the country are very reliable—the safety stock level can be reduced, along with both minimum and maximum stock levels. However, if the program is rapidly expanding or demand is unpredictable, safety stock should be maintained.

All efforts should be made to reduce the length of the supply pipeline in order to reduce product losses due to expiry. The length of the commodity pipeline (determined by adding the maximum stock levels at all levels of the system) is a key consideration in commodity management. This is especially true for ARVs and HIV tests, as a commodity’s shelf life is often less than 24 months and can be as short as 6 months.

A **forced-ordering maximum-minimum ICS is the most appropriate ICS for HIV/AIDS commodities that require uninterrupted product availability.** In light of the special requirements for ARV drugs and HIV tests, and to take advantage of some of the common characteristics of ART and HIV testing programs, the forced-ordering version of the maximum-minimum ICS has several key benefits. If ordering is linked to reporting, forced ordering will require that all facilities submit a report/order at each order interval, so facilities that are not reporting and/or not ordering can be easily identified. Additionally, any maximum-minimum system allows objective resupply decisions based on need and takes into account established levels of safety stock, with the ultimate goal of having product available each and every time it is needed. Given the lifesaving nature of ART and the public health risks associated with the emergence of ARV drug resistance, uninterrupted product availability must be the primary concern.

Setting a routine reporting period and order cycle for HIV tests, ARV drugs, and laboratory
FROM THE GROUND UP: LAYING A STRONG FOUNDATION

The information is used for calculating resupply quantities to the service delivery points in order to maintain appropriate stock levels. In all programs and for all product categories, logistics managers at all levels need to make routine decisions that affect commodity availability. They need to determine how much of each product to order or resupply, to forecast future demand for a product, and to plan procurements and commodity shipments. They also need to be able to identify potential supply problems at facilities or storage sites or to handle other issues related to commodity management. These decisions must be made using accurate and timely logistics data that are provided by an LMIS. Over the long term, data provided through the LMIS can also help inform policy and product selection decisions.

As discussed above, the LMIS helps logistics personnel collect and manage the information necessary to support sound and objective decision making in managing the supply chain. The goal of this decision making is to ensure an uninterrupted supply of commodities and to identify any problems in the supply pipeline. The LMIS is composed of all the logistics management information systems.

Supplies contributes to effective supply management. During the initial expansion of HIV/AIDS treatment and testing programs, many countries chose to implement a monthly reporting period and order cycle to limit the amount of buffer or safety stock that facilities need to hold and to more frequently to respond to changes in product requirements and adjust procurements. However, as these programs have matured, implementing a bimonthly or even quarterly reporting and ordering period is more sensible, since it relieves the reporting burden on the facility-level staff and the management burden on central-level staff. It can allow central-level staff more time to provide support and supervision to facility staff and to follow up with nonreporting facilities.

LOGISTICS MANAGEMENT INFORMATION SYSTEMS

An LMIS should not be confused with a health management information system (HMIS). The LMIS routinely collects and reports logistics data on commodity use and stock levels from service delivery points to a higher level in the system where specifically, the forms were streamlined to include only information that was being used for logistics decision making, and many of the service statistics, along with other information not directly pertinent to logistics, were removed. After this revision and implementation of the new LMIS, reporting rates from service delivery points rose from 45% to about 80%.

Country example: Logistics management Information Systems

In Zimbabwe, low reporting rates, among other issues, highlighted the need to revise the logistics system, including the logistics management information system (LMIS) tools and processes. In an effort to increase reporting, and thereby provide the central level of the Ministry of Health and Child Welfare with information for decision making, a number of key changes were made to the existing LMIS forms.

Specifically, the forms were streamlined to include only information that was being used for logistics decision making, and many of the service statistics, along with other information not directly pertinent to logistics, were removed. After this revision and implementation of the new LMIS, reporting rates from service delivery points rose from 45% to about 80%.

In an effort to increase reporting, and thereby provide the central level of the Ministry of Health and Child Welfare with information for decision making, a number of key changes were made to the existing LMIS forms.
forms and documentation used to maintain records and produce reports on the logistics system.

An effective LMIS provides regular and timely information to decision makers. Information is used to make short-term resupply decisions and long-term procurement and program management decisions. The need for timely and accurate commodity data increases when there is a rapidly expanding program, as is the case for HIV/AIDS programs, where demand for services and client uptake is highly unpredictable.

**Challenges and Lessons Learned regarding LMISs**

**Link routine reporting to commodity ordering.** There are many benefits to linking routine reports to commodity orders. For example, a system with monthly reporting and monthly ordering has inherent advantages over a system with monthly reporting and quarterly ordering. Often, commodity managers may ignore reporting that does not produce a tangible benefit or result. A tangible result in this case would be defined as receiving commodities as a result of an order linked to a report.

**Data that do not have direct benefit to the management of commodities should not be collected, in order to avoid overburdening the LMIS.** Depending on the needs of the particular program’s existing information systems and the logistics system design, data that are not required for logistics purposes may be included in the LMIS for HIV/AIDS commodities. The LMIS may be required to capture additional types of data, such as service statistics and epidemiological data, which are often needed by different program managers. These types of data can ultimately assist in making logistics-related decisions, such as forecasting. However, reporting formats should not collect any data that do not benefit commodities management. For example, in Zimbabwe, low reporting rates fueled the need to revise the logistics system, including the LMIS tools and processes. In an effort to increase reporting, and thereby provide the central level of the Ministry of Health and Child Welfare with information for decision making, a number of key changes were made to the existing LMIS forms. Specifically, the forms were streamlined to include only information that was being used for logistics decision making, and many of the service statistics, along with other information not directly pertinent to logistics, were removed.

**Always collect and report consumption data for ARV drugs and HIV tests; do not use issues data as a proxy.** While the use of issues data as a proxy for dispensed-to-user or usage data may be acceptable in general essential-medicines programs, the level of rigor and accountability required in ART programs makes this practice unacceptable for HIV/AIDS commodity management. In addition, concerns regarding the security of ARV drugs, HIV tests, and laboratory commodities from a therapeutic, safety, and financial perspective impose greater demands for accountability.

**Refrain from altering the content and formatting of the LMIS to accommodate the funding mechanism.** The landscape of supply chain management for ARVs and HIV tests is marked by the presence of multiple donors operating with different agendas, program objectives and goals, and reporting requirements. Due to these often competing agendas, there may be pressure to determine the contents or data items included on the LMIS according to the requirements of the funding mechanism. However, while funding mechanisms constantly change, typically the logistics data needed to run a system do not change significantly over time. Therefore, data collected on the LMIS forms should suit the particular program needs and be used for decision making; they should not be dictated by individual donor requirements. If funding-mechanism
reporting requirements are so specific as to require additional data or information, then those data or that information should be collected and reported separately, not within the LMIS used for commodity management.

**Lessons specific to ARV drugs include the following**:10
- The patient data that are collected and reported should be limited to the number of new and existing patients by treatment regimen—data that can be used for routine logistics decision making.
- If a system captures estimates of new patients, provide worksheets to translate patient numbers into the product numbers required for commodity management.
- Select and consistently use one unit for recording consumption and stock on hand of ARV drugs (e.g., tablet, capsule, or mL per bottle for liquid formulations).
- Clinical or programmatic information used for program monitoring should be collected separately from logistics data and patient data collected for logistics decisions.

**Lessons specific to HIV tests include the following**:
- To assist in decision making, track usage of HIV tests by purpose of use, brand, and use of test.
- Use the individual test as the unit for recording all HIV-test-related logistics data.
- Manage test-related supplies through the existing system for laboratory supplies.

**Lessons specific to laboratory supplies include the following**:
- Use issues of stock as consumption data. Use and maintain stock-keeping records. Given the difficulty of tracking actual consumption of laboratory commodities, issues from stock at the lowest level—usually within the laboratory itself—should be used as a proxy for consumption. Include commodities used for quality assurance and quality control, as well as wastage in issues when recording issues data.
- Use the unit of issue as the unit for stock-keeping and reporting. The unit of stock-keeping should be the packaging unit of the commodity as received from the source of supply. Examples include a 500 g bottle, a box of 100 slides, and a kit containing 100 tests. If a stain is distributed in 25 g bottles, the unit of stock-keeping is one 25 g bottle. Although actual consumption data will not be collected on most laboratory commodities, a few commodities, known as tracer laboratory commodities, should be tracked by actual usage with an activity register.
- Routinely report stock levels, issues, losses and adjustments, and stock-outs. If using a pull (requisition) system, link reporting with reordering.
- Use an activity register to track the actual consumption of a small number of tracer commodities.

**STORAGE AND DISTRIBUTION**

The purpose of a storage and distribution system is to ensure the physical integrity and safety of products and their packaging as they move from the central storage facility to service delivery points and into the hands of the clients/patients. A sound storage and distribution system will help ensure that products reach the client in usable condition, with minimal loss or waste.

Proper storage procedures help ensure that storage facilities issue only quality products and that there is little or no waste due to damaged or expired products. When all levels of the pipeline follow appropriate storage and distribution procedures, clients can be assured that they have received a quality product.
Acceptable storage facilities (e.g., warehouses, storage rooms) are clean and secure, and adequate distribution systems have dependable and secure delivery vehicles. It is desirable for the pipeline to be as short as possible. In the context of storage and distribution, a shorter pipeline can have a positive influence on the security and quality of the products being distributed. Having fewer levels in a system means fewer storage points and fewer instances of transporting products. Limiting the number of times products are transported reduces opportunities for product damage to occur. There are also fewer people handling the products, which can help to increase accountability and minimize loss, damage, and pilferage.

**Challenges and Lessons Learned regarding Storage and Distribution**

When feasible, the storage and distribution of HIV/AIDS commodities should be integrated into an existing system. Integrating the storage and distribution of HIV/AIDS commodities can help avoid the duplication of activities and result in better use of limited resources. However, it is critical to ensure that integrating these products into an existing system also makes sense from the perspective of overall program and product management concerns. The feasibility of operating a fully integrated system will depend on a number of factors, including the management and reporting structure, the number of facilities involved, and the available resources.

Provide greater security for the storage of HIV/AIDS commodities. Due to the high value of HIV/AIDS commodities, higher levels of security are required for these commodities. Storage facilities should include a locked storage area within the warehouse or storeroom, providing limited access to HIV/AIDS commodities; higher levels of accountability should be required, and more frequent audits performed.

Ensure increased security of HIV/AIDS commodities during transport. Transport should provide the same level of security for the product as the storage facility does. Vehicles used to transport high-value commodities must be secure, with an enclosed bed and locking doors. For personal security, drivers should be equipped with radios and be in frequent communication with their dispatchers while on delivery.

First-to-expire, first-out (FEFO) inventory management procedures should be used in order to limit losses incurred due to product expiry. Because of the short shelf life and high cost of HIV/AIDS commodities, special care must be taken to follow FEFO stock management. Product expiration dates should be monitored to ensure that products are used before expiration to reduce waste. In addition, commodity managers must take action immediately if there is a risk that products will expire before they can be used. Action may include returning the products to the supplying facility for redistribution or directly transferring the products to a facility that can use them before they expire and notifying the procurement and program management units of such actions.

When reissuing returned drugs, special attention should be given to ensure the maintenance of product integrity. In HIV/AIDS programs, excess supplies may be returned to issuing facilities. Although guidelines regarding product contamination must be respected, in some programs these products may be reissued for use by other patients or clients. If reissuing occurs, these products must first be inspected. If the product’s packaging shows no signs of tampering or damage, and if the product is not close to expiry, it can be reissued for further use.

HIV/AIDS commodities should be delivered to accredited sites only. Commodities should be distributed only to sites that are accredited or otherwise authorized to use them. This is easy to control in a vertical system; only authorized sites will
be submitting orders for those products. In an integrated system, an extra level of control or oversight may be required. This may mean separate order forms for HIV/AIDS commodities, which are submitted only by accredited facilities, or it may mean an extra signature by program personnel authorizing the order to be filled. Keep in mind that there should not be so many controls in place (e.g., extra signatures) that movement of the commodities is delayed.

Consider using private or other courier/express mail facilities. Depending on the number of sites to which commodities are being delivered and other available resources, it can be advantageous to use local courier or express mail (post office, DHL) services to distribute HIV/AIDS commodities. If the number of sites is extremely limited, it may be much less expensive to distribute products through these channels rather than maintaining one or more vehicles and the personnel needed to operate them. However, keep in mind that couriers must also be able to maintain product safety and follow security guidelines, including cool storage for those products that require it.

Ensure that products used together are distributed together. Some HIV tests come packaged with most, if not all, of the consumable supplies needed to run the tests. However, several available tests do not come equipped with the necessary supplies. ARV drugs must be used in certain combinations in a specific regimen. If one drug is missing from a regimen, no substitutions can be made, and the patient cannot be treated. In both cases, all necessary products are ideally ordered together to provide the services the customers need. It is essential that the entire complement of products ordered is distributed together, at the same time, so that services such as HIV tests and ART can be given immediately upon receipt. If a reliable supply chain already exists for laboratory consumables, including those used with HIV tests, then that supply chain can be used to order and distribute lab supplies. It is then the job of the service provider to ensure that all necessary supplies are available where and when services are provided.

ARV drug prescribing and dispensing practices and HIV testing practices should be standardized. Nonstandardized practices cause distorted consumption patterns and stock imbalances, resulting in an inability to accurately assess the stock status (months of stock on hand) of HIV/AIDS commodities for the national program. Therefore, national programs should standardize practices. For example, new programs should institute monthly prescribing and dispensing practices to allow for close monitoring of consumption and stock on hand of each ARV drug. This will help minimize stock imbalances and prevent stock-outs.

CONCLUSION

HIV/AIDS commodities pose many unique challenges to supply chain managers. In order to overcome these challenges, supply chain management activities must be executed in a coordinated and deliberate manner that is continuously linked to procurement. Creating and maintaining this link will lead to more efficient and effective supply chains, resulting in increased product availability at all levels of the health system.

The essence of the quantification process is to ensure that there is continuous availability of commodities within the system. This process should be broad based and should include inputs from all stakeholders involved in the supply and management of these commodities.

The context within which HIV/AIDS programs are implemented is constantly changing, requiring an agile supply chain that can respond to this dynamic environment. However, it is important to note that all supply chain interventions must also be implemented within the prevailing regulatory
environment. National policies and procedures must be used to inform procurement and supply chain management decisions in order to ensure continuous product availability.

It is also important to clearly define and harmonize all policies and procedures related to each supply chain, such as ART guidelines, prescribing and dispensing protocols, HIV testing protocols, and laboratory testing menus that outline specific tests and techniques at each level. These policies and procedures will effectively simplify supply chain interventions.

Finally, critical to the success of any HIV/AIDS program is the coordination and collaboration among all stakeholders involved in the procurement process, whether procurement is conducted through a single channel or multiple channels. Coordination of stakeholder inputs and activities can greatly enhance the effectiveness and efficiency of the supply chains for HIV/AIDS commodities.
REFERENCE LIST


The clinical course of HIV infection is characterized by active replication of HIV during periods of clinical latency, with resulting depletion of CD4 T lymphocytes. The rate of CD4 depletion is highly variable between individuals. Progression from initial HIV infection to AIDS can occur within months to years, and median survival ranges from approximately 8 to 12.5 years in the absence of treatment, with older age at seroconversion and higher HIV RNA levels within 12-36 months of seroconversion both associated with rate of disease progression.1-3

Current treatment guidelines recommend the initiation of combination antiretroviral therapy (ART) based on clinical status with incorporation of CD4 data where available.4,5 CD4 count and pretreatment HIV RNA levels have been correlated with risk for progression to AIDS.6 CD4 T-lymphocyte counts and HIV RNA levels once ART is initiated are associated with response to treatment7 and risk of disease and death.6 HIV RNA following ART is a surrogate marker of virologic response that has been used in clinical trials, in observational studies, and to license new therapeutic agents. Randomized clinical trials have employed outcomes including the maintenance of HIV RNA levels below 50 copies/mL or 400 copies/mL, although there is little clinical evidence of a difference in the threshold value used to assess virologic suppression. A retrospective analysis by Powderly et al, however, showed increased durability of sustained virologic response to treatment among individuals attaining HIV RNA levels below 50 copies/mL compared to nadir HIV RNA levels between 50 and 400 copies/mL, with time to virologic suppression also found to be a key prognostic factor in the durability of virologic response to treatment.9

The cost of CD4 cell count and HIV RNA testing has been a deterrent to the widespread availability of these technologies in resource-limited settings. CD4 cell enumeration is more widely available than HIV RNA testing. CD4 cell responses, however, do not necessarily correlate with HIV RNA responses to treatment. Discordant responses in CD4 cell count and HIV RNA levels during ART occur in a substantial proportion of subjects. Discordant responses include virologic response after 16-24 weeks that does not meet the currently recommended levels of <400 copies/mL using a standard HIV RNA assay or <50 copies/mL using a sensitive HIV RNA assay,
accompanied with a substantial rise in CD4 cells. Alternatively, individuals with virologic suppression to <400 or <50 copies/mL may not demonstrate an increase in CD4 cell counts. The impact of discordance in HIV RNA and CD4 cell count responses during ART was evaluated by Moore et al. Those with a concordant virologic response to <500 copies/mL and a gain of >50 CD4 cells per mm$^3$ within a median of six months of starting ART had the lowest hazard of death, and a progressively increasing hazard of death was identified among those with virologic suppression without a gain in CD4 cells, individuals with a gain in CD4 cells without virologic suppression, and—the highest hazard—those with persistent viremia and no gain in CD4 cells.

Use of a combination of CD4 counts and HIV RNA testing in the management of ART provides higher prognostic estimation of the risk of disease progression than does the use of either test alone. Viremia >1,000 copies/mL despite ART is strongly associated with increased risk of progression to AIDS among individuals whose initial CD4 lymphocyte count was >250/mm$^3$. Conflicting data exist on the importance of low-level viremia and emergence of drug resistance, with some studies demonstrating continued immunologic benefit without significant emergence of drug resistance, while other studies suggest continued evolution of drug resistance with low-level viremia.

With the advent of lower-cost alternatives, the possibility of implementing CD4 count and HIV RNA testing in the management of ART in resource-limited settings is increasing. CD4 counts are measured using fresh blood samples, while HIV quantitation and drug resistance testing can be performed on plasma stored at -70$^\circ$ C to optimally preserve viral RNA. Methods to circumvent the need for refrigeration include the use of dried blood/plasma spots, which increases the capacity for storage and transportation of samples to centralized laboratories for HIV RNA and drug resistance testing. In this chapter, we will review the various methodologies available and affordable assays in development that may be used to quantify CD4 T lymphocytes and HIV RNA, and discuss methods used to identify HIV drug resistance.

**CD4 T LYMPHOCYTE ENUMERATION**

Peripheral blood mononuclear cells (PBMCs) express unique proteins on the cell surface, often associated with immune function. Cells with different immune functions express different surface molecules. These surface proteins are designated “CD” (for “cluster of differentiation”) and are followed by a numerical designation. Over 300 CD molecules have been described.

All PBMCs display CD45 on their surface, albeit in varying concentrations—with more monocytes than granulocytes and more lymphocytes than monocytes. Monoclonal antibodies to the CD45 surface protein can therefore be used to separate PBMCs from other blood cells. T lymphocytes express different cell-surface CD proteins; while both helper and cytotoxic T lymphocytes express CD3 surface protein, helper T cells express CD4 surface protein and cytotoxic T cells express CD8 surface protein. Even though CD4 T cells comprise only about 0.1% of the cells in peripheral blood, these cells play a pivotal role in the immunology of HIV, since the death of this cell type leads to severe immunodeficiency.

Since a decrease in CD4 T cells is associated with increased risk for opportunistic infections, disease progression, and mortality, CD4 T-cell count monitoring has become the gold standard for determining prognosis and staging for eligibility for ART and antimicrobial prophylaxis against opportunistic infections. Moreover, recent studies have indicated that CD4 enumeration is a cost-effective intervention when compared to clinical monitoring alone in resource-limited settings.
There are multiple types of technologies for CD4 T-cell enumeration. Ultimately, the goal of CD4 T-cell monitoring is the determination of the absolute numbers (per μL of blood) and the percentage of CD4 T cells. In addition, CD4 T lymphocytes as a percentage of total lymphocytes is used for pediatric monitoring. Technologies for CD4 enumeration must, therefore, differentiate PBMCs from red blood cells (RBCs), lymphocytes from PBMCs, T lymphocytes from B lymphocytes, and CD4 T lymphocytes from CD8 T lymphocytes.

The technology selected for CD4 cell monitoring is best chosen based on the nature of the laboratory service being delivered. So, in advance of obtaining these technologies, a careful assessment of specific local demand for testing and laboratory capacity should be undertaken. For instance, will there be a requirement for absolute CD4 counts (adults) and/or CD4 counts as a percentage of total lymphocytes (children)? Will there be a low, medium, or high volume of patient samples? What are the projected changes in sample volume? Is an adequate supply of trained laboratory staff readily available to meet the volume demands? What are the funding limitations? Thus, it is imperative that when selecting a particular CD4 enumeration technology, the present needs of the laboratory and the requirements forecast for future expansions be considered. Methods for CD4 enumeration range from manual procedures to high-throughput systems. One size does not fit all, so the particular methods and materials chosen for CD4 enumeration should reflect the clinical demand, laboratory capacity, and budget.

**Fluorescence-Activated Cell Sorting**

*Conventional Flow Cytometry*

Globally, BD FACS Calibur, Coulter Epics XL, Coulter FC 500, Partec CyFlow SL, and Apogee A40 account for most of the conventional systems in use today for the enumeration of CD4 cells. These systems measure cells in flow. Fluorescence-activated cell sorting (FACS) simultaneously measures multiple physical characteristics of cell flux in a fluid stream through a beam of light. Fluorescence intensity, via fluorescent antibodies coating cell-surface proteins, provides an effective method for cell sorting and the enumeration of CD4 T lymphocytes.

The fluorescence-activated cell sorter is a machine that can rapidly separate the cells in a suspension on the basis of size and the fluorescence color. Briefly, a cell suspension containing cells labeled with a fluorescent dye is directed into a thin stream so that all the cells pass in single file. The dye is coupled to a monoclonal antibody and binds to those cells coated with the antigen for which the antibody is specific. This stream emerges from a nozzle vibrating at some 40,000 cycles per second, which breaks the stream into 40,000 discrete droplets each second. Some of these may contain a cell. A laser beam is directed at the stream just before it breaks up into droplets. As each labeled cell passes through the beam, its resulting fluorescence is detected by a photocell. If the signals from the two detectors meet either of the criteria set for fluorescence and size, an electrical charge (+ or -) is given to the stream. The droplets retain this charge as they pass between a pair of charged metal plates. Positively charged drops are attracted to the negatively charged plate and vice versa. Uncharged droplets (those that contain no cell or a cell that fails to meet the desired criteria of fluorescence and size) pass straight into a third container and are later discarded (Figure 1). This apparatus can sort as many as 300,000 cells per minute. The cells are not damaged by the process. In fact, because the machine can be set to ignore droplets containing dead cells, the percentage of viable cells among the sorted cells can be higher than that in the original suspension.19,20
**Optics:** Lasers, lenses, and filters illuminate cells and cause excitation of fluorescent molecules, signals that can be captured for analysis. As particles pass through the laser, light is scattered and the tagged surface molecules fluoresce. Lenses collect scattered and fluorescent light. Optical mirrors and filters route specified wavelengths of light to detectors.

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**Figure 1. Schematic representation of FACS analysis**

*Components of FACS: fluidics, optics, electronics*

The components of the FACS machine work together to determine how cells scatter laser light and emit fluorescence as the cells pass through the laser.

**Fluidics:** Fluid dynamics create a stream of liquid containing cells, spaced to pass through the laser beam one at a time. The laser beam path intercepts this line of cells.
Laboratory and pharmacy services...
training for a laboratory technician to achieve proficiency. When beads are required for calibration and to convert from a dual to a single platform, the cost of running the assay can be doubled.

Pan-leukogating (PLG) is a method for CD4 enumeration developed in South Africa. The method has been validated repeatedly.21 PLG uses specific flow cytometry labeling and gating strategies that analyze the side scatter of CD45 fluorescence and CD4 fluorescence to identify cells of interest. It is able to determine total lymphocytes and the CD4 percentage of total lymphocytes for pediatrics. Since the side scatter of CD45 and CD4 do not change significantly within a five-day period, the use of PLG has the advantage that cells may be batched and the analysis performed later in the workweek. PLG is generally used as a dual platform (the technician would need to add calibration beads to use PLG as a single platform, however, which would significantly increase the cost of the test).

**Dedicated Flow Cytometry**

Dedicated flow cytometry systems (e.g., BD FACSCount, Partec CyFlow Counter, PointCARE AuRICA) use a known concentration of whole blood (50 μL) in a tube containing the monoclonal fluorochrome-conjugated antibodies anti-CD3, anti-CD4, and anti-CD8. The monoclonal antibodies are conjugated to yellow or red fluorescent dye. A fixed number of fluorochrome-labeled polystyrene reference beads are also present in the sample tube. Labeled cells are treated with a fixative and then placed into the flow cytometer. In the flow cytometer, the labeled cells pass through a green laser beam in single file. This causes the cells and beads to fluoresce. Computer software sets a “threshold” for separate groups of cells. Only signals with intensity greater than the set threshold value will be processed. This allows signals from nontargeted cell groups and cell debris to be filtered out. The method excludes most erythrocytes, platelets, monocytes, and granulocytes. CD3 lymphocytes and reference beads appear above the set threshold. Software automatically sets fluorescence gates around groups of cells. An elliptical region (gate) is set around each cell population. The machine optimizes the position of the gate based on the cluster center, and cells are counted within the gated region.

The gate defines the numerical or graphical boundary of the targeted cell population. Different cell-surface markers and/or degrees of light scatter can be used to define cell populations. Gated cells are divided further into T cells and non-T cells based on staining and the fluorescence of the CD3 monoclonal antibody. Staining of the gated T-cell population for surface expression of CD4 or CD8 is performed using a monoclonal antibody for each CD4 and CD8 T cell, measured in separate tubes (one tube uses CD3/CD4 and the other uses a CD3/CD8 combination). The machine software counts and analyzes the cells in the appropriate gate. The instrument prints the results, which include the absolute numbers of CD4 (positive for both CD4 and CD3), CD8, and CD3 T lymphocytes; the CD4-to-CD8 lymphocyte ratio is also provided.

Two of the more commonly used dedicated instruments, the FACSCount (BD) and the CyFlow Counter (Partec), have several important differences. These single-platform technologies use either calibration beads (FACSCount) or volumetric sampling (CyFlow Counter) in place of the hematology analyzer used in dual-platform systems. In the FACSCount, reference beads are used to measure volume indirectly; one disadvantage of this technique is that the use of beads adds considerable cost to the assay. Volumetric sampling does not use reference beads and therefore is significantly less expensive. In addition, unlike the FACSCount, the CyFlow Counter allows the use of bottled water in place of sheath fluid, which not only substantially decreases the cost of the assay but also decreases the amount of waste generated.
Advantages of the dedicated systems include that they are less expensive than other flow cytometers and they fully automate the calculation of total cell counts (FACSCunt and AuRICA). They lead to less human error because operator-specific interventions are minimized. These are single-platform machines that do not require separate hematology equipment. RBC lysis may not be required, decreasing the time and cost involved (FACSCunt and CyFlow Counter). In addition, external quality assurance (EQA) programs are available to ensure ongoing accuracy. A CyFlow Counter can be powered by a 12-volt battery and AuRICA reagents do not require refrigeration. Disadvantages include the fact that dedicated systems are for adult monitoring only (FACSCunt and CyFlow Counter), because although CD4 T lymphocytes can be enumerated, these machines do not determine total lymphocyte counts. These are closed systems that use the manufacturer’s reagents, and the reagents can be relatively expensive. Importantly, these systems can be used only for CD4 enumeration and cannot be expanded to other types of assays. Moreover, there is a requirement for some computer software literacy on the part of the operator (e.g., CyFlow Counter). Incorrect reading of the sample fluid level can be a source of error. Special care must be given to distinguish CD4 lymphocytes from CD4 monocytes (CyFlow Counter, AuRICA).33-32

**Microcapillary Flow Cytometry**

Microcapillary flow cytometry technology (Easy CD4/CD8, Guava Technologies) is a relatively recent addition to the world of flow cytometry and differs from conventional methods in that it does not utilize sheath fluid to move the cell suspension. Instead, cells are adjusted in suspension to enable them to pass in a known concentration through a microcapillary filament that permits contact with the laser one cell at a time. The concentration is determined by the volume of the sample and the volume of reagents added. It uses CD3 for T-cell gating. Alternatively, CD2 + CD19 for lymphocyte gating can be used. CD2 surface protein is present on T cells and natural killer (NK) cells, and CD19 surface protein is present on B cells; T + B + NK cells = total lymphocytes. CD2 and CD19 are linked to a single fluorochrome, so if either cell-surface marker is present the cell will fluoresce the same color. Thus, since the microcapillary system is able to enumerate total lymphocytes, the CD4 count as a percentage of total lymphocytes can also be determined, allowing this method to be used for both pediatric and adult monitoring.

Microcapillary flow cytometry has several advantages: it requires only 5-10 μL of blood/sampling; the system requires minimal training, in contrast to conventional FACS; and no sheath fluid is required, which decreases cost and biohazardous waste. In addition, it is an open platform and therefore can use reagents from other manufacturers. The reagents cost relatively less than those for the other systems. Daily control is inexpensive (US$0.60/day). Since it is not a dedicated system, the instrument can potentially be used for other assays besides CD4 monitoring. Minimal daily maintenance is required, and the instrument is easy to operate. Reagents are heat stable (refrigeration is recommended, however) and can perform well when stored for up to one month at 37° C. The disadvantages of microcapillary flow cytometry include a requirement for computer literacy and knowledge of the principles of flow cytometry. The assay is operator dependent, since the operator controls gating. Also, there is a requirement for RBC lysis, which increases the processing time per sample.33-36

**Manual Methods for CD4 Enumeration**

Dynabeads and cytospheres are inert latex spheres—“beads”—that are coated with a murine monoclonal antibody. Whereas Dynabead assays use magnetic beads, cytosphere assays do not. Both of these
manual assays are highly labor intensive. Appropriate training and quality control are required to minimize operator variability and ensure confidence in the validity of the results. The advantages of manual methods are that they require simple technology with minimal equipment beyond a low-cost microscope; they can be performed at remote sites, they are useful for laboratories with few samples, there is no need to buy a flow cytometer, and costs are significantly reduced because there is no need to repair and maintain expensive instruments. The disadvantages of manual methods are that they can only be used for adult monitoring (since these methods cannot calculate the CD4 percentages of total lymphocyte counts), they have low throughput (approximately 10 samples per day), they are labor intensive (approximately 10 minutes per sample), and subjectivity is introduced since cells are counted visually. Furthermore, manual methods are impractical in large cities with large numbers of samples to be tested. Samples with higher cell counts are prone to inaccuracy due to overlying nuclei, and the absence of standardized practices for EQA may limit confidence in results. In addition, the hemacytometer is fragile and can break easily, samples must be processed within six hours, and it is difficult to differentiate monocytes from lymphocytes (cytospin assay).

**Future Technology: Microfluidics and Cell Affinity Chromatography**

Microfluidics and cell affinity chromatography is a promising technology that is currently in development and has recently been validated. The microchip device is a self-contained system that uses a direct volumetric method and requires no labels, beads, or other reagents and can thus greatly reduce the cost and complexity of CD4 enumeration. Only a small sample volume (10 µL) is necessary; an assay could be performed with a finger-prick sample of blood, avoiding venipuncture and minimizing medical waste. These advantages would make the assay feasible in remote settings with limited laboratory infrastructure and would greatly expand the types of health facilities at which CD4 cell testing could occur.

The key elements of the approach include a microfluidic channel with immobilized monoclonal antibodies for affinity isolation of CD4 cells from unprocessed whole blood, microliter volumes of sample and wash buffer, and efficient CD4 T-cell capture with minimal contamination by blood monocytes. CD4 cell counts are obtained by enumerating all cells isolated from a 10 µL volume of blood, using an inverted light microscope. The assay is rapid and requires only 10 minutes from blood collection to cell count. In its current format, only two simple accessories, a pump and a basic light microscope, are required for the entire assay. At high and low CD4 counts there may be cross-contamination by monocytes, giving falsely decreased CD4 counts. Clearly a promising technology, the microchip will need to be tested under field conditions before it can be routinely implemented in resource-limited settings.

**QUALITY CONTROL**

All systems require calibration and the use of control samples. These samples are produced by individual instrument manufacturers. Calibration samples are used to set instrument parameters. Control samples are used to test assay performance. These controls may be obtained through preserved blood samples or normal donor samples. Calibration samples and control samples must be processed daily to ensure the correct performance of the instruments and reagents used for patient testing. Many laboratories do not perform internal quality assurance (IQA), however, due to the associated cost; calibration samples can be rather expensive, and processing control samples requires the use of antibody reagents.
Internal Quality Assurance
Fluorochrome-labeled beads within test kits should be analyzed at recommended intervals. Control beads may be used to test the performance of various instruments, for example, the FACSCount Control Kit uses beads at known concentrations (zero, low, medium, high) to test the linearity of the system and to compare its results to known results for calibrators, which are used to ensure that machines are calibrated and functioning adequately.

External Quality Assurance
A particular challenge for ART roll-out programs in resource-limited settings is the need for EQA. If EQA is not performed consistently, the inaccuracies of an instrument may not be detected and may create errors in the results of CD4 enumeration. Several international EQA programs exist. Canada's International Program for Quality Assessment and Standardization for Immunological Measures (QASI) is the most attractive program, as the Canadian government is currently subsidizing the program to help reduce costs. Other programs include the United Kingdom's National External Quality Assessment Scheme (UK-NEQAS) and the U.S. National Institutes of Health's VERIQAS.

The EQA program sends the laboratory a preserved blood sample with a known number of CD4 T lymphocytes. The clinical laboratory runs the sample and sends the results back to the EQA site, which in turn analyzes the results and sends a report back to the clinical laboratory. Access to the EQA programs is platform independent, so everyone has access to the programs, regardless of product, if desired.

Several issues related to optimizing EQA must be addressed, however. How can EQA samples be sent across borders into other countries? How can the EQA test results be sent back to the program for analysis? How can the analysis be sent back to the country performing the test? The costs involved in processing the EQA samples—the costs of reagents used to process samples, shipping costs, and the tariffs and duties levied on entry to each country—are also an issue. A possible solution could be for individual countries to develop EQA programs of their own. This would solve the problem of sample transfer across borders and would reduce costs, as international shipping costs could be eliminated and it would be less expensive to pay for EQA analysis inside the country than to pay for analysis in the United States, the UK, or Canada. This approach would require a regulatory organization inside the country to certify standards, monitor the process, and report results, however.

The clinical laboratory decision to perform EQA is generally based on cost and is not universally mandated. Therefore, EQA performed at a frequency well below what is recommended by the instrument or test manufacturer, especially in remote areas, may compromise the reliability of laboratory testing services.

HIV-1 RNA Quantitation
Methods for HIV quantitation rely on the ability to detect HIV-derived nucleic acids, RNA or DNA. This can be achieved through direct amplification of HIV-derived nucleic acids or though amplification of a signal that is designed to detect the HIV target nucleic acid. The tests vary in terms of (1) the volume of patient sample required for testing, (2) the amount of time and labor required for testing, (3) the risk of contamination during the testing procedure, (4) cost, and (5) the lower limit of detection of HIV-1 RNA. Three quality-controlled commercial assays have been widely available for the quantitation of HIV-1 in plasma for over 10 years. The Amplicor HIV-1 Monitor Test (Roche Molecular Systems) relies on reverse transcription (RT) and polymerase chain reaction (PCR) amplification.
to quantify HIV-1 RNA levels. The nucleic acid sequence-based amplification (NASBA) system (Organon Teknika) employs an isothermal target nucleic amplification method in which relative quantities of amplified sample and internal control RNA are detected by hybridization with a labeled probe to quantify sample HIV-1 RNA levels. The branched DNA Quantiplex HIV-1 RNA assay (Chiron Corporation, now Bayer) uses hybridization and amplification of the RNA-probe signal as a means to quantify RNA levels. HIV RNA quantitation using these three methods generates comparable results within 0.5 log₁₀ copies/mL. Disadvantages of these systems include the large volume of plasma (2 mL) required by the Quantiplex HIV-1 RNA assay and the NASBA assay's labor-intensive RNA extraction, with a higher risk of sample contamination. The Amplicor assay requires 0.5 mL of plasma and has a built-in mechanism to prevent contamination; the most recent version (version 1.5) has been modified to allow quantitation of different subtypes of HIV-1 with better accuracy than prior versions, which underestimated HIV RNA levels, particularly in subtypes A and E. At present, the most commonly used HIV-1 RNA quantification method is RT-PCR amplification of plasma using the Amplicor HIV-1 Monitor Test, version 1.5. This method allows for varying sensitivity: the standard procedure has a lower limit of detection of 400 copies/mL, achieved by the extraction of HIV-1 RNA from a fixed volume of plasma, while the ultrasensitive procedure has a lower limit of detection of 50 copies/mL, achieved by high-speed centrifugation to concentrate virus particles prior to lysis.

Efforts to develop less costly tools to measure HIV RNA in resource-limited settings have led to the adaptation of several techniques. One of these techniques uses real-time RT-PCR to quantify HIV RNA. In this method, RNA is reverse transcribed into complementary DNA (cDNA), and PCR amplification is performed using primers targeted at conserved regions of HIV-1. A fluorescent reporter probe with an adjacent quencher is included in the reaction during amplification. The quencher probe absorbs the fluorescence from the reporter until successful PCR amplification of the target region of cDNA releases the fluorescent reporter probe away from the quencher. Separation of the reporter probe from the quencher results in measurable fluorescence emission by the reporter probe. There is a linear relationship between the amplification and hence fluorescence detected, and the quantity of cDNA and hence viral RNA in the sample. Serial dilutions of standard samples with known quantities of HIV produce a standard curve with the HIV-1 RNA copy number (log₁₀) plotted against the cycle threshold (CT), the number of PCR amplification cycles required to reach the same point of exponential amplification within the group of standards and samples being tested. The HIV-1 RNA content of the samples is then determined by plotting the CT of the sample against the standard curve generated using the standard samples with known quantities of virus.

Various groups have investigated the use of real-time RT-PCR for HIV-1 RNA level monitoring, and two real-time PCR HIV quantitation systems received approval from the U.S. Food and Drug Administration (FDA) in 2007. One of these, the COBAS AmpliPrep / COBAS TaqMan HIV-1 Test (Roche), can quantitate 48-10,000,000 copies/mL of HIV-1 with an accuracy of ± 0.3 log₁₀ copies/mL. The standard curve generated in this system uses the same quantitation standard that is incorporated into the Amplicor HIV assay. Comparable HIV-1 quantitation is achieved relative to the Amplicor HIV assay, and the assay can be used for HIV-1 group M subtypes A through H. The Abbott RealTime HIV-1 Assay (Abbott Molecular Inc.) is another real-time PCR assay for HIV-1 quantitation that has
recently received FDA approval. This assay is able to quantify 40-10,000,000 copies/mL of HIV-1 RNA. The limit of detection varies based on the volume of plasma used: use of 1 mL of plasma results in a lower limit of detection of 40 copies/mL, 0.5 mL in a lower limit of detection of 75 copies/mL, and 0.2 mL in a lower limit of detection of 150 copies/mL. HIV-1 group M and O subtypes are quantifiable using this method, within 0.3 \log_{10} copies/mL. The standard used in this assay is a viral standard from the Virology Quality Assurance (VQA) Laboratory established by the AIDS Clinical Trials Group, as well as the World Health Organization’s first international standard for HIV RNA (97/656). The Nuclisens EasyQ HIV-1 version 1.1 assay is a real-time quantitation assay that is available in Europe. This assay incorporates the NASBA target amplification with real-time detection using a molecular-beacon system. An internal RNA calibrator is added to each sample prior to RNA extraction and amplification to allow quantitation of HIV-1 in the sample. Results obtained by this method are comparable to the results of the Roche Amplicor Monitor HIV-1 ultrasensitive assay.50

Another method that has recently been explored as an alternative to HIV RNA quantitation is an RT assay (ExaVir Load Quantitative HIV-RT kit, Cavidi Tech AB). This method uses HIV RT from the lysed virus isolated from patient samples to create DNA-RNA hybrids during an overnight incubation. The quantity of DNA-RNA hybrids created is measured by colorimetric readings at baseline, two hours into incubation, and at the end of the overnight incubation. Viral RT activity is expressed as femtograms per milliliter, and dUTP values are converted to generate an estimate of copies/mL. Initial evaluation of this assay by Greengrass et al found that measurement of RT activity was not affected by concomitant administration of an efavirenz-containing antiretroviral regimen.51 Sivapalasingam et al investigated this method in samples infected with subtype B HIV-1 in the United States, as well as in patient samples from Cameroon where the predominant subtype is CRF02_AG; the correlation between RT activity and HIV-1 RNA level varied between the subtypes, with \( r=0.898 \) for subtype B HIV-1 samples, and \( r=0.669 \) for CRF02_AG HIV-1 samples. Stevens et al evaluated this method using subtype C HIV-1 infected patient samples, and found that there was no change in RT activity until the HIV-1 RNA level exceeded 3.5 \log_{10} copies (3,000 copies/mL), with increased variance seen with rising HIV-1 RNA levels.53 This RT assay is labor intensive but has potential application as a phenotypic assay for drug resistance and may be considered an additional tool in centralized laboratory settings.

HIV-1 DRUG RESISTANCE TESTING

HIV-1 drug resistance is defined as continued viral replication despite ongoing antiretroviral treatment, resulting in plasma HIV-1 RNA levels above a clinically relevant threshold due to the loss of the viral suppressive effect of antiretroviral medications. Testing for drug resistance is performed using one of two methods, genotypic or phenotypic assays. Genotypic assays identify amino acid changes in the viral genome that have been shown to correlate with clinical failure or diminished in vitro susceptibility to specific antiretroviral medications. Phenotypic assays test the activity of the reverse transcriptase or protease gene product to determine the concentration of drug required to suppress viral replication, measured as the IC50, relative to a wild-type reference strain of HIV with no drug resistance. Lack of inhibition of viral replication by addition of a specific concentration of an antiretroviral agent in a phenotypic assay is described as a fold change relative to a wild-type virus.

Population-based sequencing is the primary method used for genotypic drug resistance testing. Genotypic assays using population-based
sequencing determine the predominant nucleotide at each position along the segment of genome targeted by the antiretroviral agents in question. There are currently two FDA-approved laboratory systems to perform genotypic sequence testing to detect mutations that can arise during the use of protease and reverse transcriptase inhibitors: the TRUGENE HIV-1 Genotyping Kit and the OpenGene DNA Sequencing System (Visible Genetics Inc. / Bayer Inc.) and the ViroSeq HIV-1 Genotyping System (Celera Diagnostics / Abbott Laboratories). Both of these genotype sequencing methods are FDA approved for use with subtype B HIV-1. The ViroSeq HIV-1 Genotyping System provides all the reagents required for RNA isolation, RT, and PCR amplification of the entire protease region and amino acids 1-335 of reverse transcriptase. The recommended analyte is 0.5 mL of plasma or serum with >2,000 copies/mL of HIV-1 RNA. The reagents for dideoxynucleotide dye-terminator sequencing are included, but final sequencing requires a separate Applied Biosystems genetic analyzer or sequencer. The ViroSeq HIV-1 genotyping system software allows sequence assembly and editing of generated sequences. The recommended analyte for the TRUGENE HIV-1 genotyping assay is plasma containing >1,000 copies/mL of HIV-1 RNA. As reagents for RNA extraction are not included in the assay, RNA extraction can be achieved using any of a number of RNA extraction methods. The TRUGENE HIV-1 genotyping assay contains the reagents needed to perform RT, PCR amplification, and cross-linking and immunoprecipitation (CLIP) sequencing reactions, an alternative dye-terminator reaction to sequence the entire protease region and amino acids 40-247 of reverse transcriptase. CLIP of the amplified product is followed by the generation of sequences using the Visible Genetics Clipper sequencer, and sequence analysis using the accompanying OpenGene system software. Both assays produce a drug resistance report indicating the amino acid positions at which the viral population contains a mutation, and studies have shown that both the ViroSeq and TRUGENE HIV-1 genotyping assays are more than 98% accurate for base calling.54,55

Many groups use alternate genotype resistance tests using “home-brew” RT, amplification, and dideoxynucleotide sequencing. However, these home-brew methods may not have undergone rigorous analysis to determine the assay sensitivity, specificity, and reproducibility. The generated consensus sequence data are compared to a reference wild-type strain to determine the presence of mutations that have been associated with drug resistance on the basis of clinical outcomes or in vitro testing. Interpretation systems such as those incorporated into the Stanford HIV drug resistance database (http://hivdb.stanford.edu) or the Los Alamos HIV database (http://hiv-web.lanl.gov) are then used to determine the susceptibility of the predominant viral population to available antiretroviral agents.

Mutations that confer drug resistance result in a change in the structure or activity of the enzyme targeted by the antiretroviral drug.56 The nomenclature used to describe the mutation lists the amino acid found in the wild-type virus followed by the amino acid position followed by the mutant amino acid; for example, K103N denotes the change from an arginine to a serine at amino acid position 103 of the reverse transcriptase, this being the signature mutation associated with non-nucleoside reverse transcriptase inhibitor (NNRTI) drug resistance. Distinct drug resistance patterns are seen for some of the antiretroviral medications. While a single point mutation may confer drug resistance to some agents, such as NNRTIs or lamivudine (3TC), drug resistance to other antiretrovirals requires
the accumulation of multiple mutations before viral suppression is impaired. For example, drugs such as zidovudine and stavudine may result in a series of mutations known as thymidine analog mutations (TAMs), which cumulatively confer resistance to those drugs. An extensive analysis performed by Kantor et al evaluated the relationship between HIV-1 main group subtypes, treatment, and drug-resistance-associated mutations. The authors found that mutations that developed in the treatment setting in non-B subtypes were similar to those in subtype B HIV-1, the predominant virus in Western Europe and the United States. However, important differences in drug resistance resulting from use of various drug combinations may emerge as access to treatment and monitoring increases among individuals with non-B HIV-1 subtypes.

Population-based genotypic sequencing only identifies drug-resistant variants present in 20%–30% of the viral population, depending on the interpretation of chromatograms. There is considerable variation in the accuracy of the detection of mixtures at resistance codons by population sequencing. It is, therefore, possible that drug-resistant mutations are present below the threshold of detection by population-based techniques, and even a 20%–30% mixture may elude detection. This is particularly true where there has been poor adherence or if an individual has interrupted his or her ART. This can result in a false-negative drug-resistance assay from plasma RNA, as the wild-type virus may rapidly overgrow mutant viruses with a reduction in drug exposure. Reinitiation of treatment in an individual based on the results of a population sequence performed during treatment interruption may thus provide a false assurance of susceptibility.

There are now more sophisticated methods that allow detection of minority variants that may harbor drug-resistance-associated mutations, also known as minority quasispecies. Methods to detect and quantify minority quasispecies with drug resistance include single genome sequencing (SGS), allele-specific PCR, an oligonucleotide ligation assay (OLA), a LigAmp assay, clonal analysis, and heteroduplex analysis. These technologies are able to detect drug resistance mutations that exist below the limit of detection by population sequencing. Clonal analysis allows for ligation of a single copy of genetic material, a bacterial vector, which is then grown in culture. Plasmid DNA isolated from each bacterial colony representing a single quasispecies is sequenced. Analysis of the sequence of plasmid DNA from multiple colonies (clonal isolates) provides a representation of the viral quasispecies within the host HIV-1 RNA population. Clonal analysis is labor intensive and expensive; it is typically used primarily for research purposes rather than surveillance or patient care. SGS is also expensive and labor intensive, and, because it requires multiple clean rooms to avoid contamination, it is limited to major research centers. Multiple dilutions of cDNA are PCR amplified to identify the reaction well that contains a single copy of the viral genome. To obtain a repertoire of viruses that are thought to represent the quasispecies within an individual, sequencing is then performed on amplicons from multiple wells assumed to contain a single viral genome. Application of this technique among a group of individuals with viremia despite combination ART showed the presence of multiple drug-resistance-associated mutations below the level of detection of population-based genotypic analysis.

Technologies to detect point mutations, such as real-time PCR, OLA, and LigAmp, are relatively cost-effective, but the test must be performed separately for drug resistance at each specific amino acid position being examined. Techniques that can identify the K103N mutation at levels of 1 copy
per 1,000 viruses were able to identify persistent K103N in the majority of patients who failed NNRTI therapy, which is suggestive of the clinical importance of some of these minority drug-resistant variants. The first version of the OLA was not robust in detecting mutations in subtype C HIV-1 and was modified to improve its performance. The LigAmp assay involves ligation of mutation-specific oligonucleotides to amplified DNA and detection of the bound oligonucleotide by real-time PCR, which permits the differentiation of wild-type from mutant viruses within a viral population. This method has been applied to test for residual drug resistance to NNRTIs following the administration of single-dose nevirapine for the prevention of mother-to-child transmission of HIV, though the clinical implication of persistent low-level NNRTI resistance in this setting has not yet been defined.

Most of these sophisticated tools will likely be used in central, more technically advanced laboratories, given the instruments required to perform these tests. However, their availability will allow for public health surveillance monitoring for drug resistance as access to treatment continues to increase.


Expanding the Role of Pharmacy Staff in Antiretroviral Therapy

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The pharmacy department has a pivotal role to play in the provision of quality antiretroviral therapy (ART) care, through both ensuring an efficient supply of medicines and delivering patient-oriented services to promote appropriate use. Studies in the developed world have found that support from pharmacists can positively affect adherence and that clinical pharmacists appear to have a strong impact on promoting positive clinical outcomes in patients starting ART, particularly in economically disadvantaged areas. In many developing countries, initiatives to scale up ART have focused attention on the pharmacy and on making better use of pharmacists, whose skills and training are often underutilized. Currently, the role of the pharmacist and other pharmacy staff in supporting the ART program varies considerably between and within countries as managers explore different models of service provision and pharmacists embrace the opportunity to expand their role in ART care.

Pharmacy practice takes place at different levels: the system (national, provincial, or district), the facility (including the health-care team), supply management, the individual patient, and the community level. Substantial gaps exist in the scope and performance of pharmacy practice at all levels in most resource-limited settings. The introduction of an ART program can serve as an entry point to strengthening practices and expanding patient care activities at the pharmacy to benefit all health-care programs. The ART program is refocusing attention on the importance of traditional pharmacy activities, such as dispensing, including checking prescriptions, labeling medicines, and medication counseling. Increasingly, pharmacy responsibilities are expanding to include a wider range of patient care activities, specifically adherence monitoring, medication-related problem monitoring, and identifying and following up on defaulting patients. Supporting nonmedical staff and community caregivers in the distribution and appropriate use of medicines is another important undertaking.

Estimates of the number of pharmacy staff needed to support ART scale-up range from less than one to three staff per 1,000 patients, depending on how responsibilities for dispensing and especially counseling are allocated between cadres. In one study, Kenya was estimated to need a 50% increase from 2005 levels in the number of public sector pharmacy “specialists” to meet the U.S. President’s Emergency Plan for AIDS Relief target of supporting 250,000 ART patients by 2008. However, many countries,
especially in sub-Saharan Africa, have a severe shortage of pharmacists. Ethiopia, Mozambique, Rwanda, Tanzania, and Uganda have three or fewer pharmacists per 100,000 people, compared with the United States, which has 88 pharmacists per 100,000. Migration of pharmacists overseas is a major cause of shortages in many resource-limited countries. In Ghana, almost two-thirds of the 140 pharmacy school graduates migrated out of the country in 2003. Furthermore, pharmacists tend to be concentrated in the private sector and in urban areas. For example, in Uganda, 90% of the pharmacist workforce is located in just one of four regions of the country. Given the inadequate supply of pharmacists to support scale-up and the move to decentralize ART services to the primary health-care level, where pharmacists are few, the role of the pharmacist in ART needs to be redefined and reoriented to maximize the efficient use of the most skilled cadre of staff. In addition to pharmacists, other pharmaceutical service staff may include pharmacy technologists, technicians, or assistants; nursing staff; and other health-care workers who have been given responsibilities for dispensing or managing medicines. These other cadres of workers must learn new skills and take on new roles, thereby releasing pharmacists to focus on more specialized functions and supportive supervision.

This chapter highlights experiences in expanding the role of pharmacists and other pharmacy staff to support the introduction and scale-up of ART in developing countries.

**SUPPORTING ART INTRODUCTION AND SCALE-UP AT THE SYSTEM LEVEL**

At the national, provincial, or district level, the pharmacists and other health workers of the ministry of health responsible for managing pharmaceuticals make important contributions to planning and managing the introduction and scale-up of ART, including developing enabling legislation, regulations, and policies. In several countries, the national-level staff responsible for pharmaceutical services work closely with the national AIDS control committee and donors to coordinate ART procurement, financing, and distribution (see chapter in this section entitled “Managing Medicines and Supplies for HIV/AIDS Program Scale-Up”). Pharmaceutical management staff also work increasingly with other government departments and programs to maximize efficiency in capacity-building activities. Other important functions include contributing to proposal development and, particularly, to developing the procurement and supply management plan for applications to the Global Fund to Fight AIDS, Tuberculosis and Malaria. Other evolving roles for national-level pharmacy staff that can serve as a starting point for strengthening good pharmacy practices for all health programs include the development of pharmacy practice standards for facilities dispensing antiretroviral drugs (ARVs), national standard operating procedures (SOPs) for ART pharmacy services, and accreditation guidelines and audit tools.

Involving pharmacists responsible for implementing ART at the national and local levels in ART medicine selection committees enables them to contribute to developing treatment guidelines that are easier to put into practice. A number of countries have identified pharmacists to work with the national, provincial, and, in some cases, district AIDS control teams to tackle ART-related pharmaceutical issues and to support sites in introducing and scaling up ART services. Given the shortage of pharmacists, future considerations may include expanding the responsibilities of these staff to support implementation of all health-care programs, especially where ART programs are integrated into existing systems.
To support ART scale-up in settings where pharmacists are in short supply, the national pharmacy department will need to work with ART program managers to decide on the optimal role for each cadre of pharmacy staff and the number of each cadre needed for ART scale-up. Preservice curricula and in-service training materials for pharmacists and other levels of pharmacy staff will also need to be aligned to match competency standards with the recommended scope of practice for each cadre.

SUPPORTING ART INTRODUCTION AND SCALE-UP AT THE FACILITY LEVEL

Involving the pharmacy staff at the facility at early stages of planning and throughout implementation is crucial to a successful start-up and also promotes ownership and sustainability. As countries move to decentralize ART services to the primary health-care level, where pharmacists are scarce, the identification of pharmacists at the provincial or district level who can provide technical oversight and support to pharmacy staff at new ART sites is an important step. For example, in South Africa, almost all provinces have a pharmacist providing oversight of HIV/AIDS pharmaceutical service activities. Furthermore, initiatives to explore ARV dispensing and counseling by pharmacy assistants in primary health-care clinics and identify effective mechanisms for supervision are under way. Approaches to enabling pharmacists to fulfill this new role are discussed later in the chapter. Ideally, the pharmacists should have experience in introducing ART and managing scale-up and be able to anticipate constraints and recommend strategies to address problems that commonly occur.

The primary role of the pharmacists providing technical oversight will be to train and mentor the staff that will be responsible for managing and dispensing ARVs at new sites. In addition, they can assist pharmacy staff and the ART team to do the following:
- Assess the functionality of existing pharmaceutical management systems
- Develop implementation plans that prioritize and address gaps
- Quantify ARV and other supply needs
- Calculate storage needs for ART start-up and expansion
- Adapt and test SOPs, job aids, and recording and reporting forms
- Introduce tools to monitor adherence
- Identify needs for information resources—for example, ART guidelines and drug information for medication counseling
- Implement monitoring and reporting of medication errors, suspected adverse reactions to medicines, and other medication-related events
- Address emerging problems as patient numbers increase

PHARMACY STAFF AS MEMBERS OF THE ART HEALTH-CARE TEAM

Pharmacists and other pharmacy staff are essential members of facility ART committees or multidisciplinary teams and make important contributions to decision making on program management issues and clinical aspects of patient care. In developing countries, the role played by pharmacy staff, and particularly their degree of clinical involvement, varies considerably depending on the cadre of staff that participates and their individual capabilities and motivation. Pharmacists providing technical oversight to sites without pharmacists can mentor and assist the pharmacy staff to contribute more broadly to the ART team.

Experience has shown that including pharmacy staff in the ART team enables them to manage medicines and supplies more efficiently. For example, the team can assist the pharmacy staff
to quantify ARV needs by identifying potential changes in prescribing practice and developing and validating assumptions for expansion. Constraints at the pharmacy that may limit scale-up, such as staff shortages or lack of storage space, can be communicated to the team early on. Furthermore, health provider roles in the ART program—for example, in ART counseling—can be reviewed to identify gaps and eliminate unnecessary duplication to improve efficiency. Other benefits include improving cross-departmental coordination for the program, such as through streamlining the management and follow-up of clients who present for postexposure prophylaxis. As countries work to strengthen pharmacy systems and collect, analyze, and report data, the pharmacy role in providing information to other members of the healthcare team (for example, on ARV consumption or prescribing practices, including characteristics of patients) is increasingly appreciated. One of the key challenges is to present the data in a format that is useful to others without overwhelming the workload of existing staff.

In many resource-limited countries, the clinical role of pharmacists is evolving, allowing them to make important contributions to decision making on treatment and care and case reviews, as well as to provide scientific updates and reviews of rational ARV use, including adherence. However, their level of involvement is generally uneven among facilities. Emerging activities include reviewing the incidence of ART-related adverse events at the facility, coordinating medication event reporting, and contributing to operations research. Pharmacists are very often the link between the ART team and the facility Pharmacy and Therapeutics Committee (PTC) and play an important role in providing information for PTC decision making on facilityformularies and lists.

To be recognized as full members of the healthcare team, pharmacists and other pharmacy staff need to increase their competencies but also adopt new attitudes. These requirements are discussed later in this chapter.

**MANAGING MEDICINES AND SUPPLIES AT ART SITES**

Supply management activities, including procurement and distribution, continue to be important functions for pharmacy staff, and the adequate and continuous availability of quality ARVs is critical to the success of any ART program. In many resource-limited countries, pharmacists still devote much of their time to supply management; however, given the shortage of pharmacists discussed earlier in this chapter, some of these responsibilities are now being delegated to other cadres of pharmacy staff. In countries where responsibilities are being realigned, pharmacists still play a key role in supervising supply management activities, problem solving, assisting in complex tasks such as ARV quantification, and developing new methodologies, tools, and approaches to improve supply management practices.

**THE ROLE OF THE PHARMACY IN SUPPORTING PATIENTS ON ART**

Since the mid-1970s, the focus of pharmacy practice has been shifting from dispensing and inventory management to the provision of services and functions—some traditional and others new—that serve individual patients. In most developed countries and some developing countries, the pharmaceutical profession is working to implement patient-centered services or pharmaceutical care, namely, “the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve or maintain a patient’s quality of life.” Successful medication therapy requires individual therapeutic decisions, reaching agreement with the patient on outcomes and how to achieve them, and patient monitoring. These are all activities...
to which pharmacists increasingly contribute. In resource-limited settings, pharmaceutical care has, until recently, been mainly limited to pharmacists providing clinical pharmacy services in hospitals. However, the introduction of the ART program is increasingly serving as a gateway to strengthening practices and expanding patient care activities at all levels of the health-care system, often to the benefit of other health-care programs. Pharmacists and other pharmacy staff are progressively attaining the training, tools, resources, and supportive supervision needed to empower them to expand their role in ART care.

Key roles of the pharmacy staff include the following:
- Monitoring ART prescriptions for appropriateness and discrepancies
- Dispensing ARVs in appropriate packaging with clear instructions
- Providing medication-related counseling, including reinforcing adherence and advising on potential side effects and drug-drug interactions
- Providing drug information to providers and patients on request

Evolving roles include the following:
- Monitoring adherence to ARVs; working with patients and other providers to address difficulties
- Identifying and following up on patients who do not return for refills of their ARVs
- Working with providers and patients to identify, manage, and report adverse drug reactions and drug interactions
- Active dissemination of drug information to patients and providers
- Contributing to decision making on treatment and care for individual patients

PREPARING PHARMACY STAFF FOR A NEW ROLE

Early experiences in expanding the role of pharmacists in ART at the facility level identified training, adequate staffing levels, and access to up-to-date information as essential requirements for success. As countries move to reorient the role of the pharmacist and other cadres and to standardize and institutionalize these changes, additional policy and human resource issues need to be addressed.

Policies and Legislation

A legislative framework, together with supporting policies and procedures that define the new structure and describe how the reallocation of tasks for pharmacy staff will work, is required to standardize practices and enable each level of the health-care system to implement the changes. Policymakers will need to decide the optimal role for each cadre and the appropriate skills mix needed at each level and develop a structure to provide supportive supervision and technical oversight as staff take on new responsibilities. Legislative changes may need to be made—for example, to enable pharmacy staff other than pharmacists to dispense certain medicines.

Human Resources

Job descriptions need to be updated to reflect new responsibilities and, along with SOPs, are important for effective technical oversight and supportive supervision. Adequate staffing levels are essential to enable staff to take on new roles, such as adherence monitoring or technical oversight at other sites. An important first step in determining staffing levels is to ascertain the ratio of each cadre to the number of tasks to be completed or patients to serve. Eliminating unnecessary tasks and duplication of efforts in order to increase the efficient use of existing staff can also facilitate the reallocation of tasks.
Supporting the Expansion of ART Services in South Africa

In South Africa, the government is working with partners and stakeholders to down refer patients who are stabilized on ART from hospitals to primary health-care (PHC) clinics. In addition to reducing the patient load for the hospital’s pharmaceutical service, this strategy can also reduce transportation costs for patients returning to collect prescription refills. However, the shortage of pharmacists at PHC clinics has led to the increased use of the pharmacy’s assistants and nurses to support the expansion of the ART program and ensure that patients can get their medication. A number of different approaches are being explored.

In one approach, prescriptions are prepared at a nearby hospital and delivered to a PHC clinic closest to the patient’s home or place of work. Prescriptions are packaged with appropriate information by hospital pharmacy staff and delivered to the local clinics. At the clinic, pharmacist’s assistants or nurses dispense the ARVs and review patients’ treatment progress. The PHC clinic returns progress reports and uncollected medication to the hospital.

There is also a movement toward the initiation of ART by nurses at the PHC level. In some PHC clinics, nurses who have dispensing licenses and have been trained on HIV/AIDS dispense ARVs to patients who have been on ART for longer than six months and have been down referred to continue treatment. The nurses reinforce adherence at every visit, monitor patients for adverse events, and refer them for management of adverse events should they occur. Some changes to the applicable legislation and the National Essential Drugs List are needed to support this initiative.

In the Western Cape Province, an initiative is under way to develop a model in which pharmacist’s assistants dispense ARVs in PHC clinics under the indirect supervision of a pharmacist. Additional training is being provided to the assistants, and job descriptions, SOPs, and monitoring tools are being developed to set the standards for pharmacy practice and facilitate effective oversight.

Another model in use in South Africa is one in which a pharmacist visits the PHC clinic once a week to dispense prescriptions for ARVs or to check prescriptions that have been prepared by a pharmacist’s assistant. Prescriptions may be handed to the patient by either the pharmacist or nurses working in the PHC clinic.

Sources: Management Sciences for Health, Rational Pharmaceutical Management Plus, South Africa; Shanila Nair, MBBS, BSc, Technical Advisor, Elizabeth Glaser Pediatric AIDS Foundation, South Africa.
Laboratory and pharmacy services

Shifting Tasks to Address Severe Shortages of Pharmacists

In 2003, Médicins Sans Frontières and the Nelson Mandela Foundation, in partnership with the Department of Health of the Eastern Cape, initiated a program to provide ART through primary health-care clinics in Lusikisiki, South Africa. Because of a shortage of skilled health-care workers, tasks were shifted to make the best use of available human resources. The traditional functions of the pharmacist in HIV/AIDS care include managing the supply of medicines and overseeing prescriptions, while pharmacy assistants have a limited role and dispense medicines only under the supervision of a pharmacist at a hospital. The Lusikisiki program, however, utilized a hospital pharmacist to provide coaching to pharmacy assistants, whose responsibilities included managing the medicine supply, dispensing prescriptions, and, in some cases, checking adherence.

Source: Médicins Sans Frontières.

Capacity Building
Pharmacy staff will require training or retraining to build their skills and knowledge and to adopt essential attitudes to successfully take on new responsibilities and expand their role in ART. Training curricula will need to be aligned with new competency standards and scopes of practice for each cadre of pharmacy staff. Pharmacists will need good leadership, management, budgeting, and communication skills to mentor and assist other cadres to take on new responsibilities for the ART program. For effective medication counseling, staff need good communication and problem-solving skills to assist patients to achieve and maintain high levels of adherence. In addition to preservice and in-service training to capacitate pharmacy staff to take on new roles, they will need a mechanism to stay up-to-date with scientific advancements and changes in recommended practices. Pharmacists will need to be visible, responsible, and committed to maintaining competencies in order to play a larger role in the ART health-care team. Required changes in attitudes for all staff will include a commitment to confidentiality and patient-oriented, rather than task-oriented, practices.

Resources
An essential requirement for providing pharmaceutical care to ART patients is an information system that collects patient-specific data and documents interventions and medicines dispensed at the pharmacy. Pharmacists and other pharmacy staff need access to up-to-date information, SOPs, and job aids (e.g., pediatric ARV dosing tables) to assist them to take on new tasks. Other requirements include a confidential counseling area and validated measurement tools for monitoring adherence in resource-constrained settings.

Summary
Experiences to date have shown that pharmacists and other pharmacy staff have an important role to play in ART care in resource-limited settings by promoting appropriate use and ensuring availability of quality and efficacious medicines. To make the most efficient use of available staff, the roles of
the pharmacist and other pharmacy staff will need to be realigned. However, policymakers may need to be convinced of the value of an expanded role for pharmacy staff and will want to know the cost implications and the feasibility of implementing the necessary changes. Operations research to develop scalable models, answer important questions, and document benefits such as increasing the job satisfaction of pharmacists to slow down migration to the private sector and overseas is urgently needed.
REFERENCE LIST


MONITORING, EVALUATION, AND QUALITY OF CARE
The Third One: Monitoring and Evaluation of HIV Programs

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Introduction by Deborah Rugg, Chief, Monitoring and Evaluation Division, Joint United Nations Program on HIV/AIDS (UNAIDS), Geneva, Switzerland.

The recent rapid expansion of available resources to fight the global AIDS pandemic has brought with it a commensurate expectation from the global community for greater accountability and more effective and efficient programs. Monitoring and evaluation (M&E) activities play a crucial role in fulfilling those expectations by answering three key questions: “Are we doing the right things?” “Are we doing those things correctly?” and “Are we doing them on a large enough scale to make a difference in controlling this disease?” M&E activities are being implemented at global, national, and subnational levels and have greatly improved our understanding of the HIV epidemic and related responses. In resource-limited settings, where HIV has had the most devastating impact, there has been notable progress in M&E practice following nearly a decade of intensive efforts to strengthen activities. A major breakthrough occurred as a result of the shift from a surveillance-dominated approach to a more comprehensive, system-building approach. The latter approach focuses on the variety of data needed to inform HIV resource allocation and programming to allow for transparency and corrective adjustments in the HIV response. Establishing and maintaining a comprehensive M&E system requires a long-term vision, careful planning, and a phased implementation; in other words, not everything can be done at once. Leadership and M&E advocacy, adequate and skilled staff, as well as sustained funding are all needed to institutionalize M&E and ensure the use of M&E data to improve programs.

This chapter highlights some of the main principles, conceptual frameworks, and M&E methods currently in use. Since much of the HIV M&E efforts to date have focused on monitoring, with insufficient attention paid to evaluation, it includes a discussion of the contributions of monitoring, evaluation, and surveillance linked to a public health questions approach to M&E (i.e., the “M&E staircase” described later in this chapter). While indicators are cited as important measures of progress, they are put in their rightful place within a comprehensive M&E system, which also needs to embrace, for example, qualitative methods and data triangulation. The “Third One” principle (i.e., one national M&E system) emphasizes the need for
a coordinated effort to link and unify the various M&E activities in a country. Only then can a synergistic M&E system be realized that generates the essential information for directing and improving programs and ensuring accountability. This chapter discusses essential elements in developing the Third One at the national level.

**EVOLUTION OF MONITORING, EVALUATION AND SURVEILLANCE METHODOLOGIES FOR HIV/AIDS PROGRAMS**

One of the greatest challenges in HIV prevention, care and treatment, and mitigation is determining what impact efforts have had on the epidemic. In the late 1980s and early 1990s, it was assumed that biologic indicators could be used to evaluate prevention programs. Toward that end, many evaluation plans called for collecting data on the incidence and prevalence of HIV and other sexually transmitted infections both pre- and post-intervention. Information on self-reported behavior was collected as well. However, most M&E was conducted in a piecemeal fashion.

In the early 1990s, the World Health Organization / Global Program on AIDS (WHO/GPA) collaboratively developed a set of biological and behavioral prevention indicators for national AIDS control programs as well as standardized protocols to facilitate cross-country comparisons. However, it became increasingly evident that lack of M&E resources and experience was resulting in an inconsistent and incomplete understanding of the impact of prevention efforts. To help address those shortcomings, Family Health International pioneered the behavior surveillance survey. This method involved a series of repeated behavioral surveys in key target groups. Behavior surveillance surveys enabled national programs to track trends in HIV risk behaviors and assess the combined impact of various HIV interventions in a country. These second-generation surveillance systems monitor risk behaviors, using them to warn of or explain changes in the levels of infection. Second-generation surveillance uses data from behavioral surveillance to interpret data gathered from sero-surveillance efforts. In addition, the key indicators survey was developed by the United States Agency for International Development (USAID)–funded MEASURE (Monitoring and Evaluation to Assess and Use Results) program to help monitor and evaluate population and health programs. In addition to these useful tools, a limited number of timely qualitative studies were undertaken, which provided a much-needed look into the complexities of sexual and related behaviors to help explain HIV trends in their respective settings. In other cases, secondary follow-up analyses were conducted using data sets from previous studies or programs.

In the early-to-mid-1990s, it was becoming increasingly clear that the world was facing a complex, multifaceted HIV pandemic. Variations in infection patterns by region and often within smaller boundaries of a country were not uncommon. To enhance the sophistication of surveillance in order to match the complexities of the epidemic, processes were developed and refined for cross-referencing and understanding the epidemic from various angles. There was also a recognized need to complement the quantitative and behavioral data with qualitative information from in-depth interviews, focus group discussions, and rapid ethnographic studies. To address that need, an approach, commonly known as data triangulation, was developed that entails the “nesting” of qualitative data within a quantitative data collection plan, thereby allowing for a more well-balanced interpretation of HIV data.

As our understanding of the epidemic evolves, there is recognition that a comprehensive approach to monitoring and evaluation requires
multiple techniques and data sources so that the relationship between biomedical, behavioral, and socio-demographic data can be better examined and understood. Yet the absence of a common operational M&E framework in most countries has hampered efforts toward such a comprehensive approach. According to the Three Ones, the landmark agreement made in 2004 between donors, developing countries, and UN agencies promoting universal coordination in the fight against HIV, the Third One is the existence of an agreed-upon M&E system for overall national monitoring and evaluation.²

**PRINCIPLES OF MONITORING AND EVALUATION**

**Introduction to Planning, Monitoring, Evaluation, and Surveillance**

Monitoring and evaluation is a natural step in the program planning and implementation process. When M&E is incorporated into a program design, this helps to ensure that the project is clearly defined and articulated, is well researched, and can be objectively measured and verified with sound data collection methods. In this way, M&E provides an objective basis for describing the project and its accomplishments to others. Planning an intervention and designing an evaluation strategy are inseparable activities.

*Monitoring* can be defined as the routine tracking of information about a program/project and its intended effects. It measures the progress made toward achieving the objectives of the program/project. *Evaluation* is the periodic, in-depth, and systematic collection and assessment of information related to program activities, characteristics, and outcomes in order to make judgments about the program, improve program effectiveness, and inform decisions about future programming. This information helps to enhance understanding of a particular program or project in terms of its formulation, its characteristics, and its worth or merit. In this way, monitoring systems are a basis for determining the factors responsible for optimal or suboptimal program performance.³

The usefulness of M&E is diminished if it is performed solely to meet donor needs. The results, conclusions, and lessons learned derived from M&E are invaluable to program managers, target populations, and other stakeholders. M&E should be seen as an essential function of program management as it provides insight into what is and is not “working,” and may help identify ways to refocus strategies. M&E is *not* about assigning a grade at the end of a project but, rather, should be seen as a valuable tool for improving the effectiveness of the program, as well as one that helps to develop the capacity of individuals, organizations, and communities. M&E is, simply put, a process to determine the impact and effectiveness of a project in order to apply the lessons learned.

The following is an outline of the basic steps involved in program planning along with references as to how each element links to M&E.

**Step 1: Define the context of the problem.** Collecting information related to reducing the impact of HIV in the local context helps to identify problem areas and prioritize solutions—or potential interventions—that might address the problem. This is sometimes called a *situation analysis* or *assessment.* Whatever information gaps exist at this stage will have to be resolved early in project implementation through *formative research.* This research may form part of the *baseline assessment* against which progress can be determined.

**Step 2: Assess organizational and institutional capacity.** The success of a project depends not only on sound project design but on the strengths of the implementing organizational and the institutional environment in the country or region. An
It is in this step that decisions are made regarding which qualitative and/or quantitative methods will be used to collect data. The OVs and the MoVs constitute the monitoring and evaluation plan.

The M&E planning process should set out to answer the following questions:

- What development objective (i.e., goal or overall objective) do we want to achieve in the long run?
- What benefit (i.e., project purpose) at the level of the key stakeholders do we want to achieve upon completion of the project cycle?
- What services (i.e., outputs) do we need to provide for this benefit?
Figure 1 depicts the links that must be formed between planning and M&E if a program strategy is to be successfully implemented. This model assumes that all required resources are strategically placed to perform the requisite functions at all levels of project/program implementation.

Despite prescribed designs for linking activities, few countries have successfully built fully functional M&E systems. In the east and southern Africa region, Botswana, Malawi, Rwanda, Swaziland, Tanzania, Zambia, and Zimbabwe have all developed functional M&E systems—albeit with varied degrees of advancement—which also incorporate an aspect of planning.

Surveillance (i.e., impact monitoring) is the continuous monitoring of the occurrence and distribution of diseases and other conditions of ill health and their determinants for effective disease control and prevention. Surveillance systems in most of the countries in the east and southern Africa region are well developed and are used to generate reasonably good quality information on the HIV epidemic. HIV surveillance has been in operation in these countries since the 1990s. However, only a few countries in the region, including Botswana, Malawi, and Mozambique, have undertaken or are in the process of instituting second-generation surveillance activities to better understand their epidemics. Second-generation surveillance consists of collecting and comparing both biological and behavioral data, which enables a better understanding of the epidemic. So far, these findings have been an important planning tool for program managers and policymakers in their respective countries.

Components of HIV Programs in the Context of M&E

A program can be considered as a set of processes for transforming resources into results. In M&E terminology, program resources are referred to as inputs; program activities or operations as processes (i.e., activities); and results as outputs (i.e.,
Outputs are the immediate results obtained by the program through the execution of activities (e.g., number of commodities distributed, number of staff trained, number of people treated).

Outcomes are the short-term or intermediate results obtained by the program through the execution of activities (e.g., number of staff implementing new guidelines, frequency of stock-outs).

Impact is the long-term effect, such as changes in health status.

Any or all of these resources may be a priority for a given program, and they are defined as follows:

- **Inputs** are the resources going into conducting and carrying out the project or program. They could include staff, finance, materials, and time.
- **Processes** are the set of activities in which program resources (human and financial) are used to achieve the results expected from the program (e.g., number of workshops held).
- **Outputs** are the immediate results obtained by the program through the execution of activities (e.g., number of commodities distributed, number of staff trained, number of people treated).

In general, inputs, processes, and outputs are the three domains of information required in a monitoring system. Outcomes and impact are the domains of information required in an evaluation.

A useful starting point for M&E activities is the use of the M&E “staircase” framework as the basis for articulating the questions that need to be asked at each step of the M&E process. As depicted in Figure 2, the staircase framework is made up of eight steps: (1) problem identification; (2) determination of risk factors; (3) research on what interventions work (i.e., efficacy and effectiveness); (4) definition of specific interventions and resource needs; (5) assessment of quality of program implementation; (6) monitoring the extent of program outputs; (7) examination of program outcomes and program effectiveness; and (8) determination of overall program effects and collective effectiveness.1
Although few if any African countries are adequately covering the steps as depicted in Figure 2 and/or achieving significant success in the application of a formal M&E framework, some countries have successfully established mechanisms that generate useful data for improving program activities. In Botswana, for example, a multisectoral technical working group makes decisions about harmonization of indicators for the national HIV response, while at the same time churning out information products for policymakers. In so doing, M&E has become more accessible to government officials, thus generating a greater demand for information (see the chapter titled “The Third One in Practice: Monitoring and Evaluation of the Botswana National HIV Response”). Ethiopia has produced an information product (a succinct and user-friendly annual M&E report) from its national M&E system, albeit with a health bias.” In Zambia, Malawi, Ethiopia, Rwanda, and Botswana, the sub-national levels (provinces and districts) have started using M&E information to develop plans for HIV responses at these levels. In Botswana and Zambia, the local government uses systems that generate relevant data for development planning and budgeting.

Yet most efforts, regardless of the level at which they occur, are focused on monitoring rather than evaluation. To correct this imbalance, a deliberate shift in the direction of evaluation is needed. That will lead to a better understanding of the trends of the epidemic and the factors responsible for what is being observed. For example, it is imperative that countries are up to date on emerging issues, such as the impact of male circumcision on HIV infection and routes and modes of HIV transmission. At another level, a radical redesign of response strategies is needed, with a particular focus on prevention. The current work in Botswana to develop a national evaluation agenda represents a move in that direction.

**The Logical Framework Approach**

As mentioned earlier, the LFA is a common conceptual framework used by many donors and programs. The LFA is useful in generating clearly identified objectives and organizing them in a hierarchical framework that moves from the general (longer-term) to the specific (shorter-term). The LFA is a tool for analysis, presentation, and management of activities that can help planners and managers to

- analyze the existing situation during activity preparation;
- establish a logical hierarchy of means by which objectives will be reached;
- identify the potential risks to achieving stated objectives, including sustainable outcomes;
- establish how outputs and outcomes might best be monitored and evaluated;
- present a summary of activities in a standard format (if desired); and
- monitor and review activities during implementation.

Developers of the LFA intended it to be used as a tool for strengthening project design, implementation, and evaluation. The LFA may be used to involve primary stakeholders in a participatory planning process or to summarize the key features of a project design; it can also be used as a monitoring and evaluation tool. The goal of evaluation specialists in the LFA process is not to define the proposed objectives at each level of activities, but rather to facilitate the process by which program managers and stakeholders themselves collaboratively define the objectives. If the objectives are felt to be arbitrary or chosen by others, there will be no ownership and those involved will be less motivated to achieve the objectives and to buy into the process of measuring progress.

The LFA enhances planning, analysis, and communication by (1) clarifying the purpose of the project, (2) identifying information requirements,
Table 2. Sample Logframe Matrix and Related Questions

<table>
<thead>
<tr>
<th>Project Structure</th>
<th>Indicators of Achievement and Value</th>
<th>How Indicators Can Be Quantified or Assessed</th>
<th>Assumptions, Risks and Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal</strong></td>
<td>What are the quantative ways of measuring or the qualitative ways of judging whether this goal is realized?</td>
<td>What sources of information exist or can be provided at the lowest price?</td>
<td>What conditions, outside the control of the implementing organization, are necessary if the achievement of the project’s Objectives is to contribute to the realization of the project’s overall goal?</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>What are the intended short-term effects on the project area or target group?</td>
<td>What are the quantitative measures or qualitative evidence by which achievement and distribution of effects and benefits can be judged?</td>
<td>What sources of information exist or can be provided at the lowest price? Does provision for collection need to be made under Inputs and Outputs?</td>
</tr>
<tr>
<td><strong>Outputs</strong></td>
<td>What are the wider problems that project will help to resolve?</td>
<td>What the quantative ways of measuring or the qualitative ways of judging whether this goal is realized?</td>
<td>What external factors must be present for the outputs to be likely to lead to achievement of the objectives?</td>
</tr>
<tr>
<td><strong>Activities</strong></td>
<td>What the intended short-term effects on the project area or target group?</td>
<td>What the quan-</td>
<td>What the quantative ways of measuring or the qualitative ways of judging whether this goal is realized?</td>
</tr>
</tbody>
</table>

(3) clarifying the definition of the project, (4) analyzing the project setting at an early stage, (5) facilitating communication between all parties, and (6) identifying ways that the failure or success of the project can be measured.5

The LFA would be incomplete without the use of a practical organizing frame or matrix. This frame is known as the logframe matrix, or simply, logframe. The logframe is designed as a four-by-four matrix. Along the horizontal axis are objectives, indicators, means of verification, and assumptions; along the vertical axis are four hierarchical levels of objectives. Table 2 provides an illustration of the logframe together with accompanying steps for constructing the matrix at the program design stage.

It is worth noting that the process of developing the logframe matrix is even more valuable than its use during implementation. The following are a few useful points to keep in mind during the development of the matrix6:

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Source: Adapted from Van Leeuwen.6
Define the key assumptions at each level (working upward).

Check that the vertical logic still holds given those assumptions. Begin at the lowest level of objectives and consider potential constraints and name them. A useful methodology to determine “assumptions” is the following: if A (activity) takes place and B (assumption) is in place, then we can accomplish our higher-level objective C (output).

First define indicators for the objectives, then for the outputs (or check that these are specified with targets), then for the goal.

Define the means of assessment at goal, objective, and output levels.

Check the “horizontal logic” across each row.

Put inputs and costs for the activities in the bottom row (i.e., the budget summary).

Review the logframe design in light of past experiences with similar efforts.

Defining Goals and SMART Objectives

The goals and objectives of a program are a good starting point for setting up an M&E system. Goals and objectives, particularly in the context of the logframe, establish a foundation of what is measurable from the standpoint of M&E. The goal is the higher-level objective, stated generally, that describes the intended result of a program. Goals are achieved over the long term (5 to 10 years) and through multiple programs. The objective is a specific, operationalized statement detailing the desired accomplishment of the program. A good question to ask when defining objectives is “What changes will occur because of our activities?” A properly stated objective is action oriented, starts with the word “to,” and is followed by an action verb. Objectives address questions of “what” and “when,” but not “why” or “how.” Objectives are stated in terms of results to be achieved, not processes or activities to be performed. Without clearly defined objectives, it is virtually impossible to conduct effective M&E activities. When objectives are not clearly defined, the indicators that follow (even if well crafted) will be meaningless and thus produce little if any valuable information. To facilitate the process of clearly defining objectives, the SMART principles are used:

- **S** specificity: Is it specific? Does it cover only one rather than multiple activities?
- **M** measurability: Can it be measured or counted in some way?
- **A** attainability: Is the objective actually doable? Can we achieve this goal?
- **R** relevance: How important is this objective to the work that we are doing? How relevant is it to achieving our goal?
- **T** time: Does the objective include a time frame for when the objective will be achieved or for when the activity will occur?

The effectiveness of M&E will be greatly enhanced by good project design utilizing SMART goals and objectives. Conversely, a good M&E system will bring focus and clarity to goals and objectives, helping the project to get back on track.

Defining Indicators

Once the SMART objectives have been identified, the indicators for the program can be defined. An indicator is a unit of information that facilitates measurement over time, enabling the M&E system to document change. As such, indicators provide evidence of how much has or has not been achieved. Such measures are usually quantitative (numerical) but may also be qualitative (narrative) observations. Indicators enable a large amount of data to be reduced down to its simplest form.

It is important to reiterate that without clearly defined objectives, SMART objectives, the resultant indicators, although they may be well crafted, will yield meaningless information. This highlights the
importance of integrating M&E considerations into project design. Indicators provide a simple and reliable means to measure achievement, reflect the changes connected to an intervention, or help assess the performance of a development actor. Indicators also enable managers to track progress, demonstrate results, and take corrective action to improve service delivery.

Once indicators have been formulated, they are used as a basis for setting performance targets and assessing progress toward achieving those targets. In this way, indicators provide an “early warning system” that allows program managers to identify problems and take corrective action when performance targets are not met. Indicators also facilitate benchmark comparisons between different organizational units and districts over time. Yet in most cases, indicator data are of limited value in identifying why changes occur. At best, indicator data can suggest whether or not an in-depth evaluation or review is needed.9

Ideally, indicators should highlight key elements of change that can be attributed to program activities. Indicators should be readily available from existing data sources or should be possible to obtain on a regular basis at low cost. Efforts should be made to ensure that the indicator is well defined, easy to collect, easy to interpret, and capable of demonstrating changes over time.

Indicators should be:
- **Valid**—measure the condition or event they are intended to measure;
- **Reliable**—produce the same results when used more than once to measure the same condition or event, all things being equal (e.g., using the same methods, tools, or instruments);
- **Specific**—measure only the condition or event they are intended to measure;
- **Sensitive**—reflect changes in the state of the condition or event under observation;
- **Operational**—can be measured or quantified with developed and tested definitions and reference standards;
- **Affordable**—can be measured at a reasonable cost; and
- **Feasible**—data collection can be easily carried out.

Indicators should not be:
- used to define or conceptualize a project;
- overly complicated—key stakeholders should be able to understand them;
- developed from scratch, with much effort;
- derived for their own sake (e.g., are included in a proposal but never used by program managers); and/or
- so numerous that they are overwhelming for program managers to utilize.

Characteristics of strong indicators include:
- able to provide an at-a-glance indication of a program’s status;
- comparable across time;
- an effective means to measure progress toward objectives;
- comparable between locations (e.g., between districts or countries);
- easily understood by decision makers;
- easily communicated;
- inexpensive to collect.

Characteristics of weak indicators include:
- superficial measures of performance;
- lacking explanatory power (i.e., further investigation required to identify the causes of change in indicator value);
- open to misinterpretation.

Accurately and regularly measuring just a few indicators will be more helpful to a program than generating an extensive list of indicators that are
never used. **Selection of indicators is a critical step in the program planning and M&E design process.** It is advisable that the selection of indicators be done in a participatory way with the involvement of key program stakeholders.

**Appropriate Use of Indicator Data**

Indicator data are used as a management tool at a variety of levels within a given program, from the point of service delivery up to the subnational or collaborating partner, national management, and international donors. At the point of service delivery, organizations or implementing agencies may be responsible for conducting a formative needs assessment; monitoring of inputs, process, and outputs; collecting and aggregating data from frontline project personnel; reporting to sponsors and partners; and using results for ongoing program implementation. At the collaborating partner level, country offices may be responsible for aggregating and synthesizing results, coordinating M&E activities across projects, reporting to donors, and/or disseminating and using program results. At the national level, the national coordinating body may be responsible for the national formative needs assessment; aggregating results from collaborating partners; providing feedback of results from government-sponsored M&E activities to collaborating partners; maintaining biologic and behavioral surveillance systems; and using M&E results to advocate for policy formulation and changes. This section focuses on the use of indicators at the national, multisectoral level, for use by national coordinating bodies in shaping and guiding national responses.

As illustrated by the M&E pipeline (Figure 3), the number of indicators for which data are collected should be related to the level of effort required to collect the needed information. At the service delivery point, relatively little effort is required to collect data related to program inputs and outputs. However, such data are related specifically to the implementation of particular services and are often unique to that service. As such, program-specific indicators may have limited utility at the national level.

When selecting indicators for the monitoring of the national response, a focus on outcome indicators is appropriate. Although this does not preclude output measures at the national level, only a small number of output indicators that are common across a range of service providers are likely to be of use for guiding the national response. Counts of the numbers of condoms distributed may be an example of such an indicator. More commonly,
outcome measures, rather than output measures, are of more value at the national level. Outcome and impact indicators are difficult to attribute to specific programs and are not necessarily suited to monitoring at the program level. These should be included in the national indicator set and attributed to the response as a whole, and not to specific programs.

Although outcome measures require more effort for data collection and are more difficult to attribute to a particular program, they are more useful than output measures for determining whether the national response to HIV is achieving its desired objectives. Continuing from the previous example, condom use rates are of more value to national coordinating bodies than the numbers of condoms distributed, as they provide a more direct measure of the likelihood of infections being averted. The fact that condom use rates are a function of many factors, including both programmatic (e.g., prevention messages, condom social marketing) and social factors (e.g., female empowerment), is of secondary consequence. From the perspective of a national AIDS coordinating body, it is more valuable to know whether the national response as a whole is achieving its objectives than to know whether a particular program is achieving its particular service delivery targets.

Impact measures, such as incidence, prevalence, and mortality, require the greatest level of effort for data collection and are the most difficult to interpret. As such, they should be collected relatively infrequently and used in conjunction with outcome and process measures.

Minimum Indicator List
Historically there has been a tendency to include too many indicators in the national set. This may be partially explained by the notion that “what gets measured gets done.” Certain indicators can be used to push for different interventions and issues, and as a result, some may advocate for unnecessarily large numbers of indicators to be included in the national set on the assumption that this will drive programming in a given area. However, this trend has hampered the development of national systems, as the collection, interpretation, and reporting of large numbers of indicators is costly and impractical. Although recognizing and responding to the concerns of lobbyists is important, of even greater importance is limiting the number of indicators in the national set so that data collection, interpretation, and reporting is feasible and efficient.

The proliferation of indicators included in national sets or defined by international agencies over the previous two decades of the HIV epidemic undermine one of the main strengths of indicator data, namely, the ability to compare data between programs and across time. In response to this proliferation, a global process to review indicators for monitoring HIV programs was recently undertaken by the Joint United Nations Program on HIV/AIDS (UNAIDS) Monitoring and Evaluation Reference Group. The objective of this process was to consolidate the large number of indicators into a shortlist of those proven to be valid, reliable, and feasible to collect. Indicators from the shortlist were then selected for international reporting and recommendations made for indicator selection for national programs.

The national and international agencies represented on the UNAIDS M&E Reference Group reviewed more than 400 indicators and selected a set of 45 deemed most appropriate for monitoring the response at the national level. The recommended set includes the 25 United Nations General Assembly Special Session (UNGASS) core indicators, plus an additional 20 program indicators.

A further impediment to the operationalization of national monitoring systems has been that indicators are often defined without consideration for the feasibility or practicality of data collection.
Many indicators that do not have accessible data sources have been included in national indicator sets and are subsequently never reported. At the national level, indicators should be selected from the existing monitoring systems of national programs or from regularly planned surveys, such as bio-behavioral (second-generation sentinel) surveys used in the national surveillance system or national censuses.

As previously mentioned, not all indicators needed for effective program management should be reported to the national level. A classic example of this is the cascade of indicators used for monitoring prevention of mother-to-child transmission (PMTCT) programs. From a management perspective, it is important to monitor each step of the cascade. At the national level, where PMTCT is one of a number of strategies in the national response, it is unfeasible, impractical, and unconstructive to try to consider each of these steps. Since the main concern of the national coordinating body is the effectiveness of the national response, including a single indicator for PMTCT coverage and impact is sufficient. If the value for that indicator is low, further investigation of the cascade of indicators and additional evaluations may be appropriate. Figure 4 shows a sample PMTCT indicator cascade.

As countries scale up their national HIV response toward the goal of universal access, monitoring of the epidemic and the response is of paramount importance. Such efforts will enhance the effectiveness of interventions, inform policies and programs, and promote accountability. Building upon related international efforts, such as UNGASS, the WHO has developed a framework designed to facilitate the generation of standard information that would monitor the health sector’s progress toward universal access. The framework proposes a core set of indicators to monitor scale-up and includes 11 UNGASS indicators and seven others collected by the WHO/UNICEF Inter-Agency Task Team.\textsuperscript{10,11}

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**Figure 4. PMTCT indicator cascade**  
Adapted from UNICEF/WHO.\textsuperscript{10}

- Percentage of pregnant women who receive antenatal care (ANC) services
- Percentage of pregnant women receiving ANC services who are offered an HIV test
- Percentage of pregnant women receiving ANC services who undertake an HIV test
- Percentage of pregnant women receiving ANC services who test positive for HIV
- Percentage of HIV-positive pregnant women receiving ANC services who are offered HIV prophylaxis
- Percentage of HIV-positive pregnant women receiving ANC services who complete a full course of HIV prophylaxis
- Percentage of infants born to HIV-positive pregnant women receiving ANC services who are given HIV prophylaxis
- Percentage of infants born to HIV-positive pregnant women who are HIV-infected
Selection and Construction of New Indicators
The selection of new indicators should be done only when there are no suitable indicators currently in use within program-monitoring systems or being provided by regular national surveys. This may occur, for example, when a number of programs contribute to a desired outcome but none specifically measure that outcome. An example may be community programs providing care for orphans and vulnerable children. Among the objectives of such programs might be a reduction in the disparity of school attendance of orphans compared with non-orphans. The ability to measure orphans’ and non-orphans’ school attendance is well beyond the capacity of community programs. It might therefore be appropriate in this instance to define an outcome measure and advocate for its collection by national authorities.

Participation of key stakeholders in constructing and defining indicators is important, since they are then more likely to understand and use the indicator for management decision making. Often it is necessary to make a trade-off between picking the optimal or desired indicators and having to accept the indicators that can be measured using existing data. After more than 20 years of the HIV pandemic, more than 400 monitoring indicators have been developed and are used by international agencies or recommended in indicator manuals. It is therefore unlikely that it would be necessary to reconstruct an indicator for use for national-level monitoring. However, if all stakeholders agree that, after reviewing the indicators currently in use or previously defined, a new indicator should be constructed, the SMART principle should be followed.

Selection of Data Collection Methods
Choosing the appropriate method of data collection for indicators is as critical as choosing the indicators themselves. The perfect indicator is useless if the information cannot be obtained with the time and resources available to the project. The indicators chosen for measuring program achievements should dictate which methods are used to gather the relevant data. There are two methods, or approaches, for collecting data—quantitative and qualitative:

1. **Quantitative methods** are those that rely on structured or standardized approaches for the collection of data that are often analyzed numerically. Some common quantitative methods include censuses, population-based surveys, and facility inventories. Quantitative data are most useful for providing precise and broad data about a whole population, objective measurements, quantities, and what has happened.

2. **Qualitative methods** gather in-depth, descriptive information about how people function and how different aspects of their lives and relationships are linked together. Some common qualitative methods include participatory learning and action (PLA) and participatory rural appraisal (PRA) activities, focus group discussions, and semistructured interviews. Qualitative data are most useful in determining why things have happened and understanding the underlying dynamics of a situation. Qualitative methods help to contextualize the data derived from quantitative methods. This means that they help to understand and explain the phenomena better.

Quantitative and qualitative methods can and should be used in a complementary fashion to investigate the same phenomenon. For example, one might use open-ended, exploratory (qualitative) methods to investigate what issues are most important and the language to use in designing instruments for process evaluation. Alternatively, one might find surprising results in a survey that cannot be explained by the survey data, but might be better explained through open-ended focus group discussions.

Table 3 lists some primary sources of data for measuring indicators.
A written monitoring and evaluation plan describes all of the M&E activities to be undertaken and how they will be carried out. The goals and objectives of the program or project will provide the basis for this plan.

The M&E plan should include the following components:

- A clear description of the purpose for the M&E plan. The purpose statement helps to explain how the development of the M&E plan meets management requirements (the need for strategic information in decision making, evidence-based planning and analysis, donor reporting requirements, program steering).

- Definition of the scope of M&E to be undertaken. This will include considerations for program goals and objectives, primary questions

In addition to those listed in Table 3, other data sources include the following:

- Program data—counts of individuals served or services provided
- Survey data—percentage of the population practicing a behavior or accessing a service
- Estimates—epidemiological models of the size of populations (e.g., the number of people living with HIV, the number of people with advanced HIV infection in need of treatment, the number of HIV-positive pregnant women). The Estimation and Prevention Package for SPECTRUM software developed by WHO/UNAIDS is one tool that can be used to estimate and project adult HIV prevalence from surveillance data.\(^a\)

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\(^a\)Information and software downloads available at: http://www.unaids.org/en/KnowledgeCentre/HIVData/Epidemiology/epi_software2007.asp
MONITORING HIV DRUG RESISTANCE

HIV DRUG RESISTANCE IS THE inevitable consequence of the high mutation and replication rate of the HIV virus. In most cases, emergence of drug-resistant mutations occurs during antiretroviral therapy (ART) when the replicating virus is exposed to the pressure of antiretroviral drugs (ARVs) and selects for resistance mutations. While this acquired (secondary) drug resistance is the largest obstacle to the success of ART, the advent of convenient and highly potent ARV drug combinations has greatly reduced the rate of acquired drug resistance.\textsuperscript{12}

Transmitted (primary) drug resistance refers to the presence of drug resistance in HIV-infected individuals who have never been treated with ARVs. The majority of data concerning the magnitude of transmitted HIV drug resistance has to date been obtained in developed countries, where ARV drugs have been widely available for many years.\textsuperscript{13} However, the monitoring of transmitted drug resistance is of paramount importance for developing countries, where population-based approaches to the provision of ART have been more recently adopted.

The brief overview that follows focuses on the monitoring of primary and secondary drug resistance in resource-limited settings where large public ART programs have recently been initiated. Typically, national programs of this type offer standardized, potent first-line combination ART regimens and at least one standardized second-line (protease inhibitor-based) regimen for cases of treatment failure.

Monitoring of Acquired (Secondary) Drug Resistance

Monitoring the emergence of drug resistance among individuals receiving ART is a major challenge for most resource-limited settings. In such settings, which often lack viral load and/or genotypic resistance testing, national ARV treatment guidelines typically guide the management of treatment failure. Since standardized, potent regimens are being used in largely treatment-naïve populations in these settings, it is assumed that treatment failure due to drug resistance can be successfully managed by offering all patients that fail their first-line regimen an alternative, new regimen without the need to perform genotype resistance testing. In 2001, data obtained as part of the Botswana national sentinel surveillance showed virtually no major drug resistance in the population prior to initiating its public ARV treatment program, known as MASA. Longitudinal resistance monitoring data will soon be available from Botswana, and as larger programs in the region initiate ever-increasing numbers of qualifying persons on ART, routine longitudinal tracking of drug resistance will be critical to long-term program success.

While comprehensive documentation and evaluation of treatment failure cases is an essential activity in all ART programs, WHO and U.S. Centers for Disease Control and Prevention (CDC) have developed a standardized, minimum-resource method for sentinel monitoring of HIV drug resistance to be used in selected sites in countries where decisions on
ART regimens are made on a population basis rather than at the level of individual patients. WHO recommends that this population-based resistance monitoring method be performed annually at representative sites within a country to provide important information on the emergence of drug resistance. In accordance with the existing WHO/CDC protocol, a cohort of 100 consecutively selected patients initiating ART in a specific (sentinel) survey site will be followed over 12 months. In addition to routinely collected data, each consenting patient will also have a genotype and viral load performed at baseline and at 12 months.

Drug resistance is integrally linked with ARV medication adherence rates and drug availability. WHO has recommended that all ART sites develop and monitor specific early warning indicators (EWIs) that will assist in assessing whether or not HIV drug resistance is becoming a problem in a particular country. The specific proposed EWIs include the following:

- percentage of people initiated on first- and second-line ART regimens
- percentage of people lost to follow-up
- percentage of people who started first-line drugs and are still on first-line drugs after 12 months
- percentage of people who pick up all prescribed medications on time and who attend all scheduled appointments during a year
- percentage of people who demonstrate optimal adherence (as determined by pill counts)
- drug supply continuity
- proportion of patients who have suppressed plasma viral load 12 months following ART initiation

**Monitoring of Transmitted (Primary) Drug Resistance**

The most accurate method for detecting primary drug resistance involves performing genotypic resistance testing among those identified as being “recently” or “acutely” infected using newer detuned ELISA methodologies. Transmitted resistant virus is very often outgrown by wild-type virus within weeks or months and is not routinely detected using conventional genotypic resistance assays at the time of ART initiation. Two alternative approaches may be used to estimate the proportion of primary drug resistance, one based on identifying and genotyping persons with recent HIV infection in the community and the other based on monitoring the treatment response in patients initiated on ART.

The HIV drug resistance (HIVDR) threshold survey approach recommends monitoring high-risk individuals by socio-demographic criteria in communities with existing high (greater than 50%) ART coverage rates. WHO recommends targeting young women under 25 years presenting for their first pregnancy in settings with high ART coverage rates. While other sentinel groups could certainly be evaluated, the HIVDR survey approach can be easily added to existing annual national sentinel surveillance activities, which many developing countries participate in as recommended by UNAIDS. Specific test algorithms allow for the prediction of population HIVDR by evaluating small total numbers of genotypes (maximum 60). In the future, identification of recent HIV infection utilizing laboratory-based incidence testing will increase the accuracy and convenience of such surveys.
that M&E activities should answer, information needs of various players and stakeholders, and technical capacity for conducting M&E.

- **Selection of indicators and development of indicator protocols.** Indicator protocols would include specification and definition of indicators for each program objective and activity to be monitored or evaluated, identification of one or more data sources for each indicator, identification of the persons or groups responsible for each activity, and timeline of when information on that particular indicator will be collected.
- **Guidelines and procedures for analyzing and disseminating M&E data**
- **Required budget**

Indicator protocols are widely available and accessible on the Internet. For example, the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) has a set of indicator protocols that are updated annually. Other development partners, such as the World Bank, UNAIDS, The Global Fund, WHO and other UN organizations, have invested time and efforts in developing similar indicator protocols that can be easily replicated or adapted to meet specific M&E needs.

**Program Evaluation**

Program evaluation helps us to understand the broader effects of planned, ongoing, or completed program interventions. While it is generally accepted that a program of any scope can be evaluated, it is important to make certain distinctions from the outset. For an assessment to be considered an evaluation, it must conform to certain quality standards that guide the process and ensure that the information generated is technically sound, given the features that determine the worth or merit of the program.

**Program Evaluation Standards**

Evaluation standards help ensure that program evaluations are properly conducted. The jointly developed U.S. Program Evaluation Standards (US

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**Specimen Types for HIV Drug Resistance Testing**

Blood specimens used for resistance testing are routinely obtained in collection tubes and processed as plasma aliquots. Epidemiological studies have long relied on the dried blood spot (DBS) approach, which is simple and only requires a few drops of blood to be collected on filter paper. Dried blood spots have the advantage of being affordable, easily obtained (with minimal patient discomfort), and easily stored and shipped for analysis to a designated, qualified laboratory. DBS samples have been evaluated for HIV testing, viral load measurement, and genotypic resistance testing. One potential drawback of DBS is the smaller blood volume available for analysis, especially in ARV-treated patients with a low viral load.

In summary, monitoring of transmitted and acquired drug resistance is of high importance in resource-limited settings. Currently affordable methodologies for HIV drug resistance monitoring are being validated and should become an integral part of HIV surveillance programs.

*Available at: http://www.pepfar.gov/documents/organization/81097.pdf.*

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formative evaluations provide information for developing or forming a new program or to provide information to assist in revising or modifying an existing program. They are thus conducted during the planning or replanning phase of a program. Examples of strategies used for formative evaluations of HIV programs include needs assessments, situation/response analyses conducted prior to programming, and the midterm reviews of HIV projects or national programs (see Zambian Joint Annual Review sidebar).
THE ZAMBIAN JOINT ANNUAL PROGRAM REVIEW

Program reviews are conducted to obtain an assessment of what is happening on the ground in the multisectoral response to HIV. This is necessary to measure progress on the implementation of strategies at the national, provincial, district, and community levels. The review process itself is also helpful for overcoming delivery bottlenecks by ensuring that corrective action is undertaken in a timely manner. A program review also provides organizations/program managers with the opportunity to review the continuing relevance of programs; interim results with regard to performance indicators; the effectiveness of the approach being used to produce the results; the efficiency of program management, including the delivery of inputs and activities in terms of quality, quantity, and timeliness; and the need for corrective actions where necessary.

Over the past few years, Zambia has conducted a joint annual program review (JAPR) to review progress and agree on priorities for the national response to HIV. The JAPR is a process that brings the government of the Republic of Zambia, the National HIV/STI/ TB Council and partners together to review progress toward targets and objectives laid out in the Zambian National HIV/AIDS Strategic Framework. Following the success of the JAPRs in 2004, 2005, and 2006, the JAPR process has now become increasingly recognized, and used, to bring together cooperating partners and key stakeholders involved in supporting the national responses to HIV.

The JAPR draws almost entirely on existing documentation and ensures that the analysis and conclusions are linked to relevant government processes. A coordination team guides and supports the process and ensures that key documents and summary reports are produced in time for the main JAPR meeting. Data for the JAPR are gathered through a mix of quantitative and qualitative approaches, including literature reviews, primary and secondary data reviews, questionnaires, interviews and focus group discussions with key informants, and selected site visits to collect supplementary data, if necessary, to address specific gaps or questions that arose during the review process.

The following are some of the uses of formative evaluations:

- Assessing the need for an intervention
- Assessing acceptability of an intervention in a particular community
- Determining how best to implement an intervention or project in order to attain the intended objectives

The methods used for formative evaluations include reviews of existing information, focus group discussions, in-depth interviews with key informants, participant observation and short quantitative surveys with structured questionnaires.

On the other hand, summative evaluations aim to examine the effectiveness and/or efficiency in achieving the objectives of a program. They examine the outcome and impact of a project or program and also estimate the relative associated costs. They are normally conducted at the end of an intervention, project, or program. Here are some examples of summative evaluations:
At the planning stage, consideration should be given to the purpose of the evaluation. The purpose of an evaluation should not be limited to criteria, such as “to establish the effectiveness of the nurse-technician ARV dispensing model” or “to establish the impact of integrating TB testing in posttest services for HIV positive individuals.” While criteria are the means by which an evaluation purpose will be achieved, the purpose is an action that is made possible by the evaluation, such as facilitating decision making and learning. Thus the purpose of an evaluation could be, for example, “to help the National AIDS Coordinating Agency formulate a strategic framework for a TB/AIDS referral system” or “to provide a basis for scaling up a community-based HIV testing strategy.”

An important consideration when planning for an evaluation is having a clear understanding of the criteria for the evaluation. There are basically five agreed-upon criteria for any evaluation: effectiveness, efficiency, relevance, impact, and sustainability (see sidebar on Evaluation Criteria). There are, however, other criteria that can be developed beyond these five. For instance, additional criteria have been developed on humanitarian-related interventions. They are appropriateness, coverage, connectedness,
and coherence, and are considered as subcriteria to the five core criteria listed previously.¹⁸

In terms of timing, if an evaluation is intended to contribute to learning within the context of strengthening a selected intervention being piloted in a three-year project, then it may be prudent to plan for an evaluation midway through the project to allow for corrective action to be taken. If the intention is to extract lessons learned from a previous cycle of programming in preparation for a new one, then an evaluation might be strategically placed at the beginning of the new program cycle.

The Evaluation Matrix
The evaluation matrix is a tool that captures the evaluation plan in a matrix format. While there is no one standard, recommended evaluation matrix, Table 4 provides an example of the matrix and its contents.

Notes on how to complete the evaluation matrix:

**Column A:** This column helps you state your evaluation purpose. In stating the purpose, the fundamental consideration is use of the evaluation findings. The purpose should be an end and not a means.

**Column B:** Criteria are descriptions of the means by which evaluation purposes can be achieved. Stating the criteria helps focus and limit the number of evaluation questions. Criteria selection is, to a large extent, influenced by the intended use of the evaluation findings. Other considerations in selecting criteria include prior experience in conducting evaluations, examples from similar evaluations and advice from evaluation experts. This helps ensure the evaluation remains feasible.

**Column C:** Evaluation questions help determine the kind of information required for the evaluation. While it is possible to ask a myriad of questions for any evaluation, this may not prove useful or practical for the evaluation. To ensure focus, clarity, and conciseness, evaluation questions should be asked in the context of the criteria that have been chosen.

**Column D:** The common practice in many organizations is to list methodologies for data collection, such as surveys, interviews, etc. At this stage of the planning process, it is sufficient to state broad sources such as monitoring data (i.e., program reports), evaluation reports, and research. Details about how data will be collected will be provided in the inception report that will be handed in by the evaluation team. An “evaluability” exercise will help determine the appropriate methods for data collection.

**Column E:** This section is intended to show understanding of the dynamics of the program in its totality. Stating the timing of an evaluation in the context of the program cycle helps to address start-up, mid-, and end-of-program issues. It also brings into focus considerations of the purpose and choice of criteria for the evaluation.

**Column F:** The person responsible for an evaluation is the manager for the evaluation. This is different from the team that will conduct the evaluation and submit an evaluation report. The tendency here is to list the consultants or researchers in this column. The evaluation manager is the focal person who will ensure that the organization is reminded about the evaluation exercise when it is due. He/she will be responsible for ensuring that the steps for preparing and conducting the evaluation are adhered to and that they yield the desired result. The cost of the evaluation is computed based on several factors, including research costs (e.g., per diems, printing, equipment, supplies), dissemination activities, and others. The cost of an evaluation is influenced by several variables, including the complexity of the evaluation (internal vs. external, national vs. regional, etc.), availability of data, relative cost of hiring consultants (whether local or regional), and the cost of the evaluation as a proportion of the overall program budget. All these factors need to be considered when formulating an evaluation budget.¹⁹
### Table 4. Sample Evaluation Matrix for an HIV Counseling and Testing Program

<table>
<thead>
<tr>
<th>A. Why are we conducting this evaluation? (Evaluation purpose)</th>
<th>B. What do we want to evaluate? (Evaluation criteria)</th>
<th>C. What evaluation question(s) are we going to ask? (Evaluation questions)</th>
<th>D. How will we obtain the data? (Data sources)</th>
<th>E. When will we get the data? (Timing of the evaluation in relation to program cycle)</th>
<th>F. Who is going to manage this evaluation and what is the budget for this evaluation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>To help the HCT unit in the MOH decide whether support to AIDS Service Organization (ASO) capacity building should continue or not.</td>
<td>Relevance</td>
<td>Is the intervention consistent with the needs and priorities of its target group and the policies of the ministry?</td>
<td>Program monitoring data is not available. Research conducted will generate required information.</td>
<td>This will be conducted at the mid-point of the intervention.</td>
<td>HCT Program Manager US$70,000</td>
</tr>
<tr>
<td></td>
<td>Sustainability</td>
<td>Will the benefits produced by the intervention be maintained after the cessation of external support?</td>
<td>Selected program monitoring data are available at both the ministry and the ASOs. Further research is required.</td>
<td>Two studies are planned: Firstly a mid-term evaluation will be conducted, and secondly a postterm evaluation will be conducted two years after cessation of support.</td>
<td>HCT Program Manager US$120,000</td>
</tr>
<tr>
<td>To gather data about the effectiveness of the home-testing strategy for community-based HCT to facilitate scaling up of the intervention.</td>
<td>Effectiveness</td>
<td>Has the home-testing intervention achieved its objective of increasing the number of people testing and knowing their status by 30% from baseline figures?</td>
<td>Program data are available from three ASOs piloting the strategy. Further research data will be required from communities and organizations involved in the program.</td>
<td>The evaluation will be conducted six months before the end of the two-year intervention.</td>
<td>HCT M&amp;E Officer US$40,000</td>
</tr>
</tbody>
</table>

HCT = HIV counseling and testing  
Source: Adapted from Pact.19
Managing and Conducting an Evaluation

The following steps outline how an organization can prepare for and manage an evaluation, as well as how an evaluation team can go about conducting an evaluation.

Step One: Initial Considerations

As mentioned previously, deciding exactly why and when to conduct an evaluation is a process that begins at the program formulation stage. Program designers lay the groundwork for evaluation by ensuring that the program monitoring systems will be sufficiently robust. This allows for strategic information to be generated that will serve as the basis for asking critical questions about the effects of the HIV intervention being implemented.

Thought must be given to the involvement of stakeholders or partners in an evaluation. Stakeholder involvement enhances the credibility of the evaluation process and ensures increased acceptance of the findings. However, stakeholder involvement can be costly and time-consuming. It is advisable to conduct a stakeholder analysis early in the preparation phase to determine the different partners and interest groups that might be involved. If there is a need to involve stakeholders, they should be informed of their roles and anticipated responsibilities early on to allow for greater dialogue on the evaluation process.

Source: Adapted from UNDP.20
Evaluation utility is a critical consideration. Utilization-focused evaluation (U-FE) is based on the premise that evaluations should be judged according to their utility and actual use. During the evaluation process, the evaluation team should design the evaluation with careful consideration of how everything that is done, from beginning to end, will affect the intended use of the evaluation by intended users. In other words, the utility of an evaluation is judged by how real people in the real world apply the evaluation findings and experience the evaluation process.\textsuperscript{21}

Finally, planned program outputs and outcomes should be reviewed in the context of results from monitoring data to ensure that both are still relevant. It is advisable to review outputs and outcomes six months prior to the commencement of an evaluation as this will provide ample time to determine the relative worth of the evaluation based on monitoring data.

**Step Two: Preparation**

There are no hard and fast rules as to what preparatory tasks should be undertaken as these will depend on the complexity of the evaluation being undertaken. For instance, an evaluation of planning and implementation processes is not as complex as that of outcomes and impacts. Preparation is even simpler if the evaluation focal person or team has prior experience in conducting similar evaluations. Where outcomes and impacts are being evaluated, it is advisable to seek the services of expert evaluation consultants to guide the preparation phase. The following list outlines the stages of preparation:

1. Review selected intervention to be evaluated;
2. Formulate evaluation questions;
3. Assess “evaluability,” i.e., the extent to which the evaluation questions can be answered;
4. Develop an evaluation budget;
5. Formulate terms of reference (TORs);
6. Form an evaluation reference group;
7. Recruit an evaluation consulting team.

**Review selected intervention to be evaluated.**

It is important to examine the phases of the intervention (start-up, implementation, and closure or postproject, etc.) that will be addressed by the evaluation. This should be done within the context of the program intervention logic (i.e., conceptual, logical or results framework) and is made simpler when monitoring and reporting systems generate accurate and reliable program data and reports. An analysis of activities and outputs is essential to clearly establish what needs to be evaluated. If it is not clear what should be evaluated, it is advisable to postpone the evaluation until clarity has been achieved.

**Formulate evaluation questions.** Formulating evaluation questions is an iterative process that begins with an understanding of the scope and focus of the evaluation. Scope and focus are largely determined and defined by the program scope itself as detailed in the project document. However, the scope and focus of an evaluation are shaped by the selected criteria and standards. Selecting the criteria for evaluation and stipulating the standards to be used during the evaluation are a key step of any evaluation. With utilization as a major underlying theme, the number of questions that can be meaningfully addressed should be no more than what is practically required. Thought should be given to what information is required in order to meet the purpose of the evaluation. It is important to examine the various criteria that can be used after carefully considering the information requirements.

Reviewing evaluations that have been conducted elsewhere for similar interventions, in order to ascertain the questions that were asked and how these were arrived at, is also useful. For example, in Swaziland, Organization Y was planning to evaluate the first five-year phase of its program operations in readiness for the grant-writing process for the second five-year phase. In developing the evaluation questions for inclusion in the TOR, the M&E team from that organization reviewed similar past World
Bank evaluations of national projects for evaluation questions that were used and how bank evaluators had generated these questions. Three national evaluations were reviewed, and selected questions from these were adapted and used to formulate questions that were included in the TOR.

Assess “evaluability.” Evaluability is the extent to which the evaluation questions can or cannot be answered, thus helping to determine whether or not the evaluation is feasible. Through an evaluability assessment, modifications can be made to the evaluation and evaluations questions dropped if they are deemed too difficult or expensive to answer; new questions can also be introduced to add depth. To assess evaluability, program design factors, such as the program framework logic, should be reviewed and the availability and quality of baseline and monitoring data assessed. Often this is done during the earlier intervention review stage of the evaluation.

Develop an evaluation budget. Financial resources often significantly influence the occurrence and scope of an evaluation. The following general rules of thumb can help decide how to utilize scarce resources in order to yield the best possible outcome.

- If few resources are available, the first priority should be to establish a monitoring system. It is always advisable to set up an efficient monitoring system that can, at a minimum, demonstrate progress of implementation against stated objectives.
- If additional resources are available, some form of process evaluation can be undertaken.
- For an outcome or impact evaluation, even higher levels of financial and technical resources are required and should be planned for accordingly.

Available resources, regardless of how scarce or abundant, should be used creatively. For instance, the collection of information that is good to have but not overly important to the evaluation process should be limited. It is also important to know whether there are surveys being conducted by other groups in the same areas that may address some or all of the current areas of interest and whether they have yielded or will yield information of an acceptable quality. It is also useful to explore collaborations with other stakeholders so that resources needed for data collection can be pooled together.

Formulate terms of reference. The TORs for an evaluation team are a summary of the evaluation process that outlines all the previously mentioned preparatory steps. The TORs should include the purpose of and background for the evaluation, evaluation objectives and questions, deliverables, time frame, and required expertise and criteria for tender selection. In essence, they are a set of instructions for the evaluation team on how the evaluation should be conducted. Formulating TORs for an evaluation should be done well in advance of the evaluation to allow for stakeholder input. If an evaluation reference group exists, one of its early functions will be providing comments and input to the development of evaluation TORs.

Form an evaluation reference group. The evaluation reference group is mainly intended to serve in a quality assurance capacity and adds to the credibility of the evaluation over and above the use of external evaluators. The reference groups also acts as a check and balance to control any political biases on the part of the organization requesting the evaluation as well as the technical biases of the evaluators. Depending on the resources available, an evaluation reference group can range from two to six individuals. Appointing individuals to serve as reference group members should mirror the recruitment of evaluators, with similar criteria in regard to skill sets and qualifications.

Recruit an evaluation consulting team. Ideally, the evaluation team (external consultant team, in-house team, or a mix) should be composed of a variety of competencies capable of
STRENGTHENING THE USE OF EVALUATION FINDINGS

Traditionally, monitoring has been used effectively to serve the reporting needs of health-care organizations. However, reporting is not the same as using the findings arising from the analysis of monitoring data. Because most organizations are habitually accustomed to monitoring and reporting, evaluation has tended to follow a similar approach, wherein the focus is on reporting of findings rather than the use of those findings. The following are some practical suggestions for organizations that wish to strengthen their use of evaluation findings:

In any plan for monitoring and evaluation, ensure that resources for facilitating the use of findings have been indicated and allocated.

Deliberately set up or review structures for knowledge management and learning within the organization. Where an organization has an annual review or planning sessions and quarterly program meetings, emphasis should be placed on making sure that these structures facilitate learning and knowledge management. In preparation for such activities, the following questions should be asked:

During annual meetings, are there clear objectives that require your organization to apply lessons learned? Is documentation of program lessons arising out of analysis of program reports a requirement?

Does the organization have requirements in place for regular analysis of program data and reports for the purposes of improving program management? (Note that this requirement supersedes analysis for the purposes of reporting progress or a lack thereof.)

Are reporting processes aligned toward facilitating communication of implementation progress only? Or do they include a major component that requires the reporting agents to demonstrate/propose the use of findings through modeling and practical recommendations detailing the pros and cons of using the findings?

Create an organization-wide culture of inquiry by:

- extending an opportunity to others to work at problem solving by actively sharing skills and expertise with one another (i.e., “face-to-face” interaction without unnecessary dependence on information technology);
- unbinding knowledge from a single specific context in order to maximize knowledge transfer; for example, franchising is a well known business strategy for expanding operations in the private sector. Love Life (a South African National HIV/AIDS initiative for youth) successfully used the concept of franchising to establish what they call Love Life franchises (i.e., AIDS Service Organizations) that buy into and implement the Love Life brand. The difference in this case is that Love Life provides full funding for the establishment of the franchise as well as technical support whereas in the private sector, the interested part pays for the franchise.
- enabling others to recognize and respect what they already know as well as the knowledge that exists within their community;
- providing others with several examples of a new concept as well as fostering an understanding of how essential features of the concept are reflected in a range of
settings; For example, Prevention with Positives (PWP) is a relatively new concept that has come to the fore in many developing countries due to the proliferation of life-prolonging HIV treatment programs. In Botswana, PWP activities include setting up support groups, holding the annual Miss/Mr. Stigma free fairs, and the communication campaign—“It stops with me.”

- strengthening one’s own and others’ ability to judge when new knowledge should be used.

Step Three: Conducting the Evaluation Research
This step is characterized by the inception and monitoring/support phases of the evaluation research activities. During the inception phase, the evaluation team should submit a detailed proposal for the evaluation exercise, known as an inception report. The inception report should at a minimum contain an interpretation of the evaluation questions and how these have led to the chosen methodology for data collection and analysis, including an evaluation plan. The inception phase is also a time to make any needed changes to the TORs or amendments to the evaluation proposal. However, an inception report should not be used as a basis for further reviewing the suitability of individuals to carry out the evaluation. This should largely be determined during the recruiting stage.

During the research phase of the evaluation, communication and practical assistance are crucial to ensure minimal disruptions and successful completion of the research. Essentially, it is important to establish clear communication channels and state up front what assistance can be offered over and above what has been budgeted and planned for in the evaluation proposal, such as making of appointments, arranging of site visits and obtaining of permission from community “gatekeepers.”

Step Four: Dissemination of the Evaluation Report
An evaluation report is different from a research report. The former is intended to communicate to the users the evaluation results, their implications, and (where applicable) recommendations. Unlike a research report, few users of an evaluation report are interested in the detailed explanation of the evaluation process or the finer aspects of the defensibility of the research. These technicalities have already been dealt with at the inception phase. During the dissemination stage, the report that has been submitted is checked for completeness. It is advisable that this is done using an evaluation report review checklist (several of which are available on the Internet). Once the evaluation report has been accepted, it should be formally communicated to the evaluators and arrangements made for its dissemination. Depending on the intended users and uses of the evaluation, other means of dissemination, such as publication in a journal or submission to online evaluation interest group listings, can be considered.

Step Five: Use of the Evaluation Findings
Use doesn’t just happen naturally, but rather it needs to be facilitated. This implies that after the dissemination of findings, time and resources should be set...
aside for facilitating the actual use of the evaluation findings. There are two critical activities at this stage: modeling the use of the findings and working with users to implement the findings.

Modeling the use of evaluation findings requires a careful examination of the purpose for the evaluation, a review of any changes in the settings being looked at since the evaluation was conducted, and the involvement of new stakeholders or partners. This may require making presentations to various units or sectors on how the evaluation results can be used and their implications on current programming. The importance of dissemination activities as part of the evaluation process cannot be underestimated. Dissemination is more likely to occur if a line item for dissemination activities is included in the original evaluation budget.

While primary users may readily apply the results of the evaluation, there are capacity issues inherent in the application of findings that should be reviewed and addressed. These may include a needed change in skill sets, acquisition of new knowledge, or the implementation of new technologies. Careful consideration should be made for training to improve knowledge and skills or to orient users on the introduction of new technologies.

CONCLUSION
Monitoring and evaluation of HIV programs has progressed significantly since the early 1980s, moving from a purely bioclinical framework to a broader, multifaceted approach. Along the way, this practice has helped change the global understanding of the HIV epidemic and the responses to it. M&E also plays a crucial role in the efficient and effective implementation of projects and programs and in ensuring accountability. This chapter has highlighted some of the main M&E principles, frameworks, and methodologies currently in use. In addition, given that much of the HIV M&E efforts to date have paid insufficient attention to evaluation, the chapter has covered the basic evaluation concepts and the management of the evaluation process. The importance of integrating M&E activities into the overall design of HIV programs and the need to strengthen and expand the use of M&E has been emphasized.


The Third One in Practice: Monitoring and Evaluation of the Botswana National HIV Response

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his chapter highlights practical experiences with monitoring and evaluation (M&E) of Botswana’s national HIV response with a view to demonstrating the role of the “Third One” in harmonizing and coordinating sub-national, national, and global M&E systems. Botswana is currently moving toward the creation of one integrated country-level monitoring and evaluation system (i.e., the “Third One”). Although it still has some way to go toward achieving this goal, Botswana has gathered a great deal of practical experience in planning and implementing a national M&E system. It is hoped that the information culled from those experiences can be of use to other countries engaging in similar efforts. The chapter also includes a discussion of the country’s HIV epidemic and the national response, as well as a description of the various M&E structures and systems currently in place.

COUNTRY DESCRIPTION

Botswana is a landlocked country with a total land area of 582,000 square kilometers situated in southern Africa. The country is bordered by Zambia, the Republic of South Africa, Zimbabwe, and Namibia. Botswana’s population is roughly 1.7 million and represents one of the smallest populations of any African country. At the time of its independence in 1966, Botswana’s gross domestic product (GDP) per capita was one of the lowest in the world. Yet Botswana has experienced strong growth over the past three decades (with an average GDP growth rate of 6% per annum), and in 1993 ranked 71 out of 178 countries on the United Nations Development Program (UNDP) Human Development Index (HDI). Unfortunately, even with the state’s prioritization of economic growth, Botswana’s HDI rank fell to 114 out of 162 by 2001, mostly due to the severity of the country’s HIV epidemic.

THE EPIDEMIC AND ITS CONSEQUENCES

HIV was first discovered in Botswana in 1985. Since then, the virus has been spreading rapidly and taking an increasing toll, making Botswana one of the countries most affected by HIV. The 2004 Botswana
HIV/AIDS Impact Survey (BAIS II) showed a 17.1% HIV prevalence in the general population for people older than 18 months of age.3 According to the Ministry of Health’s (MOH) antenatal care (ANC) surveillance survey carried out in 2007, 33.7% of pregnant women in the country were HIV-positive.3 However, a declining trend in HIV prevalence among ANC attendees has been noted between 2001 and 2006. As shown in Figure 1, the largest decline between 2003 and 2006 was seen in the 15-to-19 and 20-to-24 age groups.

By the end of 2006, it was estimated that approximately 276,000 people were living with HIV in Botswana. That number is projected to reach 348,000 by the year 2019.4 The government’s central statistics office estimated that 18% of all reported deaths in Botswana in 2003 were attributed to HIV and AIDS. This sharp rise in mortality has caused life expectancy to fall, resulting in an overall reduction in the country’s population growth rate.

The epidemic has affected both urban centers and rural communities with equal intensity and has become a serious developmental and social problem, negatively affecting all sectors of society. The roll-out of antiretroviral therapy (ART) has made the disease more manageable, enabling a shift away from acute care toward a greater emphasis on chronic care. However, health systems have become inundated with HIV/AIDS patients, and subsequent pressure has been felt on all other sectors competing for both human and financial resources.

BOTSWANA’S NATIONAL RESPONSE
Strong commitment from the government of Botswana has enabled an unprecedented multisectoral response to the epidemic, with more than 5% of the national budget going toward the fight against HIV. Within the government, the Ministry of Health and the Ministry of Local Government
(MLG) are key players in the national response to the epidemic. The MOH has been tasked with planning and coordinating health care in the country and administers all hospitals, while the MLG oversees implementation of health care and administers the primary care clinics in the country. Through numerous targeted policies and legislative actions facilitating the rapid roll-out of prevention of mother-to-child transmission of HIV (PMTCT) and ART programs, Botswana has achieved nearly 90% national coverage of these services.

A number of treatment, care, and prevention programs have evolved as a response to the epidemic that fall within the MOH’s Department of HIV/AIDS Prevention and Care (DHAPC). As part of the national response, the government decided to make HIV/AIDS treatment one of its priorities in line with its “Vision 2016” goal of creating a healthy nation and the National Strategic Framework goal for the provision of treatment, care, and support. In 2002, the government initiated the national ART program (named MASA after the Setswana word for “a new dawn”), which offers free ART to citizens who meet eligibility criteria. Beginning in 2002 at the Infectious Disease Control Clinic at Princess Marina Referral Hospital in the capital city Gaborone, ART services were rapidly scaled up throughout the country. Currently, 32 ART sites are operational, each site comprising a hospital providing ART services and related satellite clinics within its population catchment area. As the ART program expanded, limited capacity within the public health sector was seen to hinder further scaling up of the program. In 2004, in light of the call for universal access to ART and building upon World Health Organization (WHO) recommendations, the ART program developed a model for partnership between the government and the private sector for the outsourcing of patients on ART from the public to the private sector. By the end of December 2007, 75,082 patients were receiving ART in Botswana’s public health sector, and a further 8,336 patients had been outsourced from the public sector to the private sector. As depicted in Figure 2, this increase in ART coverage has been associated with an overall reduction in adult mortality. The ART program is currently collaborating with MLG to scale up prescribing and dispensing of therapy at satellite clinics, facilitated by an innovative nurse care model that enables specially trained nurse practitioners to manage uncomplicated ART patients at the clinics.

Botswana established one of the first national PMTCT programs in Africa. The program was piloted in Gaborone and in the northern town of Francistown in April 1999, and rapid roll-out of the program was begun in July 2000. By November 2001, all 634 public health facilities throughout the 24 health districts in Botswana offered PMTCT. Of 8,287 new ANC clients who visited public facilities during the second quarter of 2007, 82% agreed to receive an HIV test, of which 28% were found to be HIV-positive. The Botswana National Strategic Framework for HIV/AIDS (2003–2009) calls for a reduction in the number of infants born to HIV-positive mothers who are infected by 18 months (from 21%–40%) in 2002 to 10% by 2009. Botswana appears well on its way to meeting this goal, according to a study in Francistown in 2006 that found a 6.7% rate of mother-to-child transmission of HIV.5,6

HIV testing serves as an entry point for utilization of other national response programs. The routine HIV testing and counseling (RHT) program (also known as provider-initiated testing and counseling) was initiated in Botswana in 2004 and is offered at all government health facilities across the country. According to the RHT protocol, all symptomatic patients with signs and symptoms that could be related to HIV/AIDS and all adults and adolescents
seen at health facilities are offered an HIV test and are tested in the absence of expressed refusal. RHT also incorporates voluntary counseling and testing (VCT) as one of its components. According to the 2007 fourth-quarter report of Botswana’s National AIDS Coordinating Agency, the actual uptake of RHT was greater than 90%, with 22.4% of those tested found to be HIV-positive. VCT is run by the private sector, and there are currently three service providers in this area. Tebelopele, the main provider of VCT in Botswana, has mounted an aggressive testing outreach campaign that includes the operation of temporary testing centers in low-income areas with the aim to reach more clients.

Other initiatives overseen by DHAPC and MLG include the Community Home-Based Care program, the Male Circumcision program and the Orphans and Vulnerable Children program. The country has also secured a safe blood supply.

**NATIONAL MONITORING AND EVALUATION FRAMEWORK**

In line with the “Three Ones,” Botswana has established one national HIV/AIDS coordinating body, one national strategic framework, and one national M&E system. Botswana’s National AIDS Coordinating Agency (NACA) was established in 1999 under the direction of MOH. In 2002, it was moved to the Ministry of State President in line with current thinking that HIV could no longer be seen strictly as a health problem but rather as a development challenge. The repositioning of NACA was instrumental in mobilizing a broad-based, multisectoral national response.

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**Figure 2. Association between increasing ART uptake and decline in overall adult mortality, 2003 to 2005**

NACA was assigned the function of monitoring and evaluating the national HIV response to reflect the growing recognition of the role of M&E in development management. As a first step, an epidemiology unit was set up within NACA with a key mandate for M&E. The unit laid the foundation for the Botswana HIV/AIDS Response Information Management System (BHRIMS), a multilevel, multisectoral, national M&E system that has come to play a central role in NACA’s routine business processes.

At the same time, Botswana developed the National Strategic Framework 2003–2009, building on the experience gained from previous short-term plans. The National Strategic Framework recognized the critical role of M&E in strengthening the management of the multisectoral national HIV response to such a degree that BHRIMS was identified as the vehicle by which the country would “ensure accountability, appropriate policy formulation and review, program improvement, and social justice through the direction of resources to the most vulnerable groups.”

THE NATIONAL MONITORING AND EVALUATION SYSTEM: BOTSWANA HIV/AIDS RESPONSE INFORMATION MANAGEMENT SYSTEM

BHRIMS was developed out of the need, as stated by the National Strategic Framework, “to gain a better understanding of the HIV interventions in the country, generate adequate information on the response, and improve the utilization of generated information for program planning, policy formulation and appropriate allocation of available resources.” However, the implementation of BHRIMS posed many challenges—first, the objectives of BHRIMS needed to be clearly spelled out; second, the structure of BHRIMS needed to be conceptualized; and third, an implementation strategy had to be developed.

The original objectives of BHRIMS were to:

- establish a monitoring and evaluation infrastructure;
- support the storage and analysis of all available HIV/AIDS data at different levels in the country;
- improve the accessibility of HIV/AIDS information and data;
- increase the utilization of available reports and data for action; and
- maintain institutional memory of the HIV/AIDS national response.

In recent years, various versions of these objectives have emerged; however, there seems to be a general convergence in terms of what the system seeks to achieve—that is, the promotion of evidence-based program development and management by establishing a culture of systematic data collection, storage, processing, reporting, and dissemination.

The overall structure of BHRIMS resembles that of the national HIV response, since useful data are generated continuously within programs from the various sectors (Figure 3).

The following are some important features of the BHRIMS structure:

- It is multisectoral, which is consistent with the recognition that HIV is not just a public health challenge but a development issue as well—hence the need to enlist contributions from a wide variety of stakeholders.
- Feedback is emphasized. The bidirectional arrows symbolize the importance placed on information sharing, from community-level response upward, and back down again. This ensures that the system does not end up being a “conveyor belt” of data from generation points to the top, as this would likely lead to reporting fatigue and disempowerment of implementing partners.
• NACA is positioned as an information hub. It is where all reports end up before they are collated and reported to the National AIDS Council. As none of the sectors report directly to that council, this structure enables NACA to harmonize M&E systems and standardize reporting formats. This is a critical ingredient in establishing a single national M&E system, as it facilitates data collection that meets agreed-upon national information needs.

The BHRIMS Implementation Strategy

The BHRIMS implementation strategy involved the formation of a national BHRIMS Technical Working Group (TWG). Broadly, BHRIMS TWG is a forum that brings together both local M&E experts and critical program managers to strategize on the best options for M&E system development in Botswana. A number of projects have been successfully carried out through BHRIMS TWG, such as the national M&E capacity needs assessment, development and implementation of the national M&E curriculum, the population-based Botswana HIV/AIDS impact surveys (BAIS I and II), conducting of national HIV/AIDS and related sexually transmitted infections conferences, UNGASS reporting, and numerous others. To date, BHRIMS TWG meets quarterly to review progress reports from its four subcommittees: evaluations, informatics, harmonization, and research.

The four subcommittees are organs through which various projects related to the national M&E mandate are implemented. Broadly, the evaluations subcommittee coordinates all projects and program evaluations by providing technical guidance and ensuring quality throughout the evaluation process. It is also in the process of developing an evaluation agenda for the country. The informatics subcommittee oversees the information and communication technology (ICT) requirements needed for transforming BHRIMS from a paper-based to an electronic system, mainly by working with ICT service providers to deliver an effective and efficient electronic M&E system, known as

Figure 3. The structure of the Botswana National M&E System (BHRIMS)
The single biggest challenge faced by BHRIMS since its inception has been lack of capacity, both in the area of human resources and M&E skills. As one of its first activities, BHRIMS coordinators conducted an M&E capacity needs assessment in 2002, which highlighted an immense shortage of personnel. Although pockets of M&E practice were noted in the country, most staff were “part-time M&E and full-time something else.” This meant that M&E had no dedicated staff of its own, which by extension had implications for data collection, completeness, processing, reporting, and dissemination. Further, where staff were in place, they lacked basic skills such as computing, data management, data analysis, and working knowledge of basic M&E concepts. This reduced M&E activity to simple reporting, thus heightening the risk of reporting fatigue. Simply put, the systems in place were nothing more than data conveyor belts, from the bottom to the top.

However, BHRIMS has come a long way, and these challenges have been tackled with notable success. M&E officers/experts have been recruited at various levels of the system, most notably at the district level, where there are currently two M&E officers for each health district. All of these officers are university graduates, most with a social sciences background. It is expected that involvement of this cadre at the district level will improve monitoring at peripheral levels and data quality in general as they are closer to data generation points such as health facilities and project sites. Further, a national M&E curriculum was developed under BHRIMS in 2006, which is further discussed later in this chapter.

Another notable challenge is harmonization of M&E systems. It was never the intention of BHRIMS to set up a completely new system that ignored existing systems, despite the frequent isolation of those systems. Rather, the BHRIMS strategy is to interface with existing systems and complement them with additional substructures only when deemed necessary. The main advantage of this strategy is that it utilizes already-existing system momentum, thereby improving efficiency by injecting a few innovations as needed.

The biggest challenge lies in synchronizing the different systems, which until now have operated as silos, so that they serve multiple information needs without compromising quality. This calls for detailed mapping of stakeholders’ information requirements, prioritization and reprioritization of information needs, and, in some cases, reconciliation of definitions, among other activities. It could be argued that the success of the “Third One,” or one national M&E system, heavily depends on the extent to which various components of the main system are harmonized.
Another challenge for BHRIMS is the loss of institutional memory. Many members of the pioneer implementation team have since left the system for various destinations abroad. Most of those individuals are members of the development partner community who have been redeployed elsewhere. While their contribution has been immense, it would have been helpful for partners to be more flexible in terms of length of tenure for M&E officers at the country level. For instance, some of the officers left in the middle of critical projects in which they played instrumental roles. Such departures make it difficult to establish continuity and, by extension, sustainability within program activities. It has been found that mixing national and international technical expertise is worthwhile, not only for cross-pollination of ideas but also to avoid total collapse in the event that an international expert departs the country. Currently, most national staff circulate within various organizations in the country and as such are not lost to the system; in other words, there is no brain drain in the area of M&E in Botswana, as of yet.

Lessons Learned from the BHRIMS Implementation

After more than six years of implementation, BHRIMS has provided useful lessons that can help M&E system development in other settings. Here are some of the more important lessons:

- An M&E capacity needs assessment provides information for the development of a national system. It enables understanding of what is available, in what quantities and qualities, while also exposing existing gaps; it is the identification of such gaps that informs the development of the M&E plan.
- The creation of a forum where M&E issues are discussed is essential. Botswana has BHRIMS TWG for this purpose, which has functioned well over the years. Not only does such a forum
provide a meeting point where M&E personnel from various sectors can share ideas; it also provides an entry point for various collaborative efforts between national partners as well as between national and international partners. In short, the TWG enables effective coordination and harmonized implementation of M&E activities.

- Satisfying development partner and national HIV/AIDS response program needs can be challenging. Development partners tend to have M&E expertise in relative abundance. On the other hand, government, civil society, and the private sector are less well resourced in M&E, and thus depend considerably on development partners for technical input. This implies a lot of consultation and consensus building, which leads to slow development of the national M&E system. Some donors have found it difficult to resist the temptation to set up their own systems, parallel to the national one, thereby undermining, to a large extent, the development of the national system. This has been blamed on pressure to report to their principals. Although this challenge has no immediate solution, it highlights the need for realistic M&E plans and commitment to their implementation by all partners. The situation also calls for compromise—government and other national sectors need to understand the urgency development partners attach to their own reporting needs and should move at a reasonable pace to ensure that frustrations do not occur. More important, however, development partners need to appreciate that government is a large machine and inevitably takes time to mobilize. Any attempt to take shortcuts could lead to frustration on both sides. This is one area that requires joint planning between all partners involved in national M&E development.

**DECENTRALIZED (DISTRICT-LEVEL) MONITORING SYSTEMS IN BOTSWANA**

The Ministry of Local Government is a key player in the implementation of the National HIV/AIDS Strategic Framework. MLG oversees all national programs implemented by local authorities and coordinates central government activities at the district level through policy direction, capacity building, supervision, and social and community mobilization (to facilitate community participation in the development process).

The District Multi-Sectoral AIDS Committees (DMSACs) were established in 1997 with a mandate to coordinate HIV activities at the district and/or subdistrict level. In 2002, MLG began mainstreaming HIV into local government planning and delivery systems. This led to the establishment of an AIDS Coordinating Unit (ACU) within MLG, and four work streams were established under this unit. With this step, MLG, through ACU, became part of BHRIMS. The four work streams are as follows:

- Mainstreaming HIV into district development plans and urban development plans
- Integrating the Community Home-Based Care and the Orphans and Vulnerable Children programs as a continuum of care
- “Caring for Us” programs
- Monitoring and evaluation of district response

All community-based organizations and nongovernmental organizations report on their activities to the DMSAC on a quarterly basis through their representatives in the districts. The district AIDS coordinator (DAC) collects data from national programs using the relevant BHRIMS forms designed for the collection of data on the national HIV indicators. These are mainly output indicators linked to the National Strategic Framework goals. The DAC, as the secretariat to the DMSAC, collates, analyzes,
and reports the data on the district response to the DMSAC on a quarterly basis. This information is now sent to the central level on a quarterly basis, through the BHRIMS mechanism. Additionally, national response programs report directly to their responsible ministry, which is generally the MOH.

**Toward a Computerized District Data Collection System**

As part of enhancing monitoring and evaluation, MLG took steps to improve data quality as well as to enhance the user friendliness of the process used by the DMSACs for data collection, storage, use, and submission by moving from a paper-based to a computerized system. It was thought that such a system would not only enhance further data collection systems at the district level but also enable the DMSACs to conduct “on-the-spot” analyses of their own data.

The envisaged database was one that would be universal (i.e., could be used at all levels, including the district and national levels). It had to be user friendly and amenable for use in the monitoring of intended activities/projects. On the other hand, MLG recognized that the system ultimately had to be linked to the national M&E system (BHRIMS) and other national vertical systems. For that reason, the intended system had to demonstrate a high degree of compatibility with other databases.

With the assistance of NACA, the UNAIDS Country Response Information System (CRIS) software was identified in October 2005. That software provided a basic blueprint for the e-BHRIMS system as it met most of the user requirements. A district reporting functionality was built in and set the pace for the nationwide e-BHRIMS rollout in 2006. Currently, e-BHRIMS is installed in all of Botswana’s districts and subdistricts and at the MLG headquarters. In 2006, MOH identified the DHIS (District Health Information System) software to enable reporting from the district health teams. As CRIS uses the common XML data exchange format, it is possible to exchange data with other systems including DHIS, DevInfo, and KIDS mapping software. The data exchange function leverages the strengths of multiple systems and greatly progresses the mandate of the Third One.

**PROGRAM-SPECIFIC VERTICAL MONITORING SYSTEMS**

Apart from the national BHRIMS, many individual response programs in Botswana have their own vertical monitoring systems. These usually provide data for a larger number of indicators, which are required for individual program monitoring and management. These vertical systems vary from purely paper-based systems to more elaborate electronic systems and a data warehouse at the national level. The following example is a description of the monitoring system of the national ART program (MASA), which uses a combination of both paper-based and electronic systems.

**The MASA Program Monitoring System**

ART provision within Botswana was planned according to a site model. An ART site comprises a hospital supported by four satellite clinics. Initially, prescribing and dispensing of ART was limited to the 32 hospitals in the country due to the lack of previous experience with ART, concerns about creating widespread drug resistance, the expectation of an initially large cohort of critically ill patients requiring hospitalization, and the limited availability of resources. The role of the satellite clinics was to screen patients for eligibility and provide patient follow-up. However, in keeping with the goal of universal access to treatment, the roll-out of ART services envisaged that all satellite clinics would be capacitated to prescribe and dispense antiretroviral medications. As
of December 2007, more than 50 of the 128 satellite clinics in the country were prescribing and dispensing antiretrovirals.

Data are captured electronically into a Microsoft Access–based application (called the Patient Information Management System, or PIMS) at 28 of the 32 ART sites in Botswana, while a proprietary hospital information management system, the Integrated Patient Management System (IPMS), is in use at four ART sites. These applications produce a monthly report, the indicator definitions and format of which have been standardized throughout the country. The few satellite clinics with no computers produce this report manually. The paper-based aggregate data flow monthly from the satellite clinics to the respective ART site hospital, where the data are collated for the respective ART site. This aggregated ART site report is then transferred to the M&E unit of DHACP within MOH. Monthly patient updates are produced by the M&E unit, which also provides feedback to the ART sites (Figure 4).

Patient-level data from ART sites are also obtained at the M&E unit, which enables more extensive data analysis. However, as most ART sites are not linked electronically to the central level, de-identified patient-level data are transferred on a quarterly basis from the facilities to the central level on portable flash (USB) drives.

In Botswana, there is a need to integrate all data from the ART sites, including from ART pharmacies and laboratories, and also data from tuberculosis, PMTCT, and other programs, in order to create a longitudinal and comprehensive view of a patient’s record. This is a formidable task given that the data are scattered all over the country in separate systems (for each program) or on numerous stand-alone systems (e.g., those for ART clinics). Tools are also required to analyze these data across the various programs. MOH in Botswana is currently developing a data warehouse to support these requirements.
CONCLUSION
Throughout this chapter we have seen examples and practical applications of the ways in which the drive toward one M&E system, or the Third One, can begin to harmonize and coordinate district, country, and global M&E systems. In Botswana, we have been successful in encapsulating the divergent needs of all stakeholders that are involved in measuring the effectiveness of the national response to HIV.

Many challenges have been addressed through this effort, which has resulted in the prioritization of M&E as evidenced by increased funding and the creation of a multitude of tools (e.g., frameworks, guidelines, standards, systems, M&E plans, M&E curricula, and trainings). However, many factors continue to prevent us from having a clearer understanding of the epidemic and from adequately measuring the response. Capacity constraints relating to adequate numbers of qualified personnel continue to be a major inhibitor and restrict the growth of M&E.

In our ongoing pursuit of the Third One it will be critical to consider and absorb the lessons learned from previous years. One such lesson is that our constant and sustained emphasis on monitoring has been extremely detrimental to progress on the evaluation front. Limited focus on the “E” of M&E has restricted our knowledge of program effectiveness and, in particular, our ability to measure the success of prevention efforts. However, more recently NACA has spearheaded the development of a National Evaluation Agenda identifying eight critical questions highlighting evaluation foci. The next phase of implementation of these questions will address outstanding issues that have surfaced through the routine BHRIMS. Guidelines for this process are currently being developed and will be made available.

Another challenge that has besieged the M&E field is the utilization of information. Much of the information that we have gleaned sits on the shelves of our offices or in some long forgotten database. Ultimately, it is the timely and appropriate use of information that will transform policies and programs and ultimately improve the quality of life of our people.
REFERENCE LIST


Clinical guidelines provide recommendations to assist practitioners in providing appropriate health care based on scientifically valid research. Since the 1980s, the World Health Organization (WHO) has promoted the development and use of clinical guidelines to define standards and broad treatment protocols for the effective delivery of health services. This is ideally done through an evidence-informed approach that incorporates technological and biomedical advances. In resource-limited countries, guidelines have been widely disseminated to address the management of health conditions accountable for high rates of morbidity and mortality. The introduction of new health interventions or expansion of services to the provincial or national scale has also spurred ministries of health in these settings to draft or revise national guidelines, usually adapted from WHO documents, to provide clinical and operational guidance to health-care workers. This trend is evident in the recent and ongoing efforts to enhance access to comprehensive HIV care, including antiretroviral therapy (ART).

At the level of service delivery, however, national clinical guidelines lack the necessary specificity and ease of use to adequately guide health-care workers in the day-to-day practices that promote safe and effective patient care. At all levels of care in resource-limited settings, health-care workers have had limited experience in providing HIV care, particularly ART. The challenges inherent in the rapid start-up and expansion of comprehensive HIV care at health facilities underscore the value of written procedures, based on national guidelines, which provide a detailed description of processes or steps in organizing HIV-related services and performing clinical practices. Standard operating procedures (SOPs) facilitate comprehension of technical information related to HIV care and treatment and maintain consistency in its application in daily practice. This chapter explores the role of SOPs in standardizing and promoting the effective organization and delivery of HIV services at health facilities in resource-limited settings; it also presents case studies from Tanzania and Nigeria that describe experiences and lessons learned in developing and using SOPs to optimize quality HIV care.

SOPs for HIV Care and Treatment

Building the capacity of the health sector to provide state-of-the-science HIV care in resource-limited settings entails interventions in numerous...
areas of service delivery, including staff training, infrastructure upgrading, drug and commodity management, laboratory expertise, and health information management systems. SOPs in these service areas have several objectives. First, they provide managerial and clinical staff with operational information on organizing services within the health facility and how these services relate to one another in providing patient care. One example of this is the step-by-step process describing how a counseling and testing service directs a patient who is newly diagnosed as HIV-positive to the appropriate HIV care services. Second, SOPs clarify the roles and responsibilities inherent in delivering new HIV-related interventions so that managers and health-care workers understand what personnel, timelines, methods, and materials and/or equipment are needed to effectively provide care and minimize inefficiencies.

Third, SOPs describe processes for linking with community-based HIV services, such as home-based care and support groups for people living with HIV, which are essential components in the delivery and sustainability of comprehensive HIV care. To optimize a patient’s access to community-based services, SOPs can direct health facility staff regarding the steps for conducting an effective referral within a given setting or catchment area.

Fourth, SOPs provide instructions and describe the steps followed in performing specific clinical tasks or practices to support standardization, correctness, and effectiveness of performance. For example, a clinician conducts a baseline assessment of a patient who has newly registered at the HIV service. Since this assessment includes laboratory investigations as detailed in the SOPs, the clinician refers the patient’s blood specimen to the laboratory, which can then perform these tests in accordance with the laboratory SOPs. Following a standardized process for all new patients enhances the delivery of the best care practices by ensuring that clinicians follow explicit directions based upon national/international standards and that patient outcomes can be evaluated in terms of these instructions.

The SOPs that are developed for each health facility level detail procedures in a manner that complies with each facility’s standards as well as national guidelines. SOPs assist in optimizing care while taking into account the resources and capacities available at each level of the health sector. For practices performed at multiple levels, patient outcomes at each level are expected to be the same. Thus, the baseline assessment to determine eligibility to start ART in accordance with the country’s national ART guidelines should entail the same practices whether it is performed at a primary health center or a tertiary-level facility. When services are not within the scope of practice of a health facility at a particular level of care, or resources are not available at a particular site (e.g., lack of laboratory capacity to perform required baseline tests), SOPs guide health-care workers in referring patients so that they may access the same range of services.

SOPs are also instrumental in preparing new staff for HIV service delivery and in reinforcing standards and processes for existing staff who need additional training. For example, a pharmacy technician with no prior HIV experience who is newly deployed to an HIV care and treatment facility will benefit from the detailed processes described in the SOPs (e.g., counseling for and dispensing of antiretrovirals [ARVs], drugs for opportunistic infection [OI] prophylaxis and treatment). While the technician may have completed classroom training about various drugs, including all aspects of managing the supply chain (forecasting, ordering, stocking, recording, etc.), SOPs provide a readily available resource to guide practice in the pharmacy setting. This is the case both for inexperienced staff needing detailed information about drugs or procedures
and for experienced staff needing a reminder about a specific drug or procedure.

Finally, SOPs are a mechanism for evaluating service delivery. They can serve as a checklist for supervisors in monitoring job performance and can also help in coaching staff to improve clinical practices. For example, a records department manager who observes medical records left unattended on the registration desk in view of patients can utilize SOPs for the management of medical records and safeguards for patient confidentiality to reinforce correct and consistent job performance. As a result, staff learn how to improve performance and thereby render a higher quality of care in accordance with health facility standards and national guidelines.

National clinical guidelines do not take into account the varying operational and administrative environments in which health care is delivered. Guidelines for monitoring patients on ART, for example, are the same whether the patients are managed at a tertiary-level hospital or a primary care facility. However, the modalities and resources used for program monitoring tend to vary and are based on the cadre of available staff, the drug-prescribing authority of the staff, the laboratory and pharmacy infrastructure and capacity, and other features at each level of care. SOPs are designed to address these variations and guide practice that is appropriate to the particular operational context and capacity of the health-care site. This contributes to standardizing the delivery of care so that patients, whether in urban, peri-urban, or rural settings, at a community health center, or at a large specialty hospital, have a higher probability of receiving quality care in accordance with national guidelines.

The multiple concurrent initiatives to expand the availability of HIV care and ART in resource-limited countries (e.g., WHO’s “3 by 5”; the U.S. President’s Emergency Plan for AIDS Relief; the Global Fund to Fight AIDS, Tuberculosis and Malaria) have generated tremendous momentum for the extensive and rapid scale-up of HIV-related services. Large numbers of health-care workers and lay counselors have been trained in HIV management through short formal courses. Yet numerous challenges impact the actual delivery of care in the clinical setting. This is particularly true at the district and primary levels, where a limited number of trained staff, who are already overburdened with heavy patient loads and limited infrastructural resources, face increasing numbers of patients seeking care and ART. With broader availability of ART, the management of HIV as a chronic disease has become a reality. Yet this reality is a daunting one, given the dearth of health-care workers, the large population of HIV-infected patients, and the prevailing orientation of health services toward acute disease management.

SOPs facilitate delivery of HIV care in day-to-day practice by clarifying each health-care worker’s respective areas of responsibility; by detailing the specific steps involved in conducting procedures appropriate to these areas of responsibility; by recording the specific supplies, equipment, and commodities required to perform these procedures; and by describing the linkages and referral procedures between different interfacility services (as well as between facility-based and community-based services) to promote comprehensive HIV care. New models of care delivery are also emerging in response to present challenges, such as nurse prescription of ART at the primary health level. SOPs are a practical tool for standardizing these evolving practices and guiding health-care workers in performing new tasks in a manner that optimizes patient safety and positive care outcomes.

Further impacting delivery of HIV care is the dynamic and constantly evolving science of HIV/AIDS. SOPs that are revised to include new information provide a viable way for overburdened health-care workers to deliver care based on the most current and available scientific knowledge.
The organization and design of SOPs are key to achieving optimal efficacy in the clinical setting. SOPs typically describe clinical procedures and tasks in a sequential, step-by-step format. The appropriate cadre of health-care workers for the performance of each task is defined, and minimum equipment and supplies are described. The needed documentation of the services delivered is also explained. For clinicians who have limited experience in HIV care and who manage large numbers of patients on a daily basis, SOPs that contain these elements and are clearly and concisely written facilitate rapid comprehension and application to practice.

In addition to a written compilation of procedures, SOPs that are formatted as job aids provide a quick visual reference for health-care workers in busy clinical settings. Material aids such as wall posters and laminated pocket cards can detail procedural content succinctly and thereby serve as valuable memory cues for rapid decision making.

As SOPs and accompanying job aids are introduced at a facility, health-care staff should be oriented on these new tools so that they understand their benefits and accept them for use in their everyday practice.

The process of developing SOPs for HIV care ideally includes staff from the cadres who will be the end users. In cases where no SOPs currently exist, a national-level effort, led by the ministry of health (MOH) or another governmental agency, is required to define the objectives and topics of generic SOPs for HIV-related services and to ensure participation of health-care workers and local clinical experts in their development. International partners supporting the scale-up of HIV services in the country may participate by providing technical assistance. One possible approach is to convene a task force comprised of HIV-experienced health-care workers, MOH staff, and, when appropriate, international partners to draft the SOPs using national guidelines for HIV and ART patient management as a framework. SOPs used in other settings may also be reviewed for guidance and possible adaptation. These resources—HIV clinical experts and national HIV guidelines as well as international HIV guidelines—are primary sources for identifying the specific topics to be covered in the SOPs.

The draft SOPs are then field tested in a representative sample of health facilities for a defined period of time to determine their utility for clinical practice and to conduct a performance assessment of staff and orientation of new staff. Task force members meet with health-care workers and facility managers at each site, using the draft SOPs to gather feedback, including recommendations about the content, language, and other specific aspects of the SOPs.

At the health facility level, generic SOPs are adapted for use at each particular site, incorporating both the HIV-related services currently offered and those planned for the future. The process of adaptation will be defined by the setting, but may mirror the national-level process through the formation of a team comprised of health-care workers delivering HIV services, facility managers, and provincial or district-level health authorities. Site capacities and resources will impact the content of the SOPs; for example, when specific services cannot be provided on-site (e.g., management of ART patients who are failing first-line drug regimens), alternative procedures will need to be defined (e.g., referral to the closest health facility with capacity to manage treatment failure).

It is particularly challenging to ensure that SOPs in resource-limited settings continue to keep up with new scientific knowledge and changing clinical practices in HIV care and treatment. A standardized process is required to ensure that the latest information is available to providers at the health facility level in a manner that facilitates
integration into clinical practices. At both the national and health facility level, the procedure for reviewing SOPs on a regular basis and revising them as needed must be defined.

CASE STUDIES
The following case studies describe the processes by which two countries, Tanzania and Nigeria, have introduced SOPs as a strategy for building health-care worker capacity and standardizing delivery of HIV care and treatment. In both countries, initiatives were aimed at providing a practical and useful mechanism that could assist health-care workers in effectively delivering quality health-care services to the rapidly growing numbers of people seeking HIV care, including ART.

Tanzania
In Tanzania, preparing district-level hospitals for the provision of HIV care and treatment is a cornerstone of the national strategy to expand ART access. In April 2005, the national guidelines for the comprehensive management of HIV/AIDS were revised in accordance with international standards by the National AIDS Control Program (NACP), in collaboration with international partners, in order to build health-sector capacity for HIV services including ART. As of May 2007, 2,990 health-care workers, including clinicians, nurses, and pharmacy and laboratory staff, have been trained in HIV care and ART. Infrastructure has been renovated at over 200 district-level facilities to accommodate the high volume of patients seeking outpatient HIV care and to improve the flow of these patients between essential services (e.g., counseling and testing, prevention of mother-to-child transmission, TB, pharmacy). In addition, health information systems have been standardized to strengthen documentation, analysis, and reporting.

Treatment scale-up has been particularly challenging at the district level, where facility staff who lack previous ART experience are overburdened by the scarcity of clinicians and increasing numbers of patients seeking care and treatment close to their residence. The development of SOPs was identified as a key strategy to rapidly build these workers’ capacity and confidence in providing safe and effective HIV care.

In August 2005, the NACP, with technical assistance from Family Health International (FHI), prepared a protocol for the development of SOPs for HIV clinical care. The protocol called for the SOPs to be adapted from the national guidelines and stipulated that they include a comprehensive range of facility-based services, including the organization of HIV service delivery; referrals between facility-based services to optimize patient access; HIV clinical care for adults and children (including OI prophylaxis and management and other HIV-related conditions, palliative care, and ART); pharmacy dispensing of ARV drugs; laboratory monitoring schedules; HIV post-exposure prophylaxis (PEP); health management information systems; and referrals between facility services and community-based services, such as home-based care. The following standardized format for the drafting of SOPs was developed to ensure consistency: (1) the purpose of the SOP, (2) the responsible person, (3) required equipment and supplies, and (4) step-by-step instructions or description of the procedure. To optimize clarity and ease of understanding, it was suggested that the language be concise and action-oriented.

To draft the SOPs, the NACP and FHI paired a nurse based at the Dar es Salaam City Council Diagnostic and Nursing Services, who had extensive clinical and administrative experience in Tanzania’s health sector, together with an HIV nurse specialist working at FHI’s Institute for HIV/AIDS. The pair was briefed about the initiative by the director of the NACP, the head of the Care and Treatment Unit of the NACP, the WHO.
representative in Tanzania, and the FHI country
director in Tanzania. The pair then visited second-
ary and tertiary health facilities in two regions,
Iringa and Dar es Salaam, to obtain input from
staff, particularly regarding bottlenecks in service
delivery and constraints affecting quality of care.
They also observed clinical practices and the flow
of patients between services as well as linkages with
community-based services.

The initial version of the SOPs, drafted in
accordance with the established protocol, was
completed in December 2005. The draft doc-
ument was then circulated to a broad range of indi-
viduals and organizations in Tanzania for review,
including the NACP, international partners, and
select health facility staff, and revisions were sub-
sequently made based on the feedback. This review
process has been time-consuming and frequently
delayed by competing demands for the reviewers’
attention. The slow progress, however, reflects an
overarching commitment to forge agreement on
the methodology and content of the SOPs and gen-
erate wide-scale acceptance for their adoption.

In accordance with the original protocol, the
SOPs will be field tested at district and tertiary
health facilities when the revised version has been
approved by the NACP. Field testing is essential
for determining the usefulness of the SOPs in
the clinical setting and for generating ownership
among health-care workers, facility managers, and
district and regional health supervisors. The SOPs
are expected to provide essential guidance for sup-
portive supervision visits conducted by regional
health supervisors to monitor the compliance of
health facilities with criteria for accreditation as
ART delivery sites.

While the draft SOPs were being reviewed, the
FHI Country Office worked with the NACP and the
Clinton Foundation to adapt key content from the
SOPs into job aids. These aids were developed to
provide clinical staff with ready access to essential
information about the prescription of and adher-
ence to ARV drugs. Developed as wall posters and
as smaller desk charts, the job aids are proving to
be useful both for staff who have limited experi-
ence delivering ART and for busy experienced staff
who benefit from reminders. To date, the following
job aids have been developed and are in use at the
comprehensive HIV Care and Treatment Centers
(CTCs) established at regional-level hospitals:
- ART regimens used in Tanzania (first-line and
  second-line)
- ARV drug dosage schedules
- ART adherence checklist
- Directory of HIV-related services in the region,
  including home-based care services

After the field testing and finalization of the
SOPs, the next steps planned in Tanzania are the
dissemination of the SOPs to all district and tertiary
health facilities currently delivering HIV care and
treatment and the training of health-care workers
on the SOPs. Another initiative will be the adap-
tation of the SOPs for use at the primary health-
care level. Health facilities that begin offering HIV
services in the future will receive SOPs for their
level of care as well as staff training. Additional job
aids based on the SOPs will be developed by part-
ners such as FHI, working in collaboration with
NACP, as health-care workers and managers iden-
tify the need for tools to enhance the quality of care
delivery.

The experience in Tanzania has highlighted the
importance of the commitment and active partici-
pation of the NACP, the national agency tasked
with HIV/AIDS policy and service delivery. This
level of participation is essential to the development
of SOPs for HIV clinical care. Another important
element is the involvement of health facility staff
in the review of draft SOPs to ensure that they
are appropriate to local conditions. The presenta-
ion and formatting of content also impact usage
and service delivery; in Tanzania, the availability
of SOPs that clearly and concisely describe clinical practices, and job aids that summarize their essential content, is helping to guide health-care workers in the provision of safe and effective HIV care and treatment services despite their limited experience.

Completing the SOPs for facility use, however, has taken a prolonged period of time. Over a year has been spent on the review of draft procedures and subsequent revisions, primarily because the protocol seeks to involve the widest possible range of individuals and organizations during this stage. To date, no process has been defined for rapidly updating the SOPs based on new scientific evidence and revised national guidelines. This need must be addressed to ensure the delivery of HIV care and treatment services that are consistent with updated national and international standards of care.

**Nigeria**

In 2005, Nigeria had an estimated four million people living with HIV, with over 600,000 requiring ART. Despite this, only 45,000 had access to treatment. Until 2005, ART services were available only at tertiary health facilities, limiting access for large segments of the population. There was an urgent need to establish and scale up ART services, particularly at secondary-level facilities. The government of Nigeria, in collaboration with international partners, led a vigorous response, which included the drafting of national guidelines for HIV management, including ART, in 2003, with subsequent revisions in 2005 and 2007 to incorporate new scientific findings. An extensive effort was launched to train health-care workers, including physicians, nurses, and laboratory and pharmacy staff, particularly at tertiary and secondary levels. Key interventions to strengthen the health information systems for HIV care and treatment included the development of standardized data collection and reporting instruments, intensive training of facility-based medical records staff, and the pilot computerization of HIV-related clinic-based data. As of June 2007, infrastructure upgrades and other preparations for the delivery of HIV care, including ART, were completed at 210 sites throughout the country.

As part of this initiative, the Global HIV/AIDS Initiative Nigeria (GHAIN) project, funded by the U.S. President’s Emergency Plan for AIDS Relief and managed by FHI, in collaboration with the government of Nigeria, designated eight secondary facilities in six states for the provision of ART services in the first phase of a rapid scale-up process. However, no SOPs were available for HIV care and treatment at this level of health-care delivery. Moreover, the existing national ART guidelines were directed primarily at tertiary levels of care. It was therefore necessary to work with national health authorities to ensure that the national guidelines and related SOPs were made appropriate for use at the secondary level.

To address the need for revision of the national ART guidelines, HIV-experienced clinicians with the FHI/GHAIN project made the case for the expansion of the guidelines to include settings beyond the tertiary care level to key Nigerian health authorities, including the National AIDS and STI Control Program (NASCP) in the Federal Ministry of Health (FMoH) and the National AIDS Control Agency (NACA). With a favorable response from the FMoH and NACA, the FHI/GHAIN staff collaborated with the health authorities and representatives from other HIV program implementers in Nigeria to update and adapt the national guidelines. The revised guidelines are currently being disseminated throughout Nigeria.

Simultaneous to the revision of the national ART guidelines, staff from the Clinical Services, Pharmacy, and Monitoring and Evaluation Departments of the GHAIN project began drafting procedures for ART service delivery to
expedite their availability for health facility use. Generic SOPs for ART developed by FHI were used as a starting point and were subsequently reviewed and adapted for the Nigerian health sector context and, specifically, the secondary level of care. The draft was reviewed by clinicians from FHI’s Institute for HIV/AIDS in Arlington, Virginia, and following their revisions was presented by the FHI/GHAIN team at a stakeholders’ meeting convened by the FMOH/NASCP and attended by representatives from the FMOH and staff from select secondary health facilities. During the three-day review meeting, participants worked in groups to review various components of the SOPs. The groups then presented recommendations in plenary sessions, and a final draft was produced.

The SOPs were field tested at the six secondary health facilities that had recently initiated ART interventions with FHI/GHAIN support in accordance with the protocol developed during the stakeholders’ meeting. Health-care workers in the ART delivery unit (referred to as the HIV Comprehensive Care Center), the pharmacy, the laboratory, and the records department, as well as managerial staff at each facility, were oriented on the SOPs. During the piloting, which was conducted for a period of six months, FHI/GHAIN clinical and monitoring and evaluation staff conducted twice-monthly visits to the sites to mentor staff and generate feedback on utilization of the SOPs. Key recommendations from facility staff centered on clarifying text and developing job aids to facilitate integration of the SOPs into clinical practice.

At the end of the field testing, FHI/GHAIN incorporated the recommendations from the health facility sites into the draft and circulated the finalized SOPs for the secondary level to the FMOH/NASCP, NACA, and the six health facilities where ART had been integrated into service delivery. Job aids developed based upon health-care worker requests included the following:

- First-line and second-line ART regimens used in Nigeria
- Adult and pediatric ARV drug dosages
- ARV adherence education and counseling flowchart

Since this initial phase of SOP development and testing, FHI/GHAIN has monitored compliance with the SOPs by conducting regular visits at the facility sites using a standardized tool developed by the GHAIN Monitoring and Evaluation Department. At the end of each visit, findings are reviewed with clinical and managerial staff and any challenges reported by health-care staff in the use of the SOPs are discussed. The monitoring visits have revealed a sustained high level of compliance with the SOPs at the FHI/GHAIN-supported sites. From the perspective of facility staff, health-care workers have reported that, particularly during the early phase of treatment delivery where there has been no prior experience with ART, the SOPs provide useful guidance regarding the steps for initiating treatment, drug dosages, drug side effects and their management, adherence assessment, and patient-monitoring scheduling, including specific laboratory testing requirements. Over time, however, they report that the increasing patient load is creating challenges in adhering to the SOPs and providing quality care.

In January 2007, after a year of SOP utilization by the six health facilities, a second stakeholders’ meeting was organized by the FMOH/NASCP to produce national SOPs for ART delivery at the secondary level. It was attended by FHI/GHAIN, U.S. government implementing partners, and other HIV-service-delivery organizations including advocacy groups for people living with HIV and health facility representatives. The national SOPs, drawn almost entirely from those developed by FHI/GHAIN and used at the six secondary
facilities that were the focal sites for Nigeria’s initiative to expand treatment at this level of care, are being finalized for dissemination as ART is being rapidly introduced into an increasing number of secondary health facilities throughout the country.

While FHI/GHAIN’s role in drafting the SOPs expedited their actual production, the close collaboration with health-care workers at the GHAIN-supported secondary-level facilities was instrumental in ensuring the relevance of the content and the ultimate acceptability of the SOPs for use in clinical practice. The stakeholders’ meeting convened by the FMOH/NASCP was an efficient process for the detailed review of the draft SOPs. As in Tanzania, the process for the ongoing review and updating of SOPs remains undetermined. This issue needs to be addressed, as the rapid expansion of HIV care and treatment in Nigeria is expected to impact quality of service delivery.

LESSONS LEARNED AND ONGOING CHALLENGES

Several insights have emerged from the initiatives to incorporate SOPs into HIV health-care delivery in Tanzania and Nigeria. For instance, HIV/AIDS care including ART is a dynamic, rapidly changing field in terms of science and health-care delivery practice. International and national guidelines need regular updating to reflect advances in knowledge and clinical practices, as do the SOPs that are based upon these guidelines. A protocol for updating SOPs is needed that defines who is responsible for the process (including funding sources), when it will occur (e.g., whenever international and national guidelines are revised), and how the revised version will be disseminated to health facilities throughout the country.

Another area requiring further thought concerns the use of SOPs as a mechanism for continuously promoting quality of care at the health facility level. Will district or regional health authorities conduct regular supervision of HIV-service delivery using a standardized instrument based upon the SOPs used at the facility? How will facility-based supervisors and managers use the SOPs for evaluating staff performance and determining whether services are being provided in accordance with the SOPs? Can a process of quality improvement be institutionalized at health facility sites whereby health-care workers draw upon the SOPs to self-evaluate their practices and the outcomes of the health care they provide, and take appropriate measures to enhance the care they deliver?

Finally, targeted evaluations are essential for gaining understanding of the initiatives where SOPs for HIV care and treatment have been introduced in resource-limited settings to date, such as Tanzania and Nigeria. An important area of inquiry is the utilization of SOPs by health-care workers and their perception of the benefit to clinical practice. Another need is to measure the impact of SOPs upon clinical services delivery. For example, is the length of time clients wait for consultation affected by adherence to SOPs for registration, triage, and other aspects of patient management? Is accurate drug prescription associated with the use of SOPs and their related job aids? Are health-care workers more or less likely to conduct ART adherence counseling at each client visit if they follow the SOPs that designate the responsible staff for this role and the schedule for conducting this activity?

CONCLUSION

There are undoubtedly a number of areas related to the implementation of SOPs that need to be explored and improved. Despite these challenges, SOPs constitute an important component of efforts to scale up HIV care and treatment in resource-limited settings and help standardize the application of national guidelines and international practice standards for HIV patient management in varying operational and administrative contexts.
REFERENCE LIST


Quality Management in HIV Care
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QUALITY MANAGEMENT OFFERS providers a standardized approach for addressing the appropriateness of care that can be applied in even the most resource-limited settings. The integration of quality into current efforts to provide and expand HIV care in resource-limited settings is an area of active work and investigation.

Implementing a quality-management program in a resource-limited setting involves the balancing of a number of factors, including working to measure and improve quality as soon as possible, dealing with competing demands in the absence of abundant resources, and building site-level capacity to participate in this work. In this chapter we provide an overview of quality management as an integrated approach to measuring and improving quality within the context of HIV/AIDS program scale-up.

There is some limited information in published literature on the use of different approaches to quality management and improvement in resource-limited settings.\textsuperscript{1-4} Øvretveit describes a number of approaches to improving the quality of health services in developing countries, including strengthening management, health-care reorganization, and adapting and applying quality improvement (QI) methods.\textsuperscript{1} Other approaches include quality measurement and standards (such as accreditation), engagement of teams to work on specific problems using QI methods, and community and patient participation.

The overall approach for quality improvement discussed in this chapter is based in part on the HIVQUAL framework of quality management (developed by the New York State Department of Health AIDS Institute and the Health Resources and Services Administration), which has been implemented in Thailand\textsuperscript{5, 6} as well as in a growing number of countries in sub-Saharan Africa\textsuperscript{7} (also B. Agins, MD, MPH, personal communication, July 2007). The discussion will also draw from a range of experiences in other settings. The focus will be on three core activities: measuring performance, improving quality, and building capacity and infrastructure. These activities will be discussed as they pertain to quality management at both the site and higher (i.e., program, district) levels. While QI work is of particular relevance to clinical leaders and management at the site, district, and program levels, it’s also important for supporting partners working to help ensure that quality care is provided to all those in need.
INTRODUCTION TO QUALITY AND QUALITY MANAGEMENT

The Institute of Medicine defines quality in health care as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.” In practice, quality can be defined as the degree to which a health or social service meets or exceeds established professional standards and user expectations and achieves desired outcomes. Although patient and provider characteristics and behaviors play a central role in determining whether desired outcomes are realized, the service-delivery system and organizational context in which care is delivered contribute equally to whether quality of care is achieved.

Quality management consists of the set of coordinated activities and infrastructure within an organization designed to support the activities that address the quality of care provided. The goal of quality management is to define, measure, and improve quality of care so that the desired outcomes are achieved according to accepted standards. These activities are part of the essential framework for a systematic approach to performance measurement and quality improvement. Quality management should be integrated into the planning and implementation of care and treatment programs in order for it to be carried out successfully.

Quality improvement processes address identified gaps in performance and assist in improving care to produce more consistent outcomes. Improvements are achieved through repeated cycles of testing changes to the system, measuring the impact, and then adapting or expanding the changes based on the results. Ideally, QI efforts help to strengthen critical systems by ensuring that services are delivered according to accepted standards of care and lead to desired outcomes.

Because QI is data-driven, performance must be measured in order for quality to be improved.

Performance measurement is the standardized collection of data that informs care teams how care is being provided and received and systems are functioning. These data are used to inform planning and improve care through the QI process. In the absence of good performance measurement, these planning and improvement efforts are otherwise often based primarily on people’s ideas and may not necessarily reflect what is happening. Standardized and uniformly applied indicators form the bedrock of performance measurement. These indicators let stakeholders know what is really happening in the clinic and whether changes that are made result in an actual improvement. Performance data are then used to identify opportunities to improve quality.

RELATIONSHIP BETWEEN RESEARCH, QUALITY MANAGEMENT, AND MONITORING AND EVALUATION

Quality measurement and improvement overlap with a number of other important activities that help ensure access to and delivery of effective care (see Table 1). All these activities are part of an evaluation process, helping to determine whether care is being delivered appropriately and whether desired outcomes are being achieved. However, there are important differences among these activities. Monitoring and evaluation (M&E) activities do not focus on how to address the gaps that are identified during the evaluation process. In addition, given the time frame of most formal evaluation, the results may reflect a system of care that has changed since the evaluation data were collected. Evaluation also may focus on longer-term goals that can only be measured after a number of years of program operation. However, the work done during the planning of an evaluation can feed
into QI efforts by identifying the steps of a program that are thought to be critical to achieve its stated goals. This information would then feed into decisions regarding where to focus performance measurement during program service delivery so that gaps that may serve as a barrier to achieving long-term program goals can be rapidly identified.

There is also an opportunity to learn from completed evaluations of similar programs, which may highlight areas having the greatest impact on the program’s success or failure. These are the areas that should be considered as targets for measurement. One way of determining areas of focus in evaluation is through the use of an evaluation logic model, a diagram that helps foster an overall understanding of how program inputs and processes are linked to outcomes and impact (see Figure 1, next page). For example, a logic model for a prevention of mother-to-child transmission of HIV (PMTCT) program, in which the planned impact is the improvement of HIV-free survival of children, would include an assessment of resources (inputs) invested in the program, program activities (e.g., HIV testing, dispensing of

| Table 1. Comparison of Quality Improvement, Monitoring or Accountability, and Clinical Research |
|---------------------------------|---------------------------------|---------------------------------|
| Aspect                          | Quality Improvement             | Monitoring or Accountability    | Clinical Research               |
| Aim                             | Improvement of care             | Assessment of program function; comparison, choice, reassurance, spurring of change | New knowledge                  |
| Test observability              | Test observable                 | No test, evaluates current performance | Test can be blinded             |
| Bias                            | Accept consistent bias          | Measure and adjust to reduce bias | Design to eliminate bias (e.g., randomization, case mix) |
| Sample size                     | “Just enough” data, small sequential samples | Obtain 100% of available relevant data | More data ensures adequate power, single sample size |
| Availability of data            | Collected for immediate feedback and further work | Collected for reporting, used when all data available | Data available only at end of study |
| Flexibility of hypothesis       | Hypothesis flexible, changes as learning takes place | No hypothesis | Fixed hypothesis |
| Testing strategy                | Sequential tests                | No tests                        | One large test, statistical significance critical |
| Confidentiality of data         | Data used only by those involved in the improvement project | Program/site data often available for public consumption | Research subjects’ identities protected, results of study published |

*Source: Adapted from Solberg et al.*
current performance leading to changes in processes while the program is ongoing, with the goal of rapidly improving overall quality of care.

IMPLEMENTING QUALITY-MANAGEMENT PROGRAMS FOR HIV CARE IN RESOURCE-LIMITED SETTINGS

The effectiveness of HIV care and treatment is directly linked to the quality of care provided. In the United States, measuring quality in HIV care has led to a better understanding of the patient, provider, and site factors associated with quality of care.12-14 There is also a growing effort to examine and improve the quality of HIV services in resource-limited settings. Groups such as HIVQUAL International, the Quality Assurance Project (QAP), the Institute for Healthcare Improvement (IHI), the Regional Center for
Guidelines are (ideally) evidence-based clinical recommendations that may ultimately become the standard of care. They are used to communicate overall approaches for a particular health-care activity in order to achieve the desired results. Ideally, these are national (Ministry of Health) or international (e.g., World Health Organization, Joint United Nations Program on HIV/AIDS) guidelines that have been developed based on scientific evidence and are appropriate to the program setting and available resources. Examples include guidelines for ART care, TB diagnosis and treatment, and PMTCT.

Standards of care are explicit statements of expected performance for a given health-care activity. They can be developed from guidelines but can also be developed through a community- or evidence-informed process. The latter approach can be taken when there are no available guidelines from which the standards can be derived. In this instance, a group of relevant stakeholders (experts, consumers, providers) can develop standards that reflect the available evidence and local constraints. An example of a standard of care based on WHO guidelines would be “All patients living with HIV who are WHO clinical stage IV should be started on ART.” An example of an evidence- or community-informed standard would be “All patients receiving ART should receive nutritional support if malnutrition or food insecurity is identified.”

Performance Measurement
The first step to improving quality is understanding how care is currently being provided. In deciding what to measure, it is helpful to think about quality in three categories: structure, process, and outcomes. At a clinic level, structure, process and selected outcomes are the easiest to measure, while longer-term or less common outcomes are more often the focus of longer-term evaluation and oversight (such as at the district or national level). Structure focuses on the quality of the inputs into the program (e.g., resources, staff, physical infrastructure), while process is concerned with how the planned activities are implemented (e.g., number served, percent on appropriate medication, adherence to care). Outcomes measurement focuses on the effect of the services (e.g., improved CD4 counts for patients on ART, decreased loss to follow-up) and may also offer potential targets for QI at the clinic level. To measure quality, there must also be agreement about how care should be delivered. These quality standards are broadly defined by national guidelines, and more specifically through standards of care.

Next Steps in Measuring Quality
Measuring quality requires three critical steps: (1) determining what will be measured, (2) collecting performance data, and (3) analyzing the data to identify potential areas for improvement or replication. Performance measurement can focus on quantitative data (how many, how often) or qualitative data (how it is being done, how the programmatic/system is functioning, patient satisfaction).
Routinely Measuring and Improving the Quality of HIV Care for Adults and Children: Lessons from Project HEART

The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) Project HEART, funded by the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), has been working with in-country partners (South Africa, Côte d’Ivoire, Zambia, Mozambique, and Tanzania) and John Snow Inc. to develop and implement an approach to routinely measure and improve the quality of HIV care for adults and children. This experience has highlighted the need to initially focus on measuring important areas of care, such as opportunistic infection (OI) screening and prophylaxis, HIV diagnosis in children, and management of antiretroviral therapy (ART). As the work progressed, the need to assist sites in understanding quality management was also identified, and so efforts are transitioning to focus on building internal capacity at the Project HEART country-office level initially, and ultimately at each site. Critical components of this approach have included close engagement with sites and feedback of performance measurement results, flexibility to adapt what is measured over time, and initial use of external quality experts to jump-start the efforts through performance measurement and support for improvement. Over time, these experts are transitioning into a capacity-building role by providing training and preceptorships.

The current work, which builds on the HIVQUAL approach as well as other models of measurement and improvement, focuses on building a programmatic structure and systems to support performance measurement and QI activities at the site and program level. The goal of these efforts initially is to support sites in QI efforts while building capacity so that the sites can ultimately take ownership of these efforts. Experts provide the initial on-the-ground performance measurement and QI, while at the same time infrastructure is built up through training and support to facilitate the transition to a program and site-led effort. This approach has been successfully used by a number of groups and represents a sustainable approach to measuring and improving quality during the rapid scale-up of ART. This approach also allows sites to mature at different rates until they are able to provide internal leadership and capacity for quality-management activities.

The development of indicators to identify the specific performance areas and the specific measures that define how and what will be measured is the next step in measuring quality. A quality-of-care indicator can be defined as “an aspect of patient care that is measured to evaluate the extent to which a facility provides or achieves a particular element of care.” A measure is then developed to gauge explicitly how well a clinic is providing the chosen element of care or achieving the desired outcome. The measure should ideally specify the population eligible for the element of care, what care should be delivered, and how it will be measured. The following example shows the progression in development from a guideline to an indicator, and then from an indicator to a measure:
• **Guideline:** Cotrimoxazole should be used in patients at WHO clinical stage IV or with a CD4 count less than 200 cells/mm$^3$.

• **Indicator:** Cotrimoxazole use among patients at WHO clinical stage IV or CD4 count less than 200 cells/mm$^3$.

• **Measure:** Proportion of patients at WHO clinical stage IV or CD4 count less than 200 cells/mm$^3$ who are currently being prescribed cotrimoxazole. (An alternative measure would be proportion of patients at WHO clinical stage IV or CD4 count less than 200 cells/mm$^3$ for whom cotrimoxazole is being dispensed.)

**Choosing What to Measure**

It is tempting to try to measure all aspects of care when initiating performance measurement. However, this is an overwhelming task and can result in a system that focuses only on measurement rather than on improvement. Therefore, it is important to identify specific areas for measurement and, within these areas, a limited number of indicators to measure. These decisions should be based on discussions with relevant stakeholders and should incorporate existing knowledge about how the program is currently functioning (i.e., areas of concern may be chosen as a priority). Other elements that should be considered include feasibility of measuring, relevance to the program, and whether the program can improve the area being measured. For example, although staffing may be viewed as a major issue for quality and be measurable, an individual site may not be able to change patterns of staffing directly, and so improvement by the site is not achievable. Another area, such as decreasing missed visits, would be an example where performance can be measured (number of missed visits), relevance is high, and improvements can be made (e.g., outreach efforts, linking with nongovernmental organizations, improving systems to identify missed visits).

**Coordinating Work to Measure and Improve Quality with Other Activities and Key Partners**

When developing an approach to measure quality, efforts should be coordinated with other ongoing monitoring and reporting activities that reflect the needs and requirements of national and local governmental agencies as well as other key partners. Many programs, such as TB control and treatment and maternal and child health, may have existing requirements that include substantial data recording and collection. Coordinating efforts with other programs will also help develop a standardized framework for measuring and documentation that will ultimately maximize efficiency, help to avoid duplication, and improve effectiveness by facilitating the sharing of data for improvement and planning. Integration of these data collection efforts with quality measurement will maximize the use of existing resources and increase integration and coordination between HIV and other related programs.

**Optimal Approach to Data Collection**

The development of a data collection plan will help organize the process of selecting and defining areas to be measured. This plan should include the available data, how they will be collected, how they will be analyzed, and who will analyze them. In making these decisions, the program teams should be aware of the time requirements and degree of difficulty associated with the collection of each measure, as well as the number of patients to be sampled and the data elements needed.

Data sources may include clinic forms, existing databases, and M&E data. Other valuable sources include existing clinical logs or registers, and any other data collection or evaluation that is being done at the site. Data collection should be undertaken using standardized tools and clearly defined criteria to ensure uniform collection. Borrowing
existing tools that have been successfully used and, if possible, validated in similar settings will save time and help ensure relevancy. However, simple is usually best; the skills of data capturers and site resources will often determine which procedures are used.

Data used for measurement of quality and changes in performance need to be as accurate as possible, but not so cumbersome to collect that repeated measurement is not feasible. To ensure the reliability of data, program teams should make certain that indicators are clearly defined, that measurement is standardized, and that staff involved in data collection and entry have adequate training. Ideally, data collection should be a routine activity integrated into daily tasks. For example, needed data elements can be captured in clinical records, which can then be periodically extracted as needed for performance measurement. In settings where electronic databases have been introduced, quality measures should be integrated into these information systems and queries established to produce the desired performance data. Data should be collected regularly over time, so trends in the indicators can be monitored. As various approaches to data collection are developed, it is also important to keep the goals of this activity in mind—namely, to identify the presence and causes of systemic problems that can result in poorer quality, and to guide management decisions.

Ensuring Feedback of the Data and Results
One important component of measuring quality is ensuring that data are fed back to the providers (and to the sites if data are collected by an entity responsible for oversight of multiple sites). This work will increase buy-in and the value of the data to those responsible for collection and providing services. Data should be displayed in a manner that is tailored to meet the needs and comfort level of the intended audience. Staff may have varied experience with data interpretation and may benefit from simple graphs and charts. These visual presentations allow them to easily see where change is needed and what changes have been observed, and will increase their engagement in efforts to measure and improve quality.

Quality Improvement
Quality work does not stop with measurement and feedback. Once areas for improvement are identified, appropriate interventions must be developed and implemented. To know whether quality has been improved, performance must be measured and remeasured as changes are made to address the gaps in performance. Important steps to improving quality will include the following:

- Identifying where to start (identifying problems and choosing which to address)
- Choosing the most appropriate approaches to improving quality
- Evaluating the impact of improvements
- Assessing sustainability and the extension of improvements (sharing lessons learned)

QI work is best done by a team that can focus on the areas where improvement is needed, develop potential solutions, and test them to see if change occurs. The team ideally includes individuals who are involved in the area of focus (e.g., providers, other staff) as well as other individuals who bring in relevant skills or knowledge, such as quality-management staff from district or central levels, consumers, and others.

There are a number of approaches to determine where the potential gaps in care inputs or processes may be occurring. One approach used to develop an in-depth understanding of the steps needed to achieve a desired standard of care at the clinic level is the flowchart (Figure 2). The flowchart outlines the processes that occur within a specific clinic to create a detailed sequence of events leading up to
the provision or receipt of an identified aspect of care. Engaging the care team as much as possible in developing the flowchart helps staff visualize a process so that it is easier to understand and improve, while simultaneously identifying potential sources of problems and solutions. Examples of processes conducive to this approach include CD4 testing, adherence counseling, and the tracking of patients who are lost to follow-up.

A slightly more complex approach to identifying potential causes of quality gaps and areas for improvement is the fishbone diagram (Figure 3). Fishbone, or cause-and-effect, diagrams are used to map variables that may influence whether or not a process or outcome is achieved. The fishbone skeleton is used to identify the key categories (e.g., staff, procedures, resources, and environment) contributing to a given process. The team then identifies gaps in the process and assigns causes of and solutions for these gaps to each category. From there, the team members identify areas they think will most likely improve the care process. These areas then become the target of improvement activities.

Once a specific component of the system has been targeted for improvement, the team will develop an intervention to address the area of concern. This work should be performed as rapidly as possible and tested on a small scale to determine whether it is feasible and effective (rapid cycles of change). One widely utilized method for testing QI interventions is called the Plan-Do-Study-Act (PDSA) cycle. In this method, the team plans the improvement (Plan); implements it on a small
scale (Do); evaluates it to see if the desired change occurred (Study); and then acts to modify, expand, or choose a different step in the system depending on the results (Act). The process is then repeated until an effective change has been identified and integrated into the care system. Other variations on this approach have also been used in working to improve quality in clinical care. For all these activities, training in how to use them and support for their application is important so that the approaches implemented are effective and relevant.

**EVALUATING THE QUALITY-MANAGEMENT PROGRAM**

An important activity that is sometimes overlooked is the assessment of how well the quality-management program is working. The program team should periodically assess whether the planned activities for measuring quality are being carried out and whether the expected improvements in quality are being seen. This assessment is important to ensure that the efforts and resources put into the program are achieving the desired outcomes. The process should be treated as an opportunity for self-assessment rather than a required formal evaluation. Questions asked should include: “Is performance being measured?” “Are the results being used to improve care?” and “Is quality being improved?” This self-assessment helps the members of the program team learn and respond to past performance in order to strengthen their work and sustain QI efforts.

**Engaging Consumers in Quality Management**

Ultimately it is the patients who will decide whether the services they receive are responsive to their needs and whether they are able and willing to follow through with care that is needed to achieve the desired outcomes. For example, as patients begin to feel better following initiation of ART, their motivation to keep appointments or take medication may wane, thus compromising the likelihood of achieving the promised benefits of care and treatment. Although it is a patient’s right to make decisions about his or her health, the interaction between patient and provider may often influence the likelihood that a patient adheres to the recommended care and treatment. These choices are influenced
by the consumer’s perception of whether or not his or her concerns and needs are being addressed and goals (e.g., improved quality of life, longer life) are being met. These perceptions on the part of the consumer are sometimes described as the experiential dimension of health care. While the technical dimension of health care is the traditional focus of quality measurement, the experiential dimension plays an equally important role in determining whether quality care is received.28

Consumers may identify needs or concerns that are not recognized or prioritized by providers. Soliciting consumer input about the system of care is important and can be achieved through several different methods.1,29 The simplest method involves the use of exit interviews that ask patients whether their needs have been addressed, what is their level of satisfaction with the care received, and whether they can explain what they were advised on during the visit. Other methods include group interviews and written surveys, depending on the literacy level of the population. The information obtained from these interviews or surveys can be included in the quality-management program to improve health-worker and/or system performance. As the relationship between the care providers and patient community grows over time, patients may become an integral part of the quality program and participate in processes designed to monitor and improve care.

CONCLUSION

While the demands of rapidly expanding HIV care programs can be overwhelming, focusing on quality is an important and achievable step in providing effective care. The approaches described in this chapter can easily be adapted for a range of clinical settings to engage staff in quality-management activities. Improving quality of care in the context of HIV care in resource-limited settings is achievable and will result in benefits to patients, staff, and programs in the short term and for the future.
REFERENCE LIST


Achieving and Maintaining Quality in HIV Care: Lessons Learned from Zambia

Mary Morris and Nicole M. Quiterio

W ith an increasing number of patients seeking services and treatment for HIV, the need to achieve and maintain quality of care presents major challenges to HIV providers. Between 2004 and 2007, the Zambian Ministry of Health (MOH) initiated a rapid scale-up of delivery of antiretroviral therapy (ART) to HIV-positive people who were eligible for treatment based on World Health Organization (WHO) clinical staging and CD4 cell counts. During this time 105,000 patients were enrolled in HIV care, and 54,000 people were commenced on ART. An external audit performed 15 months after the program began showed inadequate health-worker practices (e.g., failing to start eligible patients on *Pneumocystis carinii* (jiroveci) pneumonia [PCP] prophylaxis, and not ordering the appropriate laboratory investigations according to national guidelines). These errors needed to be corrected and health-worker performance improved in order to achieve improved quality of care in the face of rapid scale-up.

Quality of care is dependent upon multiple factors, including health-worker performance; the attributes of the work environment; client behavior and/or receptiveness; and the provision of structure, space, and the necessary tools, equipment, and supplies to enable health workers to do their jobs. To improve health-worker performance, the Centre for Infectious Disease Research in Zambia (CIDRZ) devised a quality assurance program based on these factors, which utilized multidimensional interventions including infrastructure development, training, mentoring, and continuous quality improvement. This chapter reports our experiences implementing this program in Lusaka, Zambia, and serves as a model for low- and middle-income countries seeking to provide patients with a high quality of care despite human resource shortages and increasing numbers of patients seeking care.

**BACKGROUND**

Project HEART is an HIV care and treatment program funded by the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) and managed by the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF). Since 2001, EGPAF has been working with its partner organization, CIDRZ, which has...
established 45 HIV care and treatment sites in four provinces. CIDRZ, with support from EGPAF, provides comprehensive, decentralized HIV treatment services in Zambia through engagement in the following activities: providing ART, improving and renovating infrastructure, providing essential laboratory equipment for diagnosis and monitoring, establishing referral and follow-up systems, training health-care providers, and strengthening health management information systems (HMIS) and supply logistics.

Zambia faces enormous challenges to enroll and maintain the 330,000 people who require treatment for HIV in longitudinal care. The greatest challenges to providing quality care for such large numbers include a shortage of human resources, infrastructure and supply deficits, and inexperience with chronic care. According to the MOH, Zambia has 646 of the recommended 2,300 doctors, and 6,096 of the recommended 16,732 nurses—a deficit of 1,654 and 10,636, respectively. The General Nursing Council recommends a nurse-to-patient ratio of 1:6; however, in many hospitals and clinics, the current nurse-to-patient ratio is 1:100, which results in increased workloads and compromised quality of care. The demand for an increased number of trained professionals is unmet due to a lack of training institutes and lengthy training programs with few graduates. The current rate of graduation from nursing schools is between 400 and 600 nurses per year. At this rate, assuming no attrition, it is estimated that recommended clinician-to-patient ratios and nurse-to-patient ratios will not be reached until 2045. Attrition is defined as health-care workers leaving government service for various reasons, such as to work in the private sector or in other countries, to change careers, or due to death from HIV itself; from 2003 to 2004, mortality accounted for 38% of staff attrition in Zambia.

THEORETICAL FRAMEWORK FOR PERFORMANCE IMPROVEMENT

In the late 1960s, Avedis Donabedian, a renowned professor of public health, first introduced the concept of assessing quality of care through evaluating structure, process, and patient outcomes. Over the next few decades, this approach became a dominant and accepted paradigm for the evaluation of quality of care. Donabedian asserted that structure, as in the facilities and staffing of a site, should be adequate in order to provide a high quality of care. Process assumes that if proper procedures are followed, improvements in health care will result. Outcomes assume that patients’ current and future health is attributed to the health care provided, and that staff benefit as a consequence of providing that care. His model provides a useful theoretical framework for the accreditation of health facilities and the development of performance appraisal methods. Yet it does not fully address the particular challenges faced by health-care workers in resource-limited settings, who may not benefit as a consequence of providing care and who may not be motivated to improve their performance. Good health-worker performance is essential for effective delivery of health services. Poor health-worker performance contributes to reduced use of health facilities and harmful health practices. If health-care performance is inadequate, adherence to guidelines is poor and interventions are not implemented to prevent sickness and death.

A number of cognitive and behavioral theories are used as a basis for understanding and changing health-worker practices. For instance, cognitive theory assumes that undesirable behavior is caused by lack of information. Therefore, we disseminate information on evidence-based guidelines through formal trainings and by circulating written guidelines. However, we also recognize that training and the dissemination of written guidelines alone will not change behavior. By disseminating written
guidelines and standard operating procedures, and conducting trainings and clinical update meetings, we clearly communicate our expectations to health-care workers.

Improving health-worker performance requires adapting to an individual’s stage of change. Depending on their environment, personal experiences, and readiness to change, people progress through five distinct stages of change: precontemplation, contemplation, preparation, action, and maintenance.7 An individual may cycle through these stages several times before maintaining change.7 The behavioral change model advocates tailoring interventions to the recipient’s specific stage of readiness.7 In our setting, expectations and intervention designs differ based on how long sites have been operating; training and support are tailored to the level of staff experience and competence at a given site. Assuming that external stimuli can influence behavior, we use interventions such as placing reminders in patient files for health workers to see (e.g., “repeat CD4 cell count to assess treatment failure”). We model desired performance while providing clinical mentoring, and regularly measure performance and provide feedback on performance to each site.2 Good performance is recognized by the provision of incentives and rewards.

Diffusion-of-innovation theory explains how social groups influence change among peers. This theory asserts that most individuals are initially reluctant to adopt new ideas. Their acceptance of change requires that they pass through several phases, including awareness, interest, evaluation, and trial.7 Health-care workers’ responses to innovation can be grouped according to the speed at which the individuals adopt innovation. Some individuals are innovators, while others are ambivalent or resist innovation, particularly if they do not see any personal benefit from doing so, have a general lack of motivation, or are burned out.7 In our twinning program, we use experienced leaders of successful sites (the “innovators”) to influence staff at poorly performing health facilities to change their practices and improve their standards of care.

QUALITY ASSURANCE TOOLS

Our quality assurance program employs a systematic approach to optimize health-worker performance through training, mentoring, and continuous quality improvement. Before implementing new sites, an assessment of structure and space is conducted so that all renovations are completed before services are commenced. Site-specific preparation first involves providing all the necessary medical equipment and supplies, and training medical staff. Information on drug toxicities, treatment failure, national guidelines, and treatment algorithms are disseminated to all clinics. Data forms guide health workers through history taking, review of symptoms, physical examinations, WHO staging, assessment, care planning, ordering of investigations, and follow-up. Detailed standard operating procedures and care algorithms guide clinicians through the management of complex conditions and drug toxicities. Thereafter, continuous training and mentoring are provided to all sites, with a designated nurse spending two days per week at the site providing ongoing mentoring and supportive supervision.

PERFORMANCE MEASUREMENT AND FEEDBACK

The objective of the quality improvement program is to measure whether sites are providing adequate and appropriate care and treatment services in accordance with national guidelines.4 To assess quality of care, indicators are selected that are relevant, measurable, and routinely available in the patient files or database. Initially developed for CIDRZ-supported sites, an electronic patient tracking
From the ground up: Laying a strong foundation

Some of the indicators that are routinely measured include the following:

- Percentage of patients who have received a baseline CD4 count
- Percentage of patients who have received a repeat CD4 count
- Percentage of patients who have received baseline liver and kidney function tests
- Percentage of patients on zidovudine who have had their hemoglobin measured
- Percentage of patients who have appropriately started PCP prophylaxis

Quality assurance reports (Table 1) provide information on the performance of each clinic, making it possible to monitor trends in performance based on certain quality indicators. Feedback is then provided to the clinics based on this information. Meetings are held to discuss each clinic’s strengths and weaknesses and to formulate interventions to improve performance. Since performance is measured every three months, sites can evaluate their performance—in individual areas and overall—compared with other clinics over time.

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Table 1. Sample Quarterly Performance Report

The system (SmartCare) has now been adopted as the national patient tracking system for HIV care and treatment programs throughout Zambia. Relevant demographic, laboratory, and clinical information on all patients enrolled in care and treatment programs, including those on ART, is entered into the system. The system is used to track patients, assess patient outcomes, and provide stakeholders with program information.
After 37 months of program implementation, in June 2007, Project HEART Zambia was operational at 39 sites in four provinces (Lusaka, Southern, Eastern, and Western provinces). More than 105,000 patients had been enrolled and 54,000 patients were on ART. Quarterly performance reports generated for the same 14 clinics in Lusaka during this period showed improvements in the majority of indicators: 85% of patients had received a baseline CD4 count, 88% of patients had received a repeat CD4 count, 89% of patients had a baseline hemoglobin measurement on file, 85% of patients had received baseline liver and kidney function tests, 67% of patients were appropriately on PCP prophylaxis, and 83% of patients had been seen by a clinician in the last three months (see Figure 1, next page).

Training and Clinical MentorIng

Medical officers, nurses, and clinical officers attend basic trainings in adult and pediatric HIV care and treatment in addition to receiving training on behavior change and counseling. Thereafter, training is provided on an as-needed basis, with clinical updates provided annually to selected staff.

Clinical mentoring is conducted at various levels within the program. The role of the clinical mentor is to provide on-site, continuous, supportive mentoring to inexperienced clinicians and nurses to improve the quality of patient care. Experienced HIV clinicians from the United States and Canada provide clinical updates and train Zambian doctors, clinical officers, and experienced nurses to become clinical mentors. Clinical mentors are trained in the latest guidelines for ART and clinical mentorship. Mentors also attend weekly clinical update meetings, participate in online medical education sessions, and attend periodic national meetings to stay current on the evolving practice of...
Recently, each clinic has established a quality committee comprised of clinic staff and community members who actively address quality issues and concerns. At some district clinics, the quality committee has placed suggestion boxes in the waiting area to obtain anonymous feedback from clients on ways to improve services. Patient suggestions to improve care are discussed at monthly quality committee meetings, and changes are implemented when possible. Every morning, group education sessions led by peer educators (community members who are HIV-positive and trained in HIV counseling) address adherence issues at each clinic; topics covered range from how to manage missed clinic visits or skipped doses to family issues relating to HIV. All patients are encouraged to attend.

**BUILDING SUSTAINABLE SYSTEMS**

Currently, each clinic has established a quality committee comprised of clinic staff and community members who actively address quality issues and concerns. At some district clinics, the quality committee has placed suggestion boxes in the waiting area to obtain anonymous feedback from clients on ways to improve services. Patient suggestions to improve care are discussed at monthly quality committee meetings, and changes are implemented when possible. Every morning, group education sessions led by peer educators (community members who are HIV-positive and trained in HIV counseling) address adherence issues at each clinic; topics covered range from how to manage missed clinic visits or skipped doses to family issues relating to HIV. All patients are encouraged to attend.

**Figure 1. Clinical care performance for 14 Lusaka district clinics in operation before June 2005**

Note: Graphs represent the percentage of patients on ART who met each specific quality-of-clinical-care indicator. ALT = alanine aminotransferase, HB = hemoglobin
Exchange visits are conducted for nurses and clinicians between city and provincial sites to encourage positive peer social influence and build sustainability, ownership, and interest in continuous quality improvement. The sites that are performing well provide supportive supervision and mentoring to less experienced sites. Since the implementation of exchange visits, the quality of care in provincial and Lusaka sites has improved significantly. The provincial and district health offices are also responsible for assessing quality of care. Meetings are held at the designated clinics to review quality performance reports, which later are presented to the MOH. By providing feedback to clinics, the provincial and district health offices enhance collaboration, communication, and ownership of the quality improvement program.

**STRATEGIES TO IMPROVE HEALTH-WORKER PERFORMANCE: CHALLENGES AND INTERVENTIONS**

**Failure to Order Appropriate Laboratory Investigations and Assess Patients on Severity of Problems**

At program initiation, many clinicians were not ordering the appropriate laboratory investigations (e.g., baseline hemoglobin for patients starting zidovudine, baseline liver function tests, or repeat CD4 cell counts per national guidelines) or were failing to switch antiretroviral (ARV) drugs due to toxicities or treatment failure. During our inquiries with the clinic staff, it became evident that nurses were not authorized to request or interpret laboratory investigations, failed to prioritize patients according to the severity of their problems, and lacked knowledge about drug toxicities and treatment failure. Once these shortcomings were identified, a triage training to address these factors was developed, which focuses on patient assessment and the management of urgent problems, the recognition of toxicities and severe illness, and the interpretation of laboratory investigations. This training has enabled nurses to triage patients appropriately and to ensure that patients receive appropriate laboratory investigations and are reviewed in a timely manner by physicians.

After triage training, nurses undergo advanced training on care of stable HIV patients based on the WHO Integrated Management of Adult and Adolescent Illness (IMAI). This five-day training focuses on several components of clinical evaluation, including HIV disease staging, opportunistic infection prophylaxis and treatment, ART eligibility, and ARV drug toxicity and management. A key focus of the training is early recognition of signs and symptoms requiring referral to a tertiary-level facility.

**Staff Shortages, Retention, and Motivation**

Recent statistics indicate that Zambia has an estimated seven doctors and 113 nurses per 100,000 people, which is less than one-third of the target number for doctors and less than one-half of the required nurses. To address these shortages, and to motivate and retain health-care workers, we provide salary support, training, and continuing education opportunities. In addition, health workers are provided with access to free, confidential health care, either on-site or at a designated clinic. Nevertheless, staff shortages, retention, and lack of motivation remain the greatest challenges to achieving and maintaining good quality of care. While the number of health-care workers remains deficient, the number of patients being enrolled and commencing ART continues to grow. To respond to the ever-increasing patient demand, we utilize task shifting, a process of delegating tasks from more specialized to less specialized health workers. This approach, which has been proposed by WHO and others as a possible short-term solution...
to the dire human resource shortages in the health-care sector, has been effective in similar settings in Africa. However, the ability to expand the role of lay and professional health-care workers is limited. As individuals take on more responsibilities, they need to receive appropriate recognition and incentives. While we offer overtime salary support, we realize that this is a short-term solution that does not address chronic staffing deficiencies.

**Deficiencies in Provincial Laboratory Capacity**

Despite multiple trainings in laboratory capacity building, the ability to maintain a consistent supply of reagents and ensure the proper functioning of laboratory equipment remains elusive. A combination of poor logistics and supply forecasting, coupled with lack of experience in maintaining equipment and staff de-motivation, have contributed to the laboratory capacity deficiencies. To address this problem, we are enlisting teams that work closely with provincial sites to build capacity for equipment maintenance. We are also considering novel ideas for performance-based financing, in which staff are paid for each test completed.

**Limited Site Capacity**

A number of sites are already operating at maximum capacity, which creates a significant strain on staff working in a limited space. Filing systems have become disorganized, consulting rooms are crowded, waiting lines are long, and staff are tired. To address these challenges, we have constructed temporary walls and filing shelves to increase the number of consulting rooms and provide additional filing space. In some clinics, we have instituted a system of preparing files the previous day for the next day’s appointments. We have lengthened the time between follow-up appointments for stable patients who are now managed by nurses. We are exploring the possibility of instituting mobile clinics, where trained clinicians and other staff from district health clinics regularly visit health posts to provide clinical care and mentoring to health post staff. This will enable staff at health posts to manage stable patients, thereby off-loading significant numbers of patients from clinics that have exceeded their capacity. This approach has been tried in a number of settings, with reported success.

**KEY POINTS SUMMARY**

- The quality of health care depends on multiple factors, including patient and health-worker behavior, as well as workplace and environmental factors.
- In order to improve the quality of care, we have implemented a number of multifaceted interventions that addressed a variety of shortcomings.
- Quality of care is monitored at regular intervals, deficiencies are identified, feedback is provided to each site, and appropriate interventions are developed to improve performance; then the cycle is repeated.
- Continuous training, mentoring, and communication are essential for high-quality performance.
- Written guidelines and job aids are needed to support both experienced and inexperienced health-care workers.
- Improving health-worker performance is dependent not only on education and clinical mentoring, but also on regular performance measurement and feedback; emphasis should be placed on understanding and addressing conditions that support staff motivation and retention.
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HUMAN RIGHTS AND HIV CARE
Universal Access: Are National Strategic Plans Sensitive to Human Rights?
Daniel Tarantola and Sofia Gruskin

Twenty-Five Years and 23 Million deaths after the emergence of HIV/AIDS, the attributes of successful national responses are known and evidence supporting the proliferation of effective interventions is abundantly available. Yet no single analytical framework—whether grounded in economics, social sciences, ethics, or human rights—can determine, to everyone’s satisfaction, who should benefit from HIV-related services and in what order of priority. It is also impossible to stipulate what level of services should be provided to each affected population and which segments of the population should benefit more quickly from the best available care. The application of a human rights framework does, however, ensure that policies and programs are as effective as possible and that the related processes, as well as their planned outcomes, are to the greatest extent possible based on the principles of justice, dignity, and fairness.

Countries that failed in their early HIV/AIDS responses, including China, Russia, and South Africa, led efforts that were characterized by inequality, persisting discrimination, denial of access, and lack of participation of affected communities. These failures, in turn, perpetuated the state of disempowerment and risk of acquiring HIV infection among vulnerable communities and individuals. Conversely, countries that achieved great strides in their initial HIV/AIDS responses, including Australia, Brazil, the Netherlands, Switzerland, Thailand, and Uganda, did so by applying human rights principles, such as participation, nondiscrimination, and access to information, as well as by establishing policies and programs for the provision of essential services and lifesaving technologies.

Yet, in some of these countries, not all populations have benefited equally from the application of these principles. In Thailand, for example, injecting drug users continue to be regularly constrained in their ability to access essential HIV-related services.

The Role of Human Rights and Their Emergence in the HIV Discourse

Human rights, as used in this chapter, comprise the legally binding commitments of governments under international human rights law. Every country in the world is party to at least one human rights treaty, and all have made rights-related commitments in relation to HIV, such as those made during various recent United Nations (UN) General Assembly sessions (e.g., the 2000 Millennium
Respect for human rights is critical to preventing the spread of HIV and reducing AIDS-related stigma and discrimination. Human rights violations against people living with HIV are often in the form of
• restricted or limited access to medical care and health services;
• barriers to employment;
• mandatory HIV testing;
• restrictions on freedom of movement;
• issues raised by practices such as name reporting, partner notification, and confidentiality; and
• deportation of HIV-positive foreigners.

In order for human rights to be respected and enforced throughout the world, states must incorporate them into domestic legislation. States commit themselves to international human rights obligations when they ratify human rights conventions. They additionally recognize human rights principles when they endorse international declarations, such as the Declaration of Commitment on HIV/AIDS, which was endorsed by 189 countries in 2001.

Human Rights in the Context of HIV/AIDS: Government Responsibilities
In the field of international law, there are no binding legal instruments regarding HIV/AIDS. However, there is an established network of international treaties, as well as other recommendations, that have achieved the status of legally binding norms.

For every human right, governments have three responsibilities: states must respect, protect, and fulfill the right.

- **Respecting the right** means that states cannot violate the right directly.
- **Protecting the right** means that states must prevent violations of rights by nonstate actors and offer reparation if a right is violated.
- **Fulfilling the right** means that states must take all appropriate legislative, administrative, and judicial measures in order to realize the right.

At the United Nations General Assembly Special Session on HIV/AIDS, states committed themselves to “by 2003 enact, strengthen or enforce, as appropriate, legislation, regulations and other measures to eliminate all forms of discrimination against and to ensure the full enjoyment of all human rights and fundamental freedoms by people living with HIV/AIDS.”

Governments are therefore accountable for their actions toward people living with HIV because of their responsibility to uphold human rights.

**Important International Human Rights Instruments and Other Declarations**
- United Nations Charter, 1945
- Universal Declaration of Human Rights, 1948
- International Covenant on Civil and Political Rights, 1976
- International Covenant on Economic, Social and Cultural Rights, 1976
Development Goals, the 2001 Declaration of Commitment on HIV/AIDS, and the 2006 Political Declaration on Universal Access).10-12

The first global strategy on HIV/AIDS, launched by the World Health Organization (WHO) in 1987, aimed to reduce the transmission of HIV, minimize its impact on individuals and communities, and foster international cooperation and solidarity. The strategy was primarily focused on risk reduction through access to information, education, and services, as well as through the creation of a supportive environment. Attention to human rights was largely grounded in the recognition that the HIV-related human rights violations occurring around the world were undermining the public-health impact of prevention initiatives. Examples of such abuses by governments or by people acting on their behalf included neglect or tolerance of violence within families and communities, mandatory testing and detainment of vulnerable populations, and denial of inheritance and property rights, as well as denial of access to food, housing, marriage, education, medical care, international travel, health insurance, and employment.3,13-16

Largely due to strong advocacy from members of civil society, as well as WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS), human rights gradually began to be included in the public discourse on HIV/AIDS; this led to human rights principles being incorporated into international as well as most national HIV/AIDS policies and plans.17 It is troubling to imagine what the HIV response would look like without attention to human rights, especially considering the tendency of governments to enact restrictive laws while condoning or turning a blind eye to human rights abuses.18 But as national responses to HIV were being formulated and put into action in the late 1980s, it was not clear how significant a commitment to human rights would actually be in terms of the practical implementation of HIV policies and programs. Even today, in countries where the government understands and acknowledges the science of HIV infection, discrimination against vulnerable populations, including men who have sex with men, sex workers, and injecting drug users, continues to be the norm. This discrimination, both explicit and in its more masked forms, has consequently deprived many vulnerable groups of lifesaving access to prevention, care, treatment, and other forms of support. Additionally, the heightened vulnerability of women to HIV, even when formally recognized, is often not addressed through targeted, effective responses. For instance, even though more women than men live with HIV worldwide, it took decades of activism before there

- Denver Principles, 1983
- Ottawa Charter for Health Promotion, 1986
- Convention on the Rights of the Child, 1989
- World Conference on Human Rights, 1993
- Paris Declaration, 1994
- International Conference on Population and Development and the Cairo Plan of Action, 1994
- Millennium Declaration, 2000
- Abuja Declaration, 2001
- Declaration of Commitment on HIV/AIDS, 2001
- International Convention on the Protection of the Rights of All Migrant Workers and Members of Their Families, 2003
was widespread support for research into effective methods that could be used by women to protect themselves from HIV infection.

We know now that anchoring HIV strategies in human rights principles requires more than making statements and signing declarations; responding to violations only after they have occurred also fails to constitute an effective response. The value of human rights to HIV efforts extends beyond their moral or legal significance. What human rights distinctively contribute is an array of principles, norms, standards, and instruments conducive to shaping policy and enhancing accountability. The application of a human rights framework can therefore help ensure that the broad spectrum of activities that constitute a national response, from the determination of priorities and strategies to the measuring of outcomes and effectiveness, are based on the promotion of justice, dignity, and fairness, and that a level of accountability is built into every step of the decision-making process.

The current global framework for confronting HIV is universal access—“the scaling up of HIV prevention, treatment, care and support with the aim of coming as close as possible to the goal of universal access to treatment by 2010 for all those who need it.” Universal access, in addition to being a laudable goal, represents a leap forward from the earlier WHO/UNAIDS “3 by 5” initiative in terms of its integration of prevention with treatment and care, as well as its focus on national-level targets.

Human rights concepts are touched upon in the core documents supporting universal access, with reference made to how the application of these concepts can help ensure acceptable and equitable implementation, generate trust between providers and clients, encourage ongoing engagement with health services, and stimulate accountability in relation to national benchmarks and targets.

The principles of universal access are also reflected in many of the national frameworks for HIV/AIDS policy and program design created by individual governments. In many countries, human rights have both shaped the expected outcomes of the national HIV/AIDS response and defined the processes by which these responses should be carried out and accounted for. Some have called this approach a rights-based approach to HIV, which is in essence a strategy that builds upon the principles of equality and equity, accountability, empowerment, participation, nondiscrimination, and attention to vulnerable groups. A rights-based approach supports the need to ensure universal access and is particularly important in settings where the vulnerability of certain populations to HIV infection and/or their lack of access to treatment arises from a lack of recognition of their human rights, as is often the case for women, minorities (racial, ethnic, and sexual), injecting drug users, and other marginalized individuals and communities.

A RIGHTS-BASED APPROACH TO HIV

The rights-based approach was initially conceptualized in the mid-1990s as a “human rights-based approach to development programming” by the UN Development Program, but the understanding of what a rights-based approach actually means in the context of HIV/AIDS efforts has varied across sectors, disciplines, and organizations. A rights-based approach to HIV calls for attention to processes as well as outcomes and requires integration of human rights norms and standards into policies and programs. This includes, for example, the participation of vulnerable and affected populations in decisions that concern them and the accountability of governments for their actions—and inactions—in preventing the spread of HIV and mitigating its impact on society. A rights-based approach to HIV requires states to set their own benchmarks and targets, to the maximum of their capacities and resources, as well as to fulfill their obligations of
accountability. By focusing attention on outcomes, a rights-based approach evaluates achievements against set program targets. When both processes and outcomes are examined through a rights-based lens, not only what has been achieved but also how these achievements have occurred is brought to light. For example, a rising uptake of HIV testing services could be due to an increase in high-quality voluntary counseling and testing (VCT) services or to the introduction of mandatory testing of certain population groups. Although the short-term outcome may appear the same, from a human rights perspective the processes used to achieve this outcome are entirely different. The approach using VCT is appropriate in both human rights and public-health terms, whereas the latter approach involving mandatory testing may, in the long term, be viewed as detrimental from both perspectives.

Anchoring strategies in human rights through the application of a rights-based approach strengthens programs by drawing attention to the legal and policy context in which they operate. A rights-based approach also allows for the incorporation of human rights principles, such as nondiscrimination, into the delivery of services and can secure the participation of affected communities in the design, implementation, monitoring, and evaluation of interventions. In addition, human rights approaches assist in holding governments and intergovernmental agencies, in particular those belonging to the UN system, publicly accountable for their actions and inactions in relation to HIV programming. Finally, assessing programs based on human rights standards, with a focus on the accessibility of essential prevention, care, and treatment services, calls attention to the availability, accessibility, acceptability, and quality of services and goods, as well as outcomes among different population groups (Box 1).

The various components of a rights-based approach and their underlying principles are drawn from the core content of the Right to the Highest Attainable Standard of Health enshrined in international human rights law. These rights place

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<th>Box 1. Definition of Terms</th>
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<td><strong>Human Rights / Rights.</strong> Human rights are legally guaranteed under international human rights law. They protect against actions that interfere with fundamental freedoms and human dignity, and support the agency of individuals and populations.</td>
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<td><strong>Stigma and Discrimination.</strong> HIV/AIDS-related stigma is the process of devaluing people because of their real or perceived HIV/AIDS status, or that of their family or community. HIV/AIDS-related discrimination refers to the legal, institutional, and procedural ways people are denied access to their rights because of their real or perceived HIV/AIDS status, or based on real or perceived membership within already stigmatized and vulnerable groups such as sex workers and injecting drug users.</td>
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<td><strong>Participation.</strong> Under human rights law, everyone is entitled to active, free, and meaningful participation and inclusion in, contribution to, and enjoyment of civil, economic, social, cultural, and political development. Ensuring the inclusion and full participation of all key stakeholders and affected communities, with particular attention to the greater involvement of people living with HIV, at every stage of HIV policymaking and programming is recognized as essential to an effective response.</td>
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<td><strong>Vulnerable/Marginalized Groups.</strong> Vulnerable and marginalized groups are broadly defined in the majority of human rights documents as comprising simply the most vulnerable or marginalized segments of the population. In HIV literature, increasingly, these groups are called most-at-risk populations. Variation exists, but in all cases these are understood to include injecting drug users, men who have sex with men, sex workers, and increasingly prison inmates, migrants / mobile populations, and women and young people. Questions exist about this more inclusive definition, which seems to leave out only adult men.</td>
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Box 1. Definition of Terms (continued)

The 3AQ: The right to health has been defined by the Committee on Economic, Social and Cultural Rights to include the availability, accessibility, acceptability, and quality of the goods and services provided. This is commonly known as the 3AQ, and the components are defined as follows:

**Availability:** This requires making available, in sufficient quantity, functioning health-care facilities, goods, and services, as well as programs to address HIV and AIDS. Although these facilities, goods, and services will vary by context, they should address the underlying determinants of health, such as safe and potable drinking water and adequate sanitation facilities; hospitals, clinics, and other health-related buildings; trained medical and professional personnel receiving domestically competitive salaries; and essential medicines, as defined by WHO.

**Accessibility:** The concept of accessibility encompasses four distinct components:
1. **Nondiscrimination:** Health facilities, goods, and services must be available to all, especially the most vulnerable and affected populations.
2. **Physical accessibility:** Health facilities, goods, and services must be physically accessible to all sections of the population, especially vulnerable or marginalized groups.
3. **Affordability:** Health facilities, goods, and services must be affordable for all. Payments must be based on the principle of equity, ensuring accessibility of needed services, whether privately or publicly provided.
4. **Access to information:** Accessibility also includes the right to seek, receive, and impart information and ideas concerning health issues, but this does not impair the right to have personal health data, including the results of HIV tests, treated with confidentiality.

**Acceptability:** Acceptability requires that all health facilities, goods, and services be respectful of medical ethics and culturally appropriate, that is, respectful of the culture of individuals, minorities, peoples, and communities; sensitive to gender and life-cycle requirements; and designed to respect confidentiality and improve the health status of those concerned.

**Quality:** Goods and services must be scientifically and medically appropriate and of good quality. Good-quality services should include, inter alia, skilled medical personnel, scientifically approved and unexpired drugs and hospital equipment, safe and potable water, and adequate sanitation.

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obligations on states regarding their own actions as well as those of nonstate actors within their jurisdiction (e.g., nongovernmental organizations, employers, the pharmaceutical industry, private health-care services, or insurance companies). The added value of a rights-based approach to HIV is to offer a method for analyzing, recognizing, and responding to the range of issues stemming from national HIV policies and programs at all stages of strategic development, operational planning, implementation, and monitoring (Figure 1).

As the resources available to support HIV/AIDS responses continue to increase, there is a widening gap between rhetorical statements that promote the integration of human rights in HIV/AIDS work and the actual operational and programmatic commitment to take action. The most troubling discrepancy may be between the commitments expressed by governments in such international forums as the World Health Assembly or the UN General Assembly and the actual practices that take place at the country level. A number of reasons can be posited for these discrepancies, including the reluctance of certain governments to acknowledge the existence and needs of communities whose behaviors are not in line with cultural mores, religious beliefs, or the law. Additionally, state authorities and sources of external support may feel that the urgency of responding to the HIV/AIDS crisis offsets concerns about human rights. In some instances, it may simply be the result of the oversights that can occur due to a lack of resources or inadequate training, or between the conceptualization stage of a rights-based approach at the policy level and the actual application of these concepts to programming. Also, a common practice among some organizations is to use human rights language to justify their work or make it more politically attractive, even though in practice nothing is being done differently. Finally, as ever larger amounts of money are available to those in the HIV/AIDS field, donors are increasingly tying future funding to program output indicators with short time frames, leaving little opportunity for attention to be paid to

Figure 1. A rights-based approach to HIV care and treatment policies, programs, and practice: core components of a rights-based approach and their relevance to stages of national strategic development and implementation
the broader structural issues raised by the application of a rights-based approach. It should be noted that an important step toward alleviating some of the obstacles mentioned here is to further expand and disseminate evidence in support of the assertion that universal access initiatives with a focus on human rights are more effective than initiatives that lack such a focus.

This chapter will review the extent to which national-level commitments on HIV prevention, care, and treatment regard human rights norms and standards as a step toward achieving more effective action. Our review examines, in a sample of countries, the congruence between national HIV strategic plans; relevant human rights norms and standards to which states subscribe when becoming party to international human rights treaties; and the stated rights-related commitments entrenched in the 2000 Millennium Development Goals (MDGs), the 2001 Declaration of Commitment on HIV/AIDS, and the 2006 UN General Assembly Resolution on Universal Access. Our review was not, however, able to examine the further gaps between the intent stated in national strategic plans (NSPs) and their actual implementation. This further analysis is highly desirable and strongly encouraged by the authors. Additional information that may shed light on such an effort could be drawn from the progress reports submitted by governments and civil society to UNAIDS in anticipation of the June 2008 UN General Assembly Special Session, during which reports on progress toward achieving the 2001 Declaration of Commitment targets were discussed.

A HUMAN RIGHTS ASSESSMENT OF HIV NATIONAL STRATEGIC PLANS

A sample of 14 countries was retained for this analysis. Countries were chosen to ensure inclusion of (1) all regions of the world; (2) different HIV prevalence/incidence rates within both generalized and concentrated epidemics; (3) nations that host the majority of people living with HIV (resulting in a deliberate over representation of African countries); (4) a mix of high-, medium-, and low-income countries; (5) a mix of those that benefit from the support of the Global Fund to Fight AIDS, Tuberculosis and Malaria; the President’s Emergency Plan for AIDS Relief (PEPFAR); and other major sources of HIV funding; and (6) importantly, those whose information was readily available from published documents and Web sites. The resulting convenience sample provides a general picture of how, under different circumstances, countries incorporate human

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aThe eight MDGs range from halving extreme poverty to halting the spread of HIV/AIDS (Goal 6) and providing universal primary education, all by the target date of 2015. See http://www.un.org/millenniumgoals/.

bThe 2001 Declaration of Commitment signed by the 189 UN members present at the UN General Assembly Special Session on HIV and AIDS details all the targets and the milestones the members should reach by 2010. Several of these are specifically concerned with human rights. See http://www.un.org/ga/aids/coverage/FinalDeclarationHIVAIDS.html.

cThe political declaration resulting from the 2006 UN General Assembly Special Session committed to set in 2006, through inclusive, transparent processes, ambitious national targets, including interim targets for 2008, in accordance with core indicators recommended by UNAIDS and affirmed the urgent need to scale up significantly toward the goal of universal access to comprehensive prevention programs, treatment, care, and support by 2010, as well as to set and maintain sound and rigorous monitoring and evaluation frameworks within national HIV/AIDS strategies. Human rights are specifically referred to in Articles 11, 29, and 31. See http://www.ua2010.org/en/UA2010/Universal-Access/Official-Papers/Political-Declaration.

dComprehensive reviews of progress toward achieving universal access were to be presented to the UN General Assembly in 2008 and 2011. One hundred thirty-two countries had submitted progress reports by January 31, 2008, the deadline for countries to submit 2008 universal access progress reports to UNAIDS. These reports are based on a set of 25 core indicators laid out in guidelines provided by UNAIDS.
Multiyear national HIV strategic planning documents were systematically examined for their inclusion of rights-based language and concepts. These documents were chosen because they provide the framework for annual or biannual operational plans.

The full list of documents reviewed is included at the end of this chapter. Drawing on the core human rights principles noted in the key components of a rights-based approach, the following keywords were searched: human rights, rights, stigma, discrimination, participation, and vulnerable groups. The following words related to goods and services in relation to the right to health were also searched: quality, availability, accessibility, access, and acceptability. The choice of keywords reflects the recognition that documents may not refer to human rights explicitly but may contain core contents of human rights norms and standards (e.g., nondiscrimination) or qualify “access” in ways that are consistent with these norms and standards. When any keyword was found in the documents reviewed, a special focus of attention was devoted to understanding the meaning of the word in context. All documents were also read for reference to core components of human rights that might have used words different from the keywords chosen for the search.

The majority of NSPs were originally published in languages other than English, and as such were searched using the English language translation, creating some uncertainty as to the correlation between the English keywords searched and their actual meaning in the original versions. When several documents of apparently equivalent significance were available for a single country, the most recent document was chosen.

Reviewers compiled their findings, and annotations were then entered in tabular form to indicate whether the keywords were present (Yes) or not (No) in the documents reviewed. Efforts to distinguish between rhetorical and operational use of these terms were made, but with limited success for reasons described later in this chapter. Table 1 summarizes the use of these terms in each NSP analyzed. The information that follows is a summary of key findings emerging from the document review, organized according to the key search terms.

**Universal Access**

Specific references to “universal access” in national plans vary according to their date of creation. The NSPs from Brazil and Nigeria predate the 2006 launch of the universal access initiative, but nonetheless use the term in relation to HIV treatment. Of those created after 2006, all countries except China use the term explicitly.

**Human Rights and Rights**

The majority of documents reviewed specifically refer to “human rights,” including those from countries that are party to most or all of the international human rights treaties (e.g., Botswana, Brazil, Germany, India, Kenya, Nigeria, Pakistan, Peru, and South Africa), as well as several that are not (e.g., Indonesia, Myanmar, and Papua New Guinea). China, even though it has ratified several international human rights treaties, avoids this language completely but gives different levels of attention to selected rights concepts, as noted in the keyword discussions that follow. A more detailed analysis of NSPs points to differences across countries in the ways core contents of human rights are referred to. For example, the plans of some countries present human rights as an overarching set of commitments with a direct reference to the right to treatment and care (e.g., Germany, India, Nigeria, Pakistan, and South Africa), while other countries’ plans refer to human rights without explicitly...
Table 1. Results of Search for Keywords and Principles in Documents Reviewed

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establishing access to treatment as a human right (e.g., Botswana, Indonesia, Papua New Guinea, and Peru).

**Stigma and Discrimination**

Even though the words *stigma* and *discrimination* represent two different concepts that are best addressed through different types of mechanisms, they are not clearly distinguished in the plans under analysis. Stigma reduction (through efforts toward attitudinal change in the population and among service providers) and nondiscrimination (which puts an obligation on states to take legal, policy, and programmatic measures to prevent the violation of human rights and create accountability and redress mechanisms) are not well clarified in these plans. Actions specified to reduce stigma and discrimination commonly consist only of the provision of information and education to the general public and, at times, to specific professional groups, such as the military. In several countries’ plans (e.g., Myanmar and Vietnam), there is also mention of the need to ensure confidentiality and privacy in order to prevent stigma and discrimination against people living with HIV. Less frequently, references are made concerning how the addressing of human rights abuses that result from stigma and discrimination will form part of national laws, policies, and programs.

**Participation**

While international guidance on HIV/AIDS programming calls for the participation of affected communities, participation remains an elusive concept in many NSPs. The need to include communities in consultation and governance is often stated, but little or no attention is generally paid to the specific participation of different affected communities, the mechanisms of their involvement, and/or the extent and quality of their participation. Mention of participation is entirely absent in a surprisingly high number of NSPs (e.g., those of China, India, Nigeria, Papua New Guinea, and South Africa). A list of those expected to meaningfully participate in consultation and governance and discussion of how principles of mutual accountability will be implemented are seldom specifically addressed. In several countries’ NSPs (e.g., Botswana, Brazil, Germany, Indonesia, Kenya, Myanmar, Pakistan, and Vietnam), participation by stakeholders, including people living with HIV, is noted generally even though groups are not explicitly named. Peru’s NSP is an exception; it names specific “vulnerable” groups, including adolescents, sex workers, people living with HIV, men who have sex with men, and drug users.
that should be included in relevant processes. Even when the need for participation of certain groups is noted, mention of specific affected communities, mechanisms for their involvement, and requirements (i.e., the extent and quality of their participation) is often absent.

**Attention to Vulnerable Groups**

The need to devote attention to “vulnerable groups” is commonly reflected in NSPs by way of a list of populations thought to be at greatest risk of not accessing prevention, care, and treatment. Little attention is paid, however, to the extent, comprehensiveness, and quality of services that would match the specific needs of these groups. Despite such shortcomings, the use of this language does represent a step forward in the global response. Of particular note is that all NSPs reviewed refer to sex workers (or sex work), injecting drug users, and men who have sex with men as populations in need of special attention. The mere acknowledgment that such populations exist in every country is a departure from the denial that characterized many countries during earlier stages of the pandemic.\(^{34,35}\) Additionally, some plans include women, young people, children, and uniformed personnel in the “vulnerable groups” category. Refugees, internally displaced persons, prisoners, or populations suffering from mental and other disabilities are mentioned less often despite their often unmet needs, high vulnerability to HIV infection, and susceptibility to human rights abuses.\(^{36,37}\) (Germany is an exception in that its NSP clearly recognizes the vulnerability of migrants and prisoners.)

Generally speaking, a clear effort has been made to consider vulnerable populations in NSPs according to a scale of risk and needs. Reviews of operating plans, however, suggest that even when certain populations are identified as being vulnerable, the priority afforded to them in actually accessing needed prevention, care, and treatment is not supported by a greater share of available resources. Typically, the main focus of national efforts was found to be the general population or young people, even in countries where the epidemic remains concentrated in highly vulnerable populations (e.g., China, India, Indonesia, and Vietnam). In the NSP for Papua New Guinea, “high-risk groups with high-risk vulnerability” are noted in the glossary but without reference to specific populations. This plan also includes a warning against identifying specific populations (as opposed to specific behaviors), as this may “exacerbate stigma and discrimination.” The plan does not, however, indicate how the recognition of such behaviors can help in targeting populations in need of specific services and support.

**Availability**

The availability of services and goods is explicitly noted in all NSPs, with the exception of Germany’s, where the brief mention of availability presumes that services are guaranteed to all through existing health systems. In general, NSPs refer to availability in a variety of ways, including limitations to availability, reasons for limited availability, inequity in availability, and the need to scale up availability through system strengthening (and, in some situations, through reductions in the price of procured commodities, such as antiretroviral drugs [ARVs]). Language often focuses on antiretroviral therapy (ART), with little attention paid to prevention or care more generally. Some countries (e.g., Botswana, Brazil, Kenya, Myanmar, Nigeria, Pakistan, Peru, South Africa, and Vietnam) are very explicit about policies and strategic approaches to ensure the availability of HIV-related structures, services, and goods. Others (e.g., China, Indonesia, and Papua New Guinea) refer only to low availability of goods and services in the context of barriers to ART, expressing a commitment to improve access but without proposing specific
strategic approaches. India proposes to address unequal availability through research and development. Overall, the NSPs reflect countries’ concerns about the availability of infrastructure, services, and goods but offer little indication of how the availability of these resources is to be ensured generally or for the particular benefit of marginalized populations. This lack of clarity may reflect the inability of national programs to guarantee availability, since they are dependent on external resources that are allocated only once a strategic plan is in place.

**Accessibility**

Access is the mainstay of all NSPs, but the use of the term varies across countries and even within most national plans. The variable use of this term raises the question of whether there is a connection between the rhetorical use of the word and its practical implications. Commonly, the term *access* is used specifically in the context of ART and, to a limited degree, in relation to other components of prevention, treatment, and care (e.g., preventive services such as sexually transmitted infection programs or commodities, such as condoms). That said, China, Myanmar, Papua New Guinea, and Vietnam all include mention of accessibility concerns in relation to VCT; China and Vietnam also refer to access to condoms.

General goals to enhance access for all people living with HIV are occasionally noted in the NSPs, but there are wide variations among the specific targets named. Reference is sometimes made to specific subpopulations, such as pregnant women, or subnational regions (e.g., certain districts in Botswana), but categories of most-at-risk populations are seldom mentioned. In fact, Vietnam and Peru are the only two countries in the sample to mention specific vulnerable subpopulations of concern. Vietnam’s NSP identifies the need to increase access for sex workers, drug users, street children, working young people, school dropouts, disabled young people, ethnic minority young people, and “other groups.” Peru’s NSP specifically mentions access by adolescents, sex workers, drug users, and men who have sex with men. Some countries (e.g., Botswana) also refer to specific access plans when describing the decentralized and progressive roll-out of treatment. The same limitation mentioned earlier, that NSPs are often formulated before resources to support them are secured, may apply here as well.

**Acceptability**

The concept of acceptability is not commonly incorporated into NSPs. In our review, the parameters used to define the concept of acceptability were extended to include NSPs that were sufficiently explicit about ways in which the most vulnerable populations should be served—including attention to their specific needs and environments, and to human rights abuses to which they might be exposed. Even with this extension of the concept, acceptability is mentioned by only a limited number of countries (e.g., Botswana, India, Pakistan, Papua New Guinea, and South Africa) and in very different ways. In some NSPs (e.g., those of India and Papua New Guinea), acceptability is equated with creating HIV interventions that are culturally acceptable; other countries use the word *acceptability* in relation to the more general goal of ensuring that STI and HIV interventions are accessible, affordable, and acceptable (e.g., Botswana and Pakistan). Finally, in the case of South Africa, the term *acceptability* is used in the context of standards for laboratory testing. In the few cases where acceptability is noted, there is no apparent consideration of policies or other measures within and outside the health sector that could help make services socially, culturally, or otherwise “acceptable.”
Quality

Quality is referred to in two distinct ways in the NSPs: with regard to ensuring quality of life and to ensuring quality of services and goods. While both types of quality are important elements of a sound response to HIV, in the majority of NSPs references to quality of life tend to overshadow the mention of quality as it relates to goods and services. Descriptions of standards of prevention, care, and treatment are usually missing from the NSPs; instead, general references are made to ARVs, ART, or prevention of mother-to-child transmission of HIV (PMTCT) as stated entitlements. Myanmar and Kenya mention the need to ensure quality of blood stores, but the NSPs lack specific information about how this is to be achieved. Germany (the only member country of the Organization for Economic Cooperation and Development [OECD] included in the analysis) is the only country to mention quality assurance systems and the need to ensure the quality of generic medicines. Even though NSPs are not necessarily the best place to include such standards, it is worth noting that few NSPs are explicit about the types and quality of treatment for which people living with HIV or people with STIs are eligible, or how quality standards will be set, monitored, and periodically reevaluated. The prevailing uncertainty regarding long-term financing of ART in low- and middle-income countries and, in some cases, the absence of national quality control and quality assurance schemes may be among the reasons for this lack of clarity.

Discussion

The congruence between commitments to achieving universal access and human rights was widely recognized by the countries selected for this review, regardless of their geopolitical characteristics and overall human rights records. This indicates that attention to human rights exists in HIV-related national strategy documents regardless of whether or not the country concerned is party to most international human rights treaties or enshrines human rights in its national legislation. This pattern likely reflects a general acceptance by countries of the relevance of human rights norms and standards to national HIV responses, as well as the fact that this language has become part of the global discourse regarding HIV.

Despite the widespread incorporation of human rights language in these documents, the rhetoric is seldom translated into strategic guidance on how, by whom, and for whom human rights principles will be respected, protected, and fulfilled. Comparisons between NSPs and operational plans generally reveal the gaps between rhetoric and intended practice; while statements on human rights are commonplace in strategic documents, their translation into operational terms or inclusion as part of monitoring frameworks is most often deficient or absent.

Overall, among the countries reviewed, it appears that national strategic documents contain many of the ingredients of a rights-based approach to HIV. Yet this approach is not incorporated into strategies in a systematic way. Additionally, a human rights analysis of the NSPs highlights the fact that certain approaches, such as legal reform, ensuring confidentiality, preventing violence against women, and caring for orphans and other vulnerable children, are still not receiving sufficient attention. This oversight is at odds with the UN political declaration and guidance extended by international institutions.12 Taken together, these findings can help point to ways in which common obstacles to achieving universal access can be overcome.

A further review is needed to determine whether related policy and legislation within these countries is consistent with the pronouncements made, or whether they serve as obstacles to an effective response (for instance, by requiring parental consent for access to HIV prevention...
suggests that, in most countries, access seems to be primarily associated with treatment and that more emphasis is needed on access to prevention as well as support. The growing imbalance resulting from the limited availability of national resources in low- and middle-income countries and the increasing availability of international HIV/AIDS funding makes national programs increasingly dependent on external support. This has potentially significant implications for the share of resources and commitments in NSPs that are allocated to treatment and care. Furthermore, while much attention is paid to the provision of treatment services, structural interventions that lie beyond the traditional domain of the health sector, such as strategies to reduce gender inequality, are mostly absent from NSPs. Additionally, constraints that may be linked to the acceptability of services were insufficiently dealt with in all the NSPs reviewed, in which the “one size fits all” approach to the provision of services commonly overlooked the specific needs and capacities of targeted populations. Taken together, these findings reveal a great deal about the ways in which national policies and programs succeed or fail in sufficiently addressing the obstacles (whether social, legal, or other) their populations may experience in accessing essential HIV-related services.

CONCLUSION
The findings of this review stress the need for governments to be more explicit about the congruence between their strategic approach to achieving HIV prevention, care, and treatment goals and the human rights norms and standards to which they are committed. Too often, the rhetoric of human rights included in national strategic documents is static, with little description of how, to what extent, and for whom human rights will be considered in the context of national care and treatment efforts. It is possible that if those countries reluctant to use human rights terminology in their NSPs were more informed and services or by criminalizing sex work or same-sex partnerships). Such a review could help ensure that the inclusion of human rights language in national documents reflects more than simply the fact that this language is part of the global discourse regarding HIV.

The reluctance on the part of many countries to explicitly name human rights concepts or approaches raises concerns about the accountability of state and nonstate actors in the context of HIV prevention, care, and treatment. This reluctance may denote uncertainty on the part of countries regarding their ability to comply with human rights standards. Some countries—regardless of their level of income—may fear that any explicit statements would be interpreted or misinterpreted as an obligation to give everyone immediate and full access to the needed services, including costly treatments.

Time-bound plans of operation are generally more explicit than NSPs about coverage and comprehensiveness of treatment in relation to set targets. One conclusion that can be drawn from this finding is that NSPs generally tend not to commit to particular levels of coverage until financial resources have been secured, perhaps reflecting the tendency of these plans to be donor-driven and/or dependent on national financing cycles that may be out of sync with the time periods covered by the NSPs. Another possible conclusion is that operational plans are crucial instruments in the planning process that are often developed wholly or partly separate from the NSP; once resources are in place, these documents may be the key to implementation and accountability. Yet operational plans are often developed late in the process, lack specifics, and are inconsistent with the general priorities set out in NSPs. This may be another result of the donor-driven, rather than need-driven, nature of many HIV responses in low- and middle-income countries.

Despite the fact that the call for universal access targets both prevention and treatment, this review
Human rights have been central to the HIV response ever since the emergence of the pandemic. While new technologies are needed to bring HIV under control, technologies alone are not sufficient. Vast resources are needed to sustain and further expand access to prevention, care, and treatment, but resource availability cannot be allowed to drive the response to HIV. Beyond theory and semantics, human rights bring *human* values into the equation while establishing a vision of greater justice, fairness, and dignity as fundamental to the success of the response to this global pandemic.

**ACKNOWLEDGMENTS**

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COUNTRY DOCUMENTS LIST

**Botswana**

**Brazil**
English Web site text from Brazil’s Ministry of Health (Ministerio da Saúde) STD/HIV page:  [http://www.aids.gov.br/data/Pages/LUMISB9C1F777ENIE.htm](http://www.aids.gov.br/data/Pages/LUMISB9C1F777ENIE.htm)

**China**

**Germany**

**India**

**Indonesia**

**Kenya**

**Myanmar**
Myanmar National Strategic Plan on HIV and AIDS 2006-2010

**Nigeria**

**Pakistan**

**Papua New Guinea**

**Peru**

**South Africa**
HIV and AIDS and STI Strategic Plan for South Africa, 2007-2011

**Vietnam**
REFERENCE LIST


THE HUMAN RIGHTS OF WOMEN ARE enshrined in the Universal Declaration of Human Rights that was adopted and proclaimed by the United Nations General Assembly in 1948. However, prevailing traditions; individual and societal prejudices; and social, economic, and political interests have converged to marginalize women from becoming equal beneficiaries of the current definitions of “general” human rights and to relegate them to secondary and/or "special interest" status within human rights considerations. The fact that women are not able to expect equal rights is largely a reflection of the persistent but often pervasive levels of existing gender inequalities, which exert formidable negative impacts on their lives. Human rights abuses generally affect women and men differently. Gender inequality manifests in power imbalance in sexual relations, as well as the discriminatory practices that women face in employment, education, access to resources and services, and other important spheres of their daily lives. Discrimination against women impacts beyond their own lives, and affects their ability to protect, support, and care for their families and to participate effectively and equitably in community life. Rights abuses and gender inequality intersect with HIV/AIDS and are fueling the spread of the epidemic. HIV/AIDS-related discrimination is most felt by those who are assumed to be at risk because of their behavior, class, gender, race, or sexual orientation, and women largely are worse off than men when these factors are considered.

During the 1980s, a great deal of attention was paid to upholding the human rights of people living with HIV. This resulted in a more informed understanding of the importance of human rights in determining not only vulnerability to HIV infection, but also the likelihood of accessing relevant care and support by those who are infected. It became apparent that the realization and protection of rights was critical in reducing vulnerability to infection and protecting those infected with and affected by HIV/AIDS. With respect to women and girls, several key strategies have been promoted to address their rights in the context of HIV/AIDS, including the advancement of women’s full enjoyment of all human rights; the promotion of shared responsibility between men and women to ensure safe sex; and the empowerment of women to have control over and decide freely and responsibly on matters related to their sexuality, to enhance their ability to protect themselves.
Consensus on the roles and responsibilities of governments have been largely driven and articulated through several international conferences addressing gender inequality, as well as the link between gender and HIV/AIDS. These international conferences include the International Conference on Population and Development, held in Cairo in 1994, which emphasized the need to “promote gender equality in all spheres of life, including family and community life, and to encourage and enable men to take responsibility for their sexual and reproductive behavior and their social and family roles”; and the Beijing Platform for Action (Fourth World Conference on Women, 1995), which affirmed the principle of shared responsibility between men and women. Following the Beijing Conference, the UN General Assembly mandated the Commission on the Status of Women to integrate a follow-up process within its program to review the critical areas of concern in the Beijing Platform for Action and to catalyze the mainstreaming of gender in United Nations activities.

More recently, the 2001 UN General Assembly Special Session on HIV/AIDS (UNGASS) stressed the need to challenge gender stereotypes and attitudes and gender inequalities in relation to HIV/AIDS. The UNGASS declaration endorsed by several governments explicitly states that gender “equality, and the empowerment of women are a fundamental prerequisite in the reduction of the vulnerability of girls and women to HIV/AIDS.” Setting specific targets for action, the Millennium Development Goals, signed by 198 countries and major development institutions, adopted benchmarks for women’s rights and empowerment and for containing the spread of HIV.

However, despite the call for national governments and international donors to overcome the obstacles to scaling up HIV services, including addressing gender inequalities that impact on the epidemic, many governments have struggled to respond. It is largely acknowledged that limited resources and several other constraints make it difficult for governments to fulfill their obligations to ensuring gender equality and the human rights of citizens, especially those vulnerable to, living with, and affected by HIV. In real terms, the presence of laws and policies has not adequately curtailed the abuse of women’s rights or the levels of their vulnerability. The successful implementation of rights-based laws, policies and programs affecting women depend on how these are viewed and received by those from whom women experience the most serious gender inequities—family and community members. Thus, in order to achieve women’s human rights—a prerequisite for women’s empowerment—and to impact on HIV/AIDS, it is necessary to implement complementary and interrelated bottom-up, broad-based strategies targeting all segments of the community rather than those that focus primarily on women.

WOMEN AND HIV/AIDS

Examining the situation of women and the HIV epidemic provides the basis for understanding the link between the epidemic and women’s rights issues. Generally, the epidemic has largely flourished in the most affected regions because women and girls have limited means and power to protect themselves—and vulnerability to HIV results from the lack of power of individuals and communities to reduce or manage their risk of exposure to HIV infection. Once infected, women and girls have limited means and power to access the care and support they need. HIV/AIDS vulnerability is gender-biased and mediated by factors that are largely out of women's control. These factors include gender-based violence, imbalance in sexual power relations, unequal access to rights, discriminatory laws and policies, traditional norms and practices, poverty, and poor access to services. For
very vulnerable subpopulations of women such as sex workers, their level of vulnerability is increased by being women as well as by engaging in an economic activity that exposes them to greater social, sexual, and physical abuse and to increased risk of HIV infection.

Increasingly, women all over the world are disproportionately affected by HIV. Sub-Saharan Africa is the region of the world most severely affected by the virus, and within this region its effects are most experienced by young women. The commonly held notion is that in Africa, HIV/AIDS has the face of a woman. The key features of the feminized African epidemic include the young age at which infection peaks in females compared with males, high-female-prevalence rates, high risk of transmission from mother to child, and the huge burden of AIDS-related care carried by women. Gender inequities and the lower status of women are largely at the root of women’s vulnerability to infection in sub-Saharan Africa and the disproportionate burden they bear. A 2007 study by the U.S.-based Physicians for Human Rights conducted in Botswana and Swaziland assessed the factors contributing to HIV infection and concluded that discrimination against women was spreading HIV. In both countries, the legal system accords women a lesser status than men and restricts several rights such as ownership of property and inheritance, among others. This situation is borne out of widespread cultural beliefs that perceive women to be inferior to men.

According to the Joint United Nations Program on HIV/AIDS (UNAIDS), globally 48% of people over the age of 15 who are living with HIV are women, and 76% of all HIV-positive women live in sub-Saharan Africa. In this region, women make up 59% of all adults living with HIV. The severity of the epidemic among women is related to the degree of gender inequality and their low social status. The view that women have the power and choice to protect themselves is not a realistic one in many parts of the world, particularly in sub-Saharan Africa. The South African situation starkly captures the particularly disproportionate vulnerability of young women and their limited power to protect themselves. National surveys of 15- to 24-year-olds showed that young women make up 77% of the 10% of people living with HIV nationally; and 16% of 15- to 24-year-old females were HIV-positive, compared with 4.8% of males in the same age group.

Socially endorsed discriminatory practices and inequities against women result in HIV-related repercussions. These not only contribute to women’s poor access to services and ownership of vital economic livelihoods and assets, but also curtail the extent to which women can seek their rights or advance their self-determination. Women’s lesser power in negotiating sexual relations and safer sex and in protecting themselves against gender-based violence, as well as their limited access to reproductive health services, underpin the slow progress in reducing their vulnerability to HIV/AIDS. For example, serious violations of rights involving rape and sexual assault against women are often underreported, mainly due to women’s fear of stigma and further repercussions, as well as apathy resulting from the often poor performance of the criminal justice systems in such cases.

Research from several countries has shown that sexual violence by men and the HIV vulnerability of women are linked. In the United States, for example, women in violent and abusive relationships are less likely to use condoms and are more likely to have sexually transmitted infections than those who have not experienced violent relationships. With specific reference to HIV infection, a study conducted in Kigali, Rwanda, found that HIV-positive women had a history of experiencing more unwanted sex than those who were not, suggesting an association between sexual assault
and HIV infection. Violent sexual behaviors by men can also impact negatively on themselves. A recently reported study in South Africa showed that men with a history of sexual assault were at significantly higher risk for HIV transmission than those who were nonassaultive. Men with a history of sexual assault were also more likely to endorse hostile attitudes toward women and to accept violence against women, although these attitudes and beliefs were common among men with or without a history of sexual assault.

South Africa’s Medical Research Council reported in 2004 that every six hours a woman is killed by her intimate partner, and conviction rates for charges of domestic violence and homicides are no higher than 37.3%. Only one in nine victims reports rape, and fewer than 10% of reported rapes lead to conviction. It has also been shown that women subjected to violence have up to three times greater risk of acquiring HIV infection. A 2007 research study reported a prevalence of 15.2% among 21-year-olds reporting one lifetime partner and 28.5% among those reporting more than three lifetime partners. These results suggest a much higher rate of male-to-female transmission than was previously acknowledged. These high levels of HIV infection in young women question our understanding of gender-related risks and the relevance and effectiveness of current prevention strategies in contexts where sexual violence and coercion, denial of women’s rights, and poor access to services place women at a heightened risk of infection.

Generally speaking, the vulnerability of women is contextually and behaviorally linked with gender and power norms that accord to men and boys a superior status and greater rights. While cultural, social, and economic factors offer men the privilege of having multiple sexual partners, society prescribes abstinence and fidelity for women. Girls are expected to maintain their virginity before marriage, but the same standard is not stipulated for boys. Virginity testing is being used in certain communities to assess how girls measure on this score, and despite the accompanying violations of rights, supporters of virginity testing continue to ignore the manner in which it is worsening the already low status of girls and exposing them to increased risk. Also, intergenerational liaisons between older men and young women, often facilitated by economic and social pressures, are condoned in many African societies. These contradictions explain to a large extent the high vulnerability of young women to HIV.

REDDUCING WOMEN’S VULNERABILITY TO HIV/AIDS

From a gender perspective, HIV/AIDS intersects at several levels and in many ways with the social injustice and oppression women suffer. Women have limited power to access their rights because of conflicts with traditional and cultural concepts of the place of women in society. Programmatic and policy responses to address HIV/AIDS need to take cognizance of this fact. Social change is required to create the atmosphere for women’s rights to become ingrained in the fabric of society and for these rights to be enforced. HIV/AIDS interventions that aim to impact on women should embrace social, human rights and cultural aspects to complement and strengthen behavioral interventions that otherwise will have limited application in the lives of vulnerable women.

With the recognition that men’s gender-related attitudes and their sexual behaviors are at the core of the HIV epidemic in most regions of the world, several programs are promoting interventions involving men and boys to transform and influence gender norms and risky sexual behaviors. These programs focus on promoting individual and group transformation of boys and men and also seek to influence broad-based community attitudes
and norms around gender equity and domestic violence. Other interventions have promoted the involvement of men in support of prevention of mother-to-child transmission (PMTCT), voluntary counseling and testing, maternal health, and care and treatment services. As shown in this chapter, it is evident that community-based programs involving men are providing the space for positive engagement to take place on issues around gender equality and male sexual norms, and for women’s human rights to be discussed and addressed.

**Promoting the Involvement of Boys and Men**

The Men As Partners (MAP) program, pioneered by EngenderHealth, recognizes the vital role that men can play in promoting gender equality, reducing violence against women, and advancing women’s reproductive health and rights. The MAP program has been implemented in over 20 countries. In South Africa, MAP has focused on challenging attitudes and behaviors that are held by men that compromise their own health as well as the health and safety of women. The evaluation of the program showed that men’s perceptions on according women the same rights as men and on gender-based violence changed positively.29

Instituto Promundo in Brazil and Community of Resource Organization (CORO) Literacy in India, in conjunction with the Population Council, an international nongovernmental organization based in the United States, have conducted interventions aimed at changing negative aspects of masculinity and reducing risky sexual behaviors among men. These programs combined group education with a community-based and gender-focused “lifestyles” social marketing campaign to reinforce gender-equity and HIV-prevention messages and promote violence-free and gender-sensitive lifestyles for young men. The results showed that participants were able to transform and change their support for inequitable gender norms and sexual harassment, and they adopted more protective behaviors.30 The Medical Research Council’s evaluation of the Stepping Stones program implemented in rural parts of the Eastern Cape Province of South Africa to build more gender equitable relationships also showed that men who participated in the program reported fewer sexual partners and improved communication between partners.31

Similarly, a program in Zambia to address the inequitable involvement of men and boys in community care and support services trained and supported boys and girls to take part in community home-based care activities and HIV prevention. The results showed that there was no difference in the level of participation and the types of care and support services males and females provided. In addition, males were less likely to perceive girls to be responsible for spreading HIV, and they showed a better level of appreciation of their risk to HIV infection.32

**ADDRESSING THE PREVENTION, CARE, AND TREATMENT NEEDS OF WOMEN**

Empowerment ought to be a critical outcome of all programs addressing HIV/AIDS, especially those that focus on women and girls. Empowerment issues for HIV-positive and negative women can be unique as well as overlapping. HIV-positive women, for example, may experience more stigma and rejection than their male counterparts, and gender-based stigma constitutes a serious form of disempowerment for women and can deter access to services. Stigma can result from activities and policies to address prevention and care for women, such as in formula feeding of infants born to HIV-positive mothers, the use of voluntary counseling and testing services, and disclosure of HIV-positive status; and women can experience stigma and
“WE CAN CHANGE THINGS AS MEN”: EMPOWERING HIV-POSITIVE MEN TO PLAY CONSTRUCTIVE ROLES IN THEIR FAMILIES AND COMMUNITIES

The following excerpt was written by Manoj, a 25-year-old, HIV-positive man from Gujarat, India. The EngenderHealth Men As Partners (MAP) program helped him gain new insights about being a man. Now he counsels other men about taking responsibility and is forging his own path in life.

I learned that I was HIV-positive when I donated blood for a friend’s operation. At first I couldn’t talk to anyone. I wanted to kill myself. But at the hospital, a counselor told me, “You have one chance to live this life, and you can live it as much as you want.” She took a great burden off of my heart. I later became a counselor with the Gujarat Network of Positive People (GSNP+) because I wanted to help others like she had helped me.

Through my experience as a counselor, I’ve learned the importance of working with men. A man can talk to his family and make a message clear to them because he is seen as the leader and the decision maker. And men need to know that they are not alone in the problems that they face. So when EngenderHealth partnered with GSNP+ to bring their Men As Partners program to Gujarat last year, I was eager to participate.

I have attended several MAP trainings and workshops. They are conducted in a very understandable way, and the topics and examples are relevant to our everyday lives. It helped me to start thinking more carefully about my everyday behavior. For example, I used to automatically ask my sister to get me water. Why shouldn’t I be the one to bring her water?

The MAP trainings also make me a better counselor. I learned practical information about positive and healthy living that I can share with my clients. Now I find it easier to talk to men about sex and about how you can be a man without engaging in risky behaviors, like having multiple partners. I tell my male clients that it is our responsibility to wear condoms and prevent spreading the virus. Taking responsibility is an important lesson that I’ve learned from MAP. When I talk to my male clients about MAP, one of the first things I tell them is that as men we can help improve the health of our families, friends, and community, and that is why they should join the program.

The MAP program has also helped me to make important personal decisions. I have a girlfriend; she is also HIV-positive and a counselor. She is a widow and has a six-year-old son. Before, I could not see a future for us because of society’s prejudice against widows and second marriages. But I learned that these ideas are simply creations of society, and I do not have to
adhere to them. My girlfriend’s son is now my son, and we are hoping to get married. I am following my heart, thanks to MAP.

I also decided to tell my family that I am HIV-positive, after years of hiding it from them. Like many others who are living with HIV, I was afraid. Recently I invited them to a World AIDS Day MAP event, where I spoke about living with HIV. My family was crying, but I knew that it was because they were proud of me. My family is so supportive, and when they see me working passionately for something that I care about, that is enough for them.


blame for providing care to an infected spouse or child. Despite this knowledge, few programs for women take adequate measures to prevent stigma and to empower women to overcome or cope with stigma. Programs focusing on women and girls have traditionally tried to get them to change their behavior, acquire skills for caregiving, and access PMTCT and treatment services.

An example of a program that has attempted to develop strategies in response to these issues is the mothers2mothers program in South Africa, an innovative program that aims to reduce mother-to-child transmission, destigmatize HIV, and empower women through a peer approach in which trained HIV-positive mothers provide psychosocial support to HIV-positive pregnant women. Results from the program showed that this peer approach was successful in facilitating the transfer of information, disclosure—particularly to partners—uptake of PMTCT, better PMTCT outcomes, and access to treatment and psychosocial well-being.33

Various female-controlled prevention methods have been piloted, including the female condom. The introduction of the female condom in 1994 was seen as an opening for women to have a tool in their hands to reverse the power imbalance in heterosexual relationships and to protect themselves from HIV and sexually transmitted infections as well as unintended pregnancy. Despite evidence to show the protective value of the female condom and its role in empowering women to negotiate safer sex, it still needs to be fully incorporated into national strategies to expand women’s choices for dual protection.34 Research into the development and testing of microbicide products to prevent HIV infection among women and among HIV-discordant couples continues to receive great attention and support for its potential value as a female-controlled method. Offering women more
effective preventive methods needs to remain a priority, especially those that can be used by women who are unable to negotiate use of the male condom.

Evidence shows that married women, in particular married adolescents, are at great risk of HIV infection. In Africa and Asia, 50% to 60% of girls get married by the time they are 18 years, often to older, more sexually experienced men. Studies have shown that married adolescent girls tend to have higher rates of HIV than sexually active unmarried girls. In rural Uganda, 88% of HIV-positive women aged 15–19 years were married, and in Kisumu, Kenya, and Ndola, Zambia, the rates were 48% and 65%, respectively. The vulnerability of married adolescents is linked to several factors, including poor education, limited peer networks, restricted social mobility, unprotected sex with older male partners, limited access to information, limited autonomy, and increased risk of gender-based violence.

Several strategies have been used to address married adolescents’ vulnerability in countries such as Bangladesh, India, Burkina Faso, and Ethiopia. These include developing safe spaces for girls; providing incentives for girls and their parents to delay marriage; removing obstacles to girls’ enrollment in school and fostering retention; increasing girls’ access to economic skills and resources; and working with parents, religious leaders, and community members to increase awareness of the need for girls to delay marriage.

Challenges around targeting HIV-positive people include fear of victimization and stigmatization, and concerns around the complex ethical issues involved. However, there are very compelling reasons for considering prevention activities that meet the particular needs of people with HIV. Among several reasons, positive prevention interventions provide the opportunity to address the gender relations and power dynamics between women and men. These become even more critical when one or both partners are living with HIV. For example, women who already have little decision-making power in a relationship may face increased levels of social exclusion, abandonment, and violence if they disclose their positive HIV status.

Gender inequities in access to treatment have been bridged considerably. Out of 30 countries for which data was available on the “3 by 5” initiative, 20 showed that women were accessing treatment equitably, but there are concerns that women may have more challenges adhering to treatment. Women’s fear of violence may be a serious barrier in access to treatment. A clinic in Zambia showed that 60% of women eligible for antiretroviral therapy opted out because they were concerned about violence and abandonment by their partners if they disclosed their status. In terms of the prevention of transmission to infants, only 9% of pregnant women in low- and middle-income countries were being offered PMTCT services. On the positive side, PMTCT programs are increasingly being utilized as a conduit to broaden the continuum of care for HIV-positive mothers and pregnant women and to implement a family-centered approach to prevention, care, and treatment, thus reducing the threats HIV-positive mothers may face at the family and community levels.

**Focusing on Socioeconomic Empowerment of Women**

Unfavorable global and national economic policies, the impact of war, natural disaster, drought, and famine are weakening women’s socioeconomic status. This, coupled with existing gender-biased cultural practices that deny women access to property, resources, inheritance, and autonomous means of livelihood, compromises their ability to prevent and cope with HIV/AIDS. Women’s right to own property and land is unequal to that of men in many parts of the world. This includes the right
to own, inherit, or dispose of property as well as unhindered access to land for farming and to other natural resources. In Kenya, for example, women constitute 80% of the agricultural labor force but only own 5% of the land. Other common rights violations in the context of AIDS in Africa include evicting AIDS widows and their children from their homes and loss of farmland and other tangible assets to relatives.

Although research evidence is inconclusive on whether a higher socioeconomic status protects against HIV infection, there is a widespread assumption that increasing the economic assets of women and girls can play an important role in HIV prevention. Direct evidence of the link between HIV risk and poverty was seen in a South African study conducted in the province of KwaZulu-Natal that showed that poorer women were more likely to have an earlier sexual debut, a nonconsensual first sexual encounter, and higher rates of forced sex. Details of the study show that risky behaviors among this group included greater likelihood of exchange of sex for money, goods, or favor, and a higher number of sexual partners. Microfinance programs have been adopted in many countries to help poor women secure a degree of economic independence, and when integrated with HIV/AIDS interventions, these programs constitute a viable strategy for addressing HIV and poverty. Examples of programs combining microfinance and HIV include those by World Vision, which has successfully linked HIV education with microfinance, involving groups of 20–30 women.

Women could lose their property and assets when the death of their spouse is perceived to be due to AIDS or when they are perceived to have AIDS. They also experience stigma and rejection and sometimes are evicted from their homes. The loss of vital assets and channels of support puts widows and their children at even greater risk of infection and curtails the likelihood that they will be able to survive. Grassroots organizations and legal professionals in countries such as Kenya, Rwanda, Zambia, and Zimbabwe have responded to these challenges by training community para-legals, village chiefs, and members of land boards about women’s property, inheritance, and legal rights. They also help women overcome ignorance about issues like how courts function and how to write a will, and help them to obtain and safeguard important legal documents.

The burden of care for people living with HIV is borne largely by women, often poor, older women who have no economic resources and who are also likely to suffer from age-related chronic illnesses. In Kenya and South Africa, for example, grandmothers become parents a second time because of the loss of their own children, and are often left responsible for the care of grandchildren. Elderly caregivers go through considerable physical, emotional, and psychological pain and have poor access to social and health services and support to care for their dependents. Several initiatives are helping to reduce the care burden experienced by women. In Swaziland, the government, with funds from the Global Fund to Fight AIDS, Tuberculosis and Malaria, intends to provide financial support to caregivers who look after orphans.

**Organizing around Women’s Rights and Empowerment in the Context of HIV/AIDS**

Organizing to foster women’s rights and empowerment has involved different stakeholders and addressed several aspects of women’s subordinate status that underpin their vulnerability. Women’s rights networks have been formed globally, regionally, and nationally as well as at the grassroots level. The common purpose of these groups is the need to change the situation of women and to empower them in order to reduce their
vulnerability. Strategies adopted have included community mobilization, education, advocacy, litigation, policy formulation, service delivery and capacity building. These interventions have resulted in greater awareness of women and HIV/AIDS issues at international and local levels, in having the voices of women heard, and ensuring the allocation of resources to support initiatives that potentially impact women and girls.

The Society for Women and AIDS in Africa (SWAA), formed in 1988 by professional African women, was one of the earliest pan-African networks established across 40 African countries to recognize the potential impact of HIV/AIDS on women in the continent and to mobilize for organized action by women and communities.\(^\text{56}\) SWAA’s core purpose is to address the root causes of the vulnerability of women to HIV/AIDS and the disproportionate impact of HIV/AIDS on women in Africa. For more than 20 years, SWAA has promoted programs that address the rights of women, their access to health care, education, economic and sociocultural rights, and rights of women living with HIV/AIDS, in particular to reduce the stigma and discrimination they face. For its pioneering work and contribution in furthering the understanding of the diverse ways in which HIV/AIDS impacts on women, families, and communities in Africa and in mobilizing and galvanizing a regional platform for women to respond to the epidemic, SWAA has been recognized internationally and regionally; and its work continues to remain responsive to the needs of women, families, and communities.

In furtherance of the rights of HIV-positive women, global-level organizing by HIV-positive women started in 1992 with the formation of the International Community of Women Living with HIV/AIDS (ICW). Since then several other women’s groups have been formed in many countries to address local issues affecting HIV-positive women. The ICW seeks to provide support, information, and services to women living with HIV worldwide and to build their capacity to influence and contribute to policy development. Despite several challenges, the ICW continues to promote efforts to enable HIV-positive women to access their rights, particularly their rights to sexual, reproductive, legal, financial, and general health-care services.\(^\text{57}\)

With respect to marginalized and stigmatized groups of women, promoting their rights is more challenging. Homophobia is still a very serious problem in Africa, and African lesbians experience multiple layers of discrimination and serious physical and sexual violence because of their sexual orientation and their gender.\(^\text{58}\) However, research and advocacy work in the continent is increasing levels of awareness about the existence of homosexuals in Africa and giving momentum to efforts by gay and lesbian groups to organize around their issues, including their rights. For example, the Coalition of African Lesbians, consisting of lesbian and feminist organizations from 14 African countries, is active in ensuring that lesbian rights issues are brought to the fore.\(^\text{59}\)

In developing countries, especially in the Africa and Asia regions, female sex workers suffer high levels of stigma, discrimination, abuse, and exploitation from the community as well as law enforcement agents.\(^\text{60}\) Despite this situation, many sex workers’ organizations and programs have developed and are addressing the human rights of sex workers. The Sonagachi Project in India is a well-known example of how female sex workers have formed a strong cooperative, reaching out to about 65,000 sex workers and their children. This sex worker–run project promotes the use of condoms, runs literacy and vocational programs, and lobbies for the recognition of sex workers’ rights and for full legalization.\(^\text{61}\)
CONCLUSION

Competing demands, lack of adequate resources, and limited capacity all curtail the comprehensiveness of local and national HIV/AIDS strategies. These factors in turn limit the promotion of appropriate interventions that integrate strategies for women’s empowerment within the broader HIV/AIDS response. Where resources are scarce, the pursuit of women’s rights is often a low priority. Generally, such settings are also plagued by weak public institutions and civil society, adverse gender norms, and poverty, all of which constitute major challenges to the development of sustainable human rights environments that could potentially reduce women’s vulnerability to HIV/AIDS. For example, HIV infection or the death of a spouse due to AIDS can further compromise the rights of women, resulting in the loss of property, resources, and assets. Thus, empowerment strategies that focus on women, without including the people who have influence over their lives, could place women at increased risk because of the potential negative repercussions they could experience.

There is clear evidence from research that the vulnerability of women to HIV is linked to denial, abuse, and violation of women’s rights. Lessons from programs and policies that seek to expand the rights of women and to reduce their vulnerability to HIV/AIDS demonstrate the importance of not focusing exclusively on women, but rather addressing the roles of men, families, and communities in the subjugation of women. Although promising results have been reported from interventions that focus on men to address women’s empowerment, gender norms, and gender-based violence, these programs are currently reaching only a small proportion of men and have not developed a close working relationship with women’s rights programs.

Given the challenges women face in seeking their rights, it is more appropriate to promote grassroots women’s rights and empowerment models while taking prevailing cultural and social conditions into account. These models provide useful and relevant frameworks for action and community participation and have the potential to have a great impact while minimizing any backlash that women may experience from asserting their individual rights or mobilizing as groups to claim their rights. Women’s rights programs addressing issues such as gender-based violence could enhance their relevance and impact by combining their predominantly legal and “punitive” approaches with support and motivation for men to become primary partners and actors in promoting women’s rights. Community-based approaches to address women’s empowerment have the potential to influence and change, in real terms, women’s subordinate status and to address the internalization and acceptance of gender-based violence and other rights violations that underpin women’s vulnerability. These approaches, together with strategies that build on positive indigenous values and traditions that accord women respect in the community, endorse women’s rights, and disapprove of gender-based violence, would facilitate broad-based participation of women, men, community-based organizations, and traditional and religious leaders in efforts to empower women.

Resource-limited settings are often the ones in which HIV/AIDS is most severely experienced and where numerous social challenges and priorities hamper adequate responses. Although challenging, these settings offer several opportunities and entry points for the promotion of women’s empowerment and for addressing entrenched gender inequities. Sensitive, feasible, and practical solutions to address the factors that put women at risk of HIV infection need to be given greater priority. The fact that women, and young women in particular, continue to be so vulnerable to HIV infection despite increasing availability and allocation of resources points out the existing gaps and weaknesses in
current strategies. Generic approaches to women’s empowerment may have severe limitations; empowerment strategies for young women, for example, must be tailored to address their specific vulnerabilities to HIV. These may be different from strategies that are designed for older women, who are less threatened by HIV infection but are overburdened by care responsibilities.

Finally, sharing local, national, and regional lessons of what works with respect to reducing HIV vulnerability and promoting women’s empowerment in the context of HIV/AIDS needs to be prioritized. While international frameworks and provisions are important guidelines for action, their limited application in resource-limited settings should be addressed. Ultimately, grassroots responses stand the most promising chance of bringing about tangible and lasting advancements in the empowerment of women and reducing their vulnerability to HIV/AIDS. More resources are needed to test, evaluate, and scale up appropriate and effective interventions that truly empower women; and genuine partnership between policymakers, program managers, nongovernmental organizations, and communities is essential.
REFERENCE LIST


Overcoming Obstacles to Care and Treatment for Women Living with HIV

Deloris Dockrey and Lynde Francis

The lens of HIV is a great revealer of the problems that existed before we got HIV.
—Lynde Francis

After more than 25 years of the global HIV pandemic, the infection rate among women continues to increase. The Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization report that out of the estimated 33 million people living with HIV, half are women aged 15 years and older. In sub-Saharan Africa, roughly 55% of adults living with HIV are women, and 3 out of 4 (74%) people living with HIV are young people aged 15 to 24 years. In Asia, Eastern Europe, Latin America, and the Caribbean, an increasing proportion of people living with HIV are women and girls.

The increase in the proportion of women living with HIV is primarily due to heterosexual transmission. This trend is especially visible in sub-Saharan Africa and the Caribbean, although women in industrialized countries are increasingly bearing a greater burden of the disease. In the United States, for example, women comprise the fastest growing population of people living with HIV.

The stigmatization of HIV infection makes it difficult for people living with HIV to access care and treatment services. This is often due to their fears of being judged or discriminated against. These fears can be especially acute among women, because they are often more vulnerable to abusive treatment by their spouses, family members, and the greater community. Despite these challenges, women are working to find ways to overcome various forms of stigma and discrimination, just as they have done for generations. It is hoped that through their determined efforts, HIV-positive women can gain greater access to care and treatment services as the scale-up of these services continues. Access to health care for women is a critical component of HIV control and prevention, not only to address women’s health needs and the needs of their families, but also to provide an opportunity to address the serious inequities women have been experiencing since time immemorial.

In many ways, HIV is a “great revealer,” highlighting the many political, socioeconomic, and cultural injustices that disproportionately affect the lives of all women, not just those living with HIV. These injustices include denial of equal rights, gender discrimination, violence, lack of access to education, lack of economic opportunities, and
poverty. As Julie Hamblin writes in the article “The Role of the Law in HIV/AIDS Policy,” “The people who remain most vulnerable [to HIV] are those who are denied the means of protecting themselves against the risks of HIV because of economic need or powerlessness to control the basis upon which their sexual relationships take place.”

In other words, the powerlessness of women fuels the spread of HIV. In order to reverse this trend, the underlying causes of this powerlessness must be addressed. Women living with HIV are a critical voice in the public debate surrounding HIV/AIDS and access to health care. This chapter discusses strategies for empowering women living with HIV to improve their health and well-being alongside personal views of HIV-positive women who have overcome obstacles to accessing care and treatment in resource-limited settings in the United States, the Caribbean, and sub-Saharan Africa.

PEER SUPPORT PROGRAMS: THE WELLNESS COMMUNITY

Programs that focus on women’s well-being and coping skills, such as the Wellness Community for people living with HIV/AIDS at Hyacinth AIDS Foundation (New Jersey, United States), have proven very successful. The Wellness Community at Hyacinth creates an emotionally supportive peer community and provides a setting that actively facilitates interpersonal growth and self-advocacy skills that are predictors of adherence and positive health outcomes. In addition, it fosters an environment in which participants are more willing to assess and address mental health issues. The program is based on the Wellness Community Patient Active concept for people with cancer diagnoses. The Wellness Community helps HIV-positive women take a more active role in their health and health care. They learn how to reduce stress and how to improve the quality of their lives. The program continuously assesses the clients’ progress. Clients are assessed at the start of the program and then again at three and six months. As members of the Wellness Community, women can participate in groups that address stressful issues like loss of control, loss of hope, and unwanted aloneness. Wellness activities build positive relationships, reduce feelings of isolation, and give women a sense of hope. Most importantly, other HIV-positive women in the group provide peer support and make it easier for women to talk about the HIV virus.

Gail, a 55-year-old African American woman, joined the Wellness Community at Hyacinth in 2004. She had been diagnosed in 1989 with AIDS-related syndrome and was told she had less than a year to live. She was so afraid and ashamed of having AIDS that she kept silent about her infection for 12 years. Her silence took its toll in 2001 when she became ill. In desperation, she reached out and was welcomed into a Women’s Wellness group. Within a year of joining the group, she found hope, a sense of community, and the ability to take control over her own health. She remembered the first time she walked into her doctor’s office with a list of questions. She could still see the look of astonishment on his face. He stopped and put down her file, and after 12 years they had their very first conversation about how best to manage her health.

With joy, she said, “It took nearly 13 years to find my voice, but once I did, everything turned around. It wasn’t that my health circumstances had changed, but my ability to manage my life had, and I was a different person than when I first walked through the doors.”

*More information on the Wellness Community at Hyacinth can be found at www.hyacinth.org.*
AM AN HIV-POSITIVE MOTHER, grandmother, public health professional, advocate, and activist in the fight for HIV care and treatment access, and becoming educated on the virus and being involved in the health-care process at every level has helped me to overcome the many obstacles in my life. After working in the HIV arena for more than 10 years, I have come to understand the importance of involvement and advocacy in the lives of people living with HIV.

I remember that my deepest fears, shame, and secrets erupted like lava from a volcano when I was diagnosed with HIV in 1994. Before being diagnosed, I had run away from Jamaica, wanting to make a fresh start in the United States of America. As a young girl in Jamaica, I was sexually abused by a male relative, which I had kept as a secret. When I became pregnant in my teens, I had to live with the disgust and disappointment of my family. I was a single mother with no support from a husband. I thought that emigrating to the United States would erase my past and provide a bright future for myself and my son. But my HIV diagnosis threatened to kill those dreams! For more than 14 years, I have worked to overcome the troubles of my past by educating and empowering myself. I am very active in advocating for my health care and for the public health policies that impact my life and the lives of other HIV-positive women.

But my story is not unique; it is the story of many women. An HIV-positive diagnosis compounds and reveals the problems and challenges in our lives. Over the years, I have experienced the power of telling my story. It has been a significant part of my healing process. Today, I feel stronger and freer than ever before. I believe that what we do to overcome the obstacles in our lives and in our society, and that our choice to forge ahead, is our legacy.

I have found that the support programs that are most successful create an environment where HIV-positive women can freely discuss issues of stigma, sexuality, sexual violence, inequities, and poverty in their lives as they learn about their bodies and the virus.

In 1998, I joined the Sister Connect program offered by the New Jersey Women and AIDS Network.¹ The program is an intensive educational training program designed to provide women with knowledge about HIV/AIDS and related treatments. By the end of the 12-session program, I had learned how to advocate for adequate treatment and appropriate care from health-care providers. We (HIV-positive women) increased our sense of personal empowerment as we learned about our anatomy, our sexuality, the HIV virus, treatment options, and how to read and understand our laboratory reports.

¹More information on the New Jersey Women and AIDS Network Sister Connect program can be found at http://www.njwan.org/sisterrise.html.
OVERCOMING THE OBSTACLES: AN AFRICAN WOMAN’S PERSPECTIVE
By Lynde Francis

I AM A 60-YEAR-OLD, HIV-POSITIVE grandmother, living and working in what could arguably be described as the eye of the storm, sub-Saharan Africa, where UNAIDS estimates that 60% of those infected with HIV are women. Since my HIV diagnosis 21 years ago, I have witnessed a quiet but remorseless revolution taking place. Unlike in Europe and the United States, in Africa, from the onset of the HIV/AIDS epidemic, women have borne the major brunt of its effect. Initially, the women’s movement failed to respond to HIV; the messages surrounding its transmission focused entirely on promiscuity and other immoral behavior, with which women’s movements did not immediately identify. Within this context, marriage was being promoted as a form of protection.

The process of public realization closely mimicked the personal process from HIV diagnosis to acceptance: first, denial and disbelief; then, fear and panic (the “blame game”); after that, depression, hopelessness, and isolation. Ultimately, with increasing information, acceptance brought with it the final stage: “What next?” and “What can we do to fight back?”

Even in the late 1980s, there was already a vanguard of brave and farsighted “women warriors”—women like Auxillia Chimusoro, the first woman to publicly declare her status in Zimbabwe; Winnie Chikafumbwa in Malawi; and Bridgette Syamalevwe in Zambia—unsung heroines for the most part. They sounded a call to action and put their own lives on the line to alert others to the danger confronting them.

In the face of stigma and ignorance, they founded support groups and networks of people living with HIV/AIDS. Against all odds, they reached across borders and came together in what was to become the International Community of Women Living with HIV/AIDS to demand access to rights and treatment, rights that would not be realized in their own lifetimes. One of the most striking aspects of the emerging movement of people living with HIV/AIDS, from the beginning, was its exclusivity. It seemed that the stigma and isolation inflicted on those living with HIV superseded other socioeconomic, race, and class barriers. HIV-positive women from all walks of life found they had more in common than they had differences; and a “positive community,” almost a “POZ family,” became the fertile ground from which change would grow.

At a conference in Mozambique in 1992, I presented a paper entitled “Sexuality after Seropositivity.” This was an inconceivable concept at that time; HIV infection meant the end of any normal emotional, romantic, or sexual existence. It was then that I gave HIV my own personal name, “The Great Revealer,” as I was besieged afterward by people who had never thought beyond the health/medical paradigm. They wanted to know how I could find anything positive about seropositivity. It seems self-evident now, but back then, we had not yet fully grasped the implications of HIV as a vehicle for change.
Women are using the Wellness Community to empower and improve their lives, and some are returning to work. Many women have become active in public policy advocacy and campaigning groups, calling on their legislators to address public health policies that affect them. HIV-positive women are encouraged to tell their stories, to give voice to their struggles, and to use their stories as weapons for change.

ADDRESSING VIOLENCE AGAINST WOMEN

In some households, domestic violence is an obstacle, and nonconsensual sex is pervasive in the lives of many women and girls. Marta Dillon, in her article “In Front of the Mirror,” writes of a woman named Janaina from Pernambuco in Brazil who was barely 30 but had a long and bleak story that was difficult to tell. Janaina lives with her two children at a shelter for female victims of violence. When she was 9, she was given to a family to work as a maid. At 13, that family sold her into a prostitution ring. Janaina never went to school but taught herself to read. When she finally got away from prostitution, she found out that she was HIV-positive. Her story illustrates the strong link between violence against women and HIV.

The international campaign Women Won’t Wait is a coalition of organizations and networks committed and working to promote women’s health and human rights in the struggle to comprehensively address HIV and end all forms of violence against women and girls. The campaign focuses on gender-based violence against women and girls. Among its many activities, the campaign collects stories of women, like Janaina, who have experienced violence and abuse in their lives. These women speak of how they overcame their struggle and how they have improved their lives and the lives of their families.

NETWORKS FOR THE EMPOWERMENT OF WOMEN LIVING WITH HIV

HIV-positive women who are educated about the progression of the disease and who are allowed a safe environment to share their experiences emerge stronger and more determined to take control of their lives. Networks of people living with HIV/AIDS create safe spaces for women to become educated and involved in the issues that affect them. Once a woman begins to advocate for her needs, she begins to share her knowledge with others. The strongest supports for women are other women who can share their experiences. The principle of greater involvement of people living with HIV (GIPA) is embraced by many HIV-positive networks. GIPA aims to realize the rights and responsibilities of people living with HIV, including their right to self-determination and participation in the decision-making processes that affect their lives.

The Global Network of People Living with HIV/AIDS (GNP+) spearheads the GIPA principles. Representing people living with HIV, GNP+ is a global network that works on equal footing with all of its six affiliated regional networks in Africa, Asia, the Caribbean, Europe, Latin America, and North America. The role of GNP+ is to provide a platform for the diverse voices of people living with HIV globally, to present evidence in the global arena, and to support capacity building of individuals at the regional, national, and local levels. The core business of GNP+ is advocacy. GNP+ programs and platforms are based on the following broad key objectives:

*More information on the Global Network of People Living with HIV/AIDS can be found at www.gnpplus.net.
• Increased access to treatment, care, and prevention programs for all people living with HIV
• Decreased stigma and discrimination directed toward people living with HIV
• Increased and more meaningful involvement of people living with HIV at all levels and in every aspect of the HIV response, including service implementation and decision making

As women and girls become empowered and educated, they can clamor for the right to become involved in the scale-up of care and treatment programs. With the support of networks for people living with HIV, women can continue to advocate for changes in how society addresses the disparities and inequities that women experience. Women must become active and demand that decision makers be held accountable for the promises on women’s rights that they have endorsed. Government leaders must be made accountable for providing greater access to treatment and care for women, their children, and their families.

EXPLORING LINKAGES AND MOBILIZING COMMUNITIES

Today, HIV is considered a cross-cutting topic in all areas of discussion and all aspects of development. The mainstreaming of HIV has become the golden key to unlock donor doors. But most of all, it has enabled dialogue around areas previously considered taboo. Domestic violence, gender inequity, rape, and incest are now out in the open. Sexual and reproductive health and rights are no longer discussions held only behind closed doors but are part of the strategy to eliminate HIV.

For the first time, we are grappling with the inextricable linkages between economic and social development, health, environment, gender equity, and long-term survival of the whole human race. What could not be spoken is now exposed to the relentless spotlight of our vulnerability to HIV. This vulnerability will persist unless we come together and address the challenges we face in a united effort.

A major part of this change is the realization that our greatest weapon in this enterprise is the education and empowerment of women and girls. This can only be done through realistic, practical, and down-to-earth skills-training that enables women and girls to improve their own livelihood and that of their communities. An important aspect of this empowerment is to inform women and girls of the rights they possess, thus helping them to realize that culture and tradition are not immutable and that they do possess the power to change it.

An example of this concept in action is offered by the program run by The Centre (Zimbabwe) and funded by The River Fund to train 30 HIV-positive rural women from 10 provinces in western Uganda. Prior to the training, none of them had secondary education, and the sole criterion for attendance was a basic understanding of English and literacy in the vernacular. Most of the original group consisted of widows or divorcées with children, aged 25 to 60. The initial training in 2005 was on long-term survival skills for living positively with HIV and took place at a mission school in Tororo. The women were taught basic HIV information, nutrition, disclosure, self-care, stress management, infant and child feeding, and basic home-based care skills, among other topics. At the end of the one-week training, they went home with instructions to put these skills into practice in their personal and community lives.

One year later, in 2006, the same group returned to Tororo with only one dropout. They shared how the training had changed their lives and their position in their community, their successes, and their failures. Through a SWOT (strengths, weaknesses, opportunities, and threats) analysis, they looked at how they could improve on areas where they felt they had failed. Without exception, all of these women had gone further than their own
immediate family circles and had initiated skills-sharing sessions with other women in their communities. They had also approached gatekeepers and stakeholders, and many of them were now sitting on clinic community boards, working with community-based organizations, or collaborating with others to provide home-based care to neighbors and friends.

They then underwent a second training that taught the women how to assess local resources and how to perform a needs analysis. They learned to plan and mobilize resources and to open gates once kept closed by community leaders. They learned how to assess the needs and expectations of the target community and compile a program agenda. Participatory training techniques were taught, as well as how to build indicators for monitoring and evaluation into their programs. The last three days of this one-week training were completely managed by the women themselves as a “learning by doing” exercise. All participants contributed to planning the program, presenting the sessions, conducting focus-group discussions, and giving feedback to the plenary group.

In September 2007, each provincial group involved in the original training nominated one representative to attend the third session, training of trainers (TOT), phase III. Each representative in this TOT group brought with them two women they had done baseline training with in their community during the previous year. Twelve representatives of the original cohort, together with 24 new participants, attended this session. After an initial team-building exercise, the TOT group was given a day to design the program for the second-stage (phase II) training of the new group over a two-day period, while a one-day baseline debriefing workshop was conducted to ascertain the level of knowledge achieved by the new participants.

Our new participants completed an evaluation of each session run by the TOT group and scored them on content, style, communication, participation, and fun (something they would never have thought themselves capable of a week before!). The feedback reports from the provinces showed that the women from the original cohort had held direct training or interactive sessions with over 5,000 people in the previous year! This was confirmed by the new group of 24 participants, who had been involved in the baseline training the previous year and told of the workshops held in church halls, schools, fields, and even at football matches.

By October of the same year, the 12 representatives, now TOT graduates, were holding phase I trainings in four other provinces, thus completing the ownership and continuation of the program by and for the community. The monsignor and bishop of the mission where this program has evolved was proud to hand out certificates to the women and confirmed that, at the outset, he had not expected such a complete transformation of the women involved “from mice to roaring lions”!

CONCLUSION

Nelson Mandela, former president of South Africa, stated, “For every woman and girl violently attacked, we reduce our humanity. For every woman forced into unprotected sex because men demand this, we destroy dignity and pride . . . For every moment we remain silent, we conspire against our women. For every woman infected by HIV, we destroy a generation.” As women work to educate, train, and empower themselves, they are also demanding that their government, their men, and the larger community change some of the norms and traditions of the past. As a society, we must change current socioeconomic and political conditions and build opportunities for women as well as men to address the issues of stigma, gender inequity, and disparities that negatively impact how women access HIV care and treatment.
TRANSFORMING MALE GENDER NORMS TO ADDRESS THE ROOT CAUSES OF HIV AND AIDS
Andrew Levack
EngenderHealth, United States

It is widely recognized that gender norms—societal expectations of men’s and women’s roles and behaviors—fuel the global HIV epidemic. Women’s low status in many societies contributes to limiting the social, educational, and economic opportunities that could help protect them from infection. Traditional gender norms also give women the message that they need to be submissive or to let men take the lead in relationships, which further contributes to putting them at risk for HIV. At the same time, traditional male gender norms encourage men to equate a range of risky behaviors—the use of violence, substance abuse, the pursuit of multiple sexual partners, the domination of women—with being manly. Rigid constructs of masculinity also lead men to view health-seeking behaviors as a sign of weakness. These gender dynamics all play a critical role in increasing both men’s and women’s vulnerability to HIV.

A Model for Working with Men
Over the past decade, a growing number of innovative HIV-prevention programs around the world have worked with men to challenge traditional gender norms and develop alternative, healthier gender norms. They are unique in allowing men to participate in a reflective process that explores how gender inequities and rigid messages about masculinity contribute to HIV, sexually transmitted infections, gender-based violence, and other health-related problems. These programs allow men to understand how traditional masculinities can lead to unhealthy behaviors that put both them and their partners at risk. These “transformative” programs ask and encourage men to challenge harmful gender norms and embrace alternative models of masculinity that support their own health. This can lead to improved communication with partners, increased condom use, reduction of sexual partners, delayed initiation of sex, increased utilization of HIV services, increased support of their partner’s use of services, and an increased role in the care and support of people living with HIV/AIDS.

Transformative approaches share a set of operating principles. First, they view men in a positive light. Rather than portraying men as vectors of disease, these programs recognize that many are already playing a constructive role in the lives of their families and supporting the rights of women. They also acknowledge that masculinity can be defined and expressed in a variety of ways. Using the term “masculinities” suggests that gender norms are diverse, complex, and dynamic. Transformative programs explore how masculinities are deeply intertwined with culture, race, class, age, socioeconomic status, and sexuality. Additionally, they recognize that men have a personal investment in challenging current norms and can be allies in improving their own and their family’s health. Finally, all transformative programs recognize the need
to work with women’s groups to ensure partnership with and accountability to women. In the end, the goal of this work is to develop respectful, trusting, and egalitarian relations between men and women that will attack the deep roots of HIV infection and enhance the lives of both sexes.

Implementing Transformative Approaches
Transformative programs for men exist in many countries, with most initiated by local and international nongovernmental organizations (NGOs). However, as this work expands, local and national governments are joining the process in settings such as schools, prisons, police wards, and military bases.

Most transformative programs offer some type of intensive group process that encourages a very personal reflection on gender values, examining the costs to both sexes of negative gender dynamics. The workshops also provide an opportunity to explore progressive views of gender relations in a safe and supportive environment. Following the initial activities, participants are given information on a range of health issues, including HIV, and engage in exercises that constantly refer back to the issue of gender. For example, an activity about HIV transmission would explore the societal messages men receive that put them at higher risk for HIV.

Transformational educational processes can work with men alone or bring men and women together. One of the best examples of the latter is Stepping Stones, a participatory gender-focused process that brings together men and women from a community to engage in a discussion and analysis of factors in their environment that make them vulnerable to HIV. This training methodology was designed in 1995 in Uganda and has since been adapted and modified to suit the needs of populations in varied settings throughout the world. Stepping Stones uses a series of 18 workshops with four groups of older men, older women, younger men, and younger women. At the end, the groups come together, and the entire community entertains “requests for change” as the groups perform dramas reflecting the lessons learned. A great strength of the Stepping Stones approach is that it works directly with a diverse group of community members to challenge harmful social norms within that environment.

An Ecological Model
Workshops with small groups of individuals in a community can be very powerful but can also be limited in creating large-scale social change. Once a workshop ends, participants return to a patriarchal society where change is not supported. To address this, many transformative programs with men have adopted an ecological model that addresses multifaceted aspects of an environment to effect personal and social change. This includes implementing small workshops; mobilizing communities; supporting local institutions such as schools, NGOs, and religious bodies to implement this work; working with media partners to conduct large-scale campaigns; and supporting government structures to develop supportive policies and legislation.

There are many excellent examples of this holistic ecological model. In South Africa, for example, EngenderHealth’s Men As Partners program establishes community action teams made up of workshop participants to promote
and sustain change in their personal lives and in their communities. The teams work closely with trained staff from NGOs to support events such as health fairs, community theater productions, and mural paintings with gender-related themes. Working together, team members reinforce a new social norm in which men take an active stand for HIV/AIDS prevention and the elimination of gender-based violence, also introducing this norm in the environments where they live.

Other NGOs have adopted a variety of creative ecological efforts. In Brazil, Instituto Promundo’s Project H implemented a lifestyle social marketing campaign that disseminated messages about gender equality through advertisements, peer promoters, and magazine articles. The campaign also associated gender equality with a specifically designed brand of condom.

Another example comes from India, where a coalition of local NGOs and gender activists established a statewide campaign called Men’s Action for Stopping Violence against Women, creating a social movement of men taking an active stand against gender-based violence. The campaign involves marches, rallies, and large community events that reach thousands of men.

Larger media efforts are also starting to take hold. In South Africa, a consortium of NGOs working on men’s issues has convinced the South African Broadcasting Corporation to devote news coverage and public service announcements to gender issues. Meanwhile, MenEngage—an international alliance of organizations working on gender issues—is recruiting national and international male celebrities to serve as gender equality ambassadors who will be mobilized to reinforce progressive gender social norms.

Challenges for the Future

The emerging movement of work with men and boys brings optimism and also challenges. As the field grows, programs are being challenged to scale up their interventions to reach larger numbers of men while also accounting for the complex nuances involved in adapting to different regions, countries, and communities. Programs cannot be generically replicated in new settings, and communities are initially likely to resist the idea of challenging existing gender norms. To address this, programs must identify gender activists and professionals from within communities to champion this work and navigate it in an appropriate manner. As these leaders initiate new male programming, they should always retain the shared operating principles of this important work: to always serve the shared interests of women and men, and to view men as a positive resource in creating a healthier, more gender-equitable world.
REFERENCE LIST


In ‘Remembrance

Sadly, Lynde Francis passed away on March 31, 2009 at the age of 62. Lynde will be remembered and respected around the world for her devotion to advocacy and education on all aspects of holistic management of HIV, as well as for her role as an advocate for the meaningful involvement of people living with HIV. She was a true pioneer who embraced life to the fullest and whose spirit will continue to inspire us all for generations to come.
Adopting Human Rights Standards in the Scale-Up of HIV/AIDS Care: Lessons Learned from Argentina, Botswana, and Thailand

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This chapter sets out three narrative summaries from resource-limited settings in three continents, across the global south. From Argentina in South America, to Botswana in sub-Saharan Africa, and across to Thailand in Southeast Asia, activists in the field strive for the adoption of human rights standards in the scale-up of HIV/AIDS care, premised on the most fundamental tenet of human rights: the dignity inherent in every human being. Human rights standards are best realized in a legally and socially enabling environment that upholds justice and respects equality. The arguments of proponents of a rights-based approach derive added strength in contexts where stigma still tends to be a central challenge to HIV/AIDS, in an era when, in principle at least, the primacy of human rights in the care and prevention of the epidemic is accepted. The challenges in this sphere are aggravated by increasing poverty, consumerism, and socioeconomic inequity in the age of globalization. Gender inequality, lack of sexual education, and the feminization of poverty and HIV/AIDS are more common in countries that are developing and/or in transition. These countries are also where certain members of society are particularly vulnerable, especially women, young people, people living with HIV/AIDS, and injecting drug users (IDUs).

ARGENTINA

Latin America and the Caribbean constitute a region with an enormous wealth disparity. In Argentina, recent economic decline has further widened the wealth gap and left an increasing number of impoverished people. This increase in poverty combined with the stimulation of consumerism by publicity geared toward adolescent boys and girls promoting eroticism, and poor access to sexual education, family planning services, and condoms as a result of religious influence, specifically the Roman Catholic Church, facilitate an increase of adolescent pregnancies and HIV infection. Studies have shown that...
adolescent pregnancy in Argentina increased specifically within the 10–14-year-old age group. Since 2004 the Argentine Ministry of Health reported that new HIV infections among young people 15–24 years old predominate in women over men. This increase of infection rates was also accompanied by an increase in poverty mainly affecting women and girls. According to the 2001 census, 70% of all young people in Argentina live in situations of poverty, and so do 43.6% of all women living in Argentina’s urban centers. This feminization of poverty has translated into the feminization of HIV/AIDS.

Since its creation, the Foundation for Studies and Research on Women (FEIM) has focused its approach on the right to information of adolescents and young people based on the Convention on the Rights of the Child (CRC) and the Convention on the Elimination of All Forms of Discrimination Against Women (CEDAW). FEIM works to promote access to information about sexuality and HIV/AIDS from a gender perspective through peer education. FEIM recognized the lack of understanding and knowledge on these issues among youth at a national awards event in 1994 when young people were asked to express their opinions and concerns about adolescent pregnancy. Many had romantic and conservative views on teen pregnancy and didn’t perceive the risk of HIV/AIDS because it is only associated with men who have sex with men, sex workers, and drug users. They were also unaware of their right to information and health care due to their ignorance of the CRC, and their right to health afforded by the constitution. They didn’t recognize sexual inequalities, women’s rights, or the impact of stereotyped gender roles. FEIM decided to train peer educators to reach out to young people who could become advocates themselves on issues of sexuality and HIV from a gender perspective based on human rights. This peer-based approach has been notably successful in Argentina. The United Nations Development Fund for Women (UNIFEM) and United Nations Children’s Fund (UNICEF) invited FEIM in 2000 to publish their experience in “Sexuality and Health in Adolescence: Theoretical and Practical Tools to Exercise Our Rights.”

It was out of this success that FEIM received funding to create a national network of young people to promote sexuality and HIV/AIDS prevention. This network, RedNAC (National Network of Adolescents and Youth for Sexual and Reproductive Health), has served as a structure for the multiplication of sexuality and HIV/AIDS awareness as well as advocacy training on these rights. Since its inception in 1999, RedNAC has been a point of reference for more than 5,000 young peer educators throughout the country.

FEIM and RedNAC took on the responsibility of raising awareness among secondary school students that otherwise have no formal access to sex education. The workshops highlight issues relating to sexuality and HIV from a gender perspective and raise awareness on the principles of the CRC, particularly the right to access education, information, and health care, as well as those of CEDAW. The workshops also encourage young people to access health-care services so that they may protect themselves from HIV infection and unwanted pregnancy. FEIM and RedNAC continue to successfully build the capacity of youth to secure their right to information on sexuality and HIV/AIDS in a Catholic and conservative country like Argentina. Challenges have included overcoming school authorities’ fears of being reported for allowing people to talk about sexuality and opposition from a number of professors. However, there has been support from the majority of parents and students, who have asked for and even demanded the workshops in their schools.
The Botswana Network on Ethics, Law, and HIV/AIDS (BONELA) was established in 2001 with the aim of facilitating the use of a human rights approach to the national response to HIV/AIDS. Initially a small organization with very limited resources, BONELA recognized early on that the main challenge of using a human rights approach to HIV in Botswana was the lack of understanding on the part of different stakeholders regarding the meaning and applicability of human rights in their own cultural, political, and social contexts. This lack of understanding was prevalent not only among community members engaged in diverse activities such as the provision of home-based care, testing and counseling, HIV treatment, and support of people living with HIV, but also among strategic decision makers such as heads of government agencies and parliamentarians.

Many national governments, including the government of Botswana, are committed to human rights as a convincing approach to HIV. The “Declaration of Commitment on HIV/AIDS,” which resulted from the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) in 2001, is widely supported by governments from around the globe and is an outstanding example of the international commitment to use a human rights–based approach to HIV. The declaration emphasizes the need for a realization of human rights and fundamental freedoms for all in order to reduce vulnerability to HIV/AIDS and further declares that the “respect for the rights of people living with HIV/AIDS drives an effective response.” Many national governments initially agreed in principle to the declaration, but it was not immediately clear how they would translate these principles into their national programs. A further difficulty in Botswana was the general lack of understanding of human rights concepts in all sections of society. In this environment, BONELA set to work. The first step was to sensitize as many community members as possible at all different levels of society on the link between human rights and HIV and in ways of adopting a human rights approach. It soon became evident that there was a need for contextualized and innovative training materials that could be utilized in different communities. In 2004 and 2005, BONELA engaged in an extensive project that involved researching, writing, and pilot testing its own training materials, resulting in the publication of Human Rights and HIV: A Manual for Action, a 14-module training program, partly bilingual (English and Setswana, the two national languages in Botswana). The aim of the manual is to increase awareness among all stakeholders on how to apply human rights concepts in their practice, in order to ensure nondiscrimination toward people living with HIV/AIDS. It also demonstrates how those who have experienced discrimination due to their real or perceived HIV status can be assisted. The manual covers a diversity of topics, such as HIV and the law, the right to health, confidentiality, sexuality, and human rights, and makes a concerted effort to discuss culturally sensitive topics such as the inclusion of sexual minorities in HIV care and prevention.

The questions posed most often when discussing human rights concepts in Botswana center around two themes: First, are human rights concepts applicable in Botswana, or are they imported Western concepts that are being imposed by international agencies and foreign governments? Second, is there a need to discuss human rights protections with regard to people living with HIV in a country that has undeniably set a new standard on the African continent by providing free antiretroviral medication? BONELA continues to answer both questions through their public education and advocacy. A starting point to contextualize human rights in Botswanan society is to explain them in relation to the local concept of *botho*, which can be roughly translated in English as “humanness.” It is
request BONELA to assist with training and education. The increased engagement with communities further highlighted the need for a greater understanding of provisions in Botswana law to counteract discrimination of all forms. In early 2005, BONELA started legal literacy workshops specifically aimed at people living with HIV and service providers to enable them to understand existing legislation with regard to discrimination and HIV. Of particular importance in this area is the understanding of labor laws. These workshops are facilitated by the BONELA legal officer, a lawyer by training, who also facilitates legal aid clinics during those workshops in all the geographic areas of Botswana.

However, the increased awareness of stakeholders with regard to the law has also brought to light the many human rights challenges experienced by people living with HIV. Although BONELA initially offered only very limited legal services, the organization now runs a full legal aid clinic that represents people who have experienced discrimination based on their real or perceived HIV status. Botswana does not provide legal assistance to those who are poor or disadvantaged, and the BONELA legal clinic addresses an obvious gap in this regard. It is disappointing to see the increasing number of clients who are seeking help from the clinic, indicating the dire need for more stringent laws to protect people from HIV-related discrimination, in particular at the workplace. Law reform is only one strategy to protect people from possible discrimination, and such reforms will need to be accompanied by public education about the laws and the monitoring and enforcement of such laws. In an attempt to make legal advice available to an even greater number of people, BONELA also has run a regular call-in show on national radio since mid-2007.

In the past three years, BONELA has made the training of health workers and people infected with HIV a priority in all education activities. Training is based on the understanding that the provision of
high-quality care needs to be carried out within an environment that protects and promotes human rights. As noted above, Botswana provides antiretroviral therapy (ART) in its public health facilities. However, it has become increasingly clear that many patients are not well informed about the medication they are taking. Ignorance about antiretrovirals (ARVs), biomedical issues with regard to HIV infection, and appropriate therapy for HIV and opportunistic infections often makes it difficult for patients to make informed choices about their health. With this in mind, BONELA created a coalition of civil society groups on treatment literacy, which resulted in a Treatment Literacy Program managed by BONELA. The program utilizes community treatment literacy trainers who, in turn, educate communities on treatment literacy issues. Repackaging scientific medical information to be easily communicated among community members is a first step in empowering communities to take charge of their own health and making them active participants in their health care. Ideally, this program will result in many informed and active community members who will monitor government services and vigorously contribute to the provision of adequate and high-quality care services to people infected with HIV in Botswana.

BONELA has been successful in training communities at the grassroots and institutional levels. However, it has been difficult to communicate a human rights approach successfully to policymakers, decision makers, and parliamentarians. People at these levels may be present at international gatherings during which human rights standards are agreed upon, but they are difficult to reach in terms of in-depth training on the practical application of a human rights approach. It is imperative that organizations, such as BONELA, enter into creative partnerships with institutions within government to initiate innovative, interesting, and targeted trainings on HIV and human rights that will be accepted by policymakers and opinion leaders.

THAILAND

The government likes to say there are no more injecting drug users. Well, they are sort of right. Thanks to them, we’re all in prison, or in heaven. —Paisan Suwannawong

On International Human Rights Day (December 10), 2002, 50 drug users (primarily IDUs, many HIV-positive) organized in Bangkok to found the country’s first network of people who use drugs. “If we don’t do it, nobody will,” said one HIV-positive former user. “How much longer can we watch our friends die of AIDS, in prison, untreated, with no dignity?” Its seminal project was a peer-to-peer human rights documentation project among IDUs that examined barriers to accessing health-care services and abuses by law enforcement officials and within the criminal justice system. That historic meeting in December was a report-back on the findings and on how to move advocacy forward, ultimately leading to the birth of the Thai Drug Users’ Network (TDN).

The network committed itself to “promote the basic human rights of people who use drugs, in order to be able to live equally and with dignity in society.” For nearly 20 years, the government had ignored a staggering HIV epidemic among people who inject drugs and, despite a 50% prevalence rate, eschewed evidence-based approaches including methadone maintenance and distribution of clean injecting equipment for a “just say no” approach to drugs that relied on law enforcement rather than public health principles and strategies. Later, as antiretroviral therapy became increasingly available through the government’s generic production and national health insurance schemes, the lack of access by people who use drugs was another acute injustice.

From TDN’s perspective, the time was right for drug-user activism to bring attention to the critical human rights situation: within two months of TDN’s founding, the government announced a
“war on drugs” of unprecedented severity; and within the crackdown’s first three months, more than 2,000 people were extrajudicially executed. Tens of thousands more were arbitrarily arrested and detained and forced into military-run boot camps to clear their names from blacklists. Yet the public, including AIDS and human rights nongovernmental organizations (NGOs), was largely silent. The climate of fear induced by the repressive nature of the campaign and strong-arm measures used to implement it was overwhelming but did not hamper TDN’s activism. “What do we have to lose?” said one cofounder. “How can I live with myself as thousands die and with no one speaking out about the injustices that are being committed? How will I feel later, looking back on this time, if I stay silent?”

TDN’s first demonstration was a march on the Government House, where they held a mock funeral for those who had died of AIDS or were killed in the drug war, and demanded the prime minister stop the drug war and investigate the killings. Protestors carried signs proclaiming, “Thai government drug policy = Drop Dead!” and “Protect the rights of people who use drugs.” Body bags and funeral wreaths were set up in front of the gates of the prime minister’s offices.

Over the next months and years, TDN used numerous strategies to bring national and international attention to the health and human rights crises facing people who use drugs in Thailand. As the drug crackdown worsened, the prime minister and other government officials made regular pronouncements in the media that people involved with drugs were “enemies of the state” and a “threat to national security” warranting harsh punishment and imploring local citizens to get involved in surveillance and reporting. TDN approached numerous government bodies including the parliament and the National Human Rights Commission, and even implored the king to intervene and stop the abuse and killing.

TDN contacted allies across the globe to help organize an “International Day of Solidarity against the Thai War on Drugs,” where activists in at least a dozen countries from South Africa to Nepal brought the network’s demands to their Thai embassies and spoke out against the human rights violations on Thai drug users to the media, attracting global attention. TDN raised the visibility of the government’s failure to respect and protect the rights of people who use drugs at two major international conferences held in Thailand, the International Conference on the Reduction of Drug-Related Harm (2003) and the International AIDS Conference (2004), belying Thailand’s claims of success in responding to HIV/AIDS and promoting “access for all.”

Human Rights Watch conducted a special investigation into HIV, drug use, and the war on drugs at TDN’s request, and UN Special Rapporteurs were at the same time condemning Thailand’s lack of attention to the negative impact of its approach and requesting urgent investigation into the drug war killings. TDN’s harm reduction proposal for US$1.3 million was granted by the Global Fund in 2003, the first award of its kind to a community group and one which had bypassed its country-coordinating mechanism due to the political sensitivity of the issue.

TDN has made efforts to promote the involvement of people who use drugs in national policymaking and programming and to spearhead peer-driven services and advocacy campaigns to demand that the government fulfills its human rights obligations, in particular the rights to life and health for people who use drugs. Despite these efforts, the criminalizing and stigmatizing environment continued to push people who use drugs to the margins and undermine their efforts at every turn. Despite amendments to the drug laws that reclassify certain drug users as “patients,
not criminals,” police continue to interfere with access to methadone and other services. Despite the abolition of nonmedical exclusion criteria for ART access due to TDN’s own advocacy, people who use drugs (and even methadone patients) are routinely denied access at the hospital level. Extreme ignorance and discrimination by health-care providers and others in society and deeply entrenched political aversion to legally recognizing people who use drugs as people with dignity and rights conspire to push drug users further underground and away from essential information, services, and support.

People who use drugs continue to be subjected to compulsory drug treatment of no proven efficacy, mandatory testing without counseling, substandard or denial of HIV treatment, lack of access to information, unequal treatment before the law, and numerous other injustices. UN agencies working in Thailand, particularly the Joint United Nations Program on HIV/AIDS and United Nations Office on Drugs and Crime, have not responded positively to TDN’s requests for assessments of the impact of the drug war and criminal justice approach on drug users’ enjoyment of basic human rights.

TDN and other drug user advocates recognize that people who use drugs should and must be at the center of the response to the health and rights situation of their community; however, without a conducive legal and social environment to promote and support their empowerment and access to information and skills, as well as active participation in planning and programming, people who use drugs will continue to be subject to increased vulnerability to HIV, hepatitis, overdose, incarceration, and further risks without equal access to remedies and equal treatment before the law. History will continue to repeat itself until the government and other complicit actors are held accountable.

**REFLECTIONS AND RECOMMENDATIONS**

The following reflections distill recommendations from some of the more successful efforts in this area, while documenting important lessons learned from less successful efforts:

- Although human rights should be a core element in the global struggle against HIV/AIDS, they often constitute the missing link, especially in practice. Making the transition from theory to practice is a key challenge in adopting human rights standards in the scale-up of HIV/AIDS care, support, prevention, and treatment. Efforts should focus on program implementation that treats human rights as an inherent part of the comprehensive care framework. This will help move us forward in both the human rights and HIV/AIDS arenas.

- A range of proactive strategies can be successfully adopted in promoting rights-based approaches, including (where appropriate) peer-based approaches and gender perspectives. Actions taken should include training for sensitization, awareness raising, and education and capacity building and should target peer educators, focal people, community activists and members including people living with HIV/AIDS, health-care providers at different levels (grassroots and within institutions, e.g., government, private, NGO), and communities at large. The creation of a group of key stakeholders for the application of human rights standards to the national response to HIV is important. Methodologies used can include workshops, legal and treatment literacy programs, advocacy, legal aid, comprehensive training materials, peer-to-peer human rights documentation projects, and legal and policy review aimed at reform. Strategies may sometimes be more extreme and/or reactive, when necessitated by the immediacy of the situation.
• Policy and programming need to be evidence based and take account of public health principles and human rights. People surviving at the margins of society tend to get excluded, stigmatized, and criminalized by unequivocal adherence to law enforcement and the criminal justice system, which predate the realities of HIV/AIDS. Human rights standards mandating elimination of discrimination through ignorance and prejudice would complement rather than contradict public health objectives.

• Contextualization/assimilation of concepts related to human rights that are ingrained in local cultures makes the ostensibly “Western” ideology of human rights more acceptable to non-Western societies. At times, these indigenous human rights principles can be used to help discuss issues when political, cultural, and religious beliefs pose barriers to the equitable scale-up of prevention and care services.

• Policymakers and administrators at the highest levels have often been the least receptive to human rights concerns, leading to suggestions of targeted training and innovative approaches. There appears to be a lack of understanding between activists and political leadership, manifested at different levels, ranging from apathy and indifference to outright abuse. This is both unfortunate and ironic, given that human rights as well as related responsibilities are an embodiment of the very obligations undertaken by governments in international relations, policy, and law. Here it is important to recognize the space between entrenched political power and social activism, which provides ground for constructive engagement by all parties and a role for academics, jurists, judges, and other independent stakeholders in the quest for responses that seek to reconcile conflicting interests. Where national governments have been uncompromising, international institutions, the media, and pressure at global, regional, and national levels have been helpful in promoting the human rights dimension.

• Scientists and state officials at key decision-making levels need to be more open to human rights and social realities. Given the cross-cutting nature of HIV/AIDS, responses require all parties, including activists, to transcend the comfort of their own fields to understand the unknown. Traditionally belonging to the disciplines of public health, medicine, and the natural sciences, the all-embracing nature of the epidemic leads to its consideration in the social sciences including law, policy, economics, and sociology. In relation to research methodologies to ground policy, most research in relation to HIV/AIDS still involves only or mostly quantitative study. HIV/AIDS and responses to it, however, involve a range of social and human factors. These are less measurable and amenable to quantitative study, and essentially require qualitative study.

• Human rights and HIV/AIDS discourse would benefit from the overall understanding that this linkage is not unique, isolated, or revolutionary. The link is natural, logical, and established in theory. Beyond HIV/AIDS, it is part of a slow evolution, involving a broader paradigm shift in policy at the national, regional, and global levels that includes good governance; human security (and not merely state and national security); and human, social, and sustainable development including rights-based approaches to development. Key values common to each of these approaches include protection, inclusion, and nondiscrimination; access to information and to support and services (especially health care and education); justice and legal redress; participation and empowerment; and transparency and accountability. All these approaches tend to be people centered, and people affected by related policies, planning, and programs need to play a decisive role.
• When many varied interests lie in one-and-the-same terrain, conflicts arise. For instance, the interests of human rights may sometimes appear to run counter to the interests of public health. Contradictions, whether apparent or real, can be eliminated through appreciating the complexities that arise in a multidisciplinary field; by balancing conflicting interests, for example through laws, policies, and programs that involve multisectoral responses; and most of all, through understanding the cyclical relationship between HIV/AIDS and human rights: when stigma and discrimination are a primary challenge, responses need to address this reality; just as people with HIV/AIDS experience abuse of rights, vulnerability to HIV/AIDS thrives on violations of rights. To break this vicious circle, we need to integrate human rights standards in the scale-up of HIV/AIDS care as well as prevention.
REFERENCE LIST


HIV Care, Treatment, and Prevention in Conflict Settings

Susan Purdin, Wendy Venter, and Roxanne Saucier

International Rescue Committee, United States

IN THIS CHAPTER WE DESCRIBE ISSUES that the International Rescue Committee (IRC) has encountered when addressing HIV in war zones—settings where human rights violations are rampant and providing HIV programming is fraught with challenges. First we discuss the characteristics of humanitarian crises. We then cover the variables of the HIV epidemic in these settings. Next we explore the unique challenges and opportunities of providing assistance in these settings. Finally, we provide case studies and lessons learned illustrating IRC’s experiences in selected field sites and a framework used to guide such interventions.

CHARACTERISTICS OF HUMANITARIAN CRISSES

A humanitarian crisis is defined as a situation that “threatens the lives and well-being of large numbers of people and requires extraordinary action to ensure their survival, protection, and adaptation.” Humanitarian crises may result from natural disasters or armed conflicts; in this chapter we focus on humanitarian crises in the context of armed conflicts as these are the settings where IRC operates. Founded in 1933, the IRC is a global leader in emergency relief, rehabilitation, protection of human rights, postconflict development, resettlement services, and advocacy for people uprooted or affected by conflict and oppression.

In the past 50 years, violent conflicts have taken the lives of millions of civilians and displaced tens of millions more. Current global estimates show that more than 38 million people are living as forced migrants, having fled their homes as the result of conflict. There are an estimated 13.9 million refugees (people who “owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion are outside their country of nationality”). An additional 24 million people have fled conflict seeking safety but have not crossed an international border; they are called internally displaced persons (IDPs). The vast majority of conflict-related displaced people reside in resource-limited settings—either within the country experiencing conflict or the country hosting refugees.

Conflict and HIV intersect dramatically in sub-Saharan Africa. The region not only is the most affected by the AIDS pandemic but also is profoundly affected by the movement of people fleeing conflict and persecution. The 22.5 million people living with HIV in sub-Saharan Africa constitute...
nearly 90% of the children and 68% of the adults infected with HIV worldwide. In this region, where 21 countries are experiencing ongoing political conflicts, 76% of the world’s AIDS-related deaths (1.6 million) occurred in 2007.7-9 A humanitarian crisis is usually seen as a sudden event that threatens life and results in large population movement. An example of this type of crisis is the flight of Rwandans to the Democratic Republic of Congo (then Zaire) and Tanzania in 1994. However, many humanitarian crises persist; conflicts can take years to resolve and the average length of stay for refugees in host countries is more than 16 years. For example, camps hosting Burmese refugees along the Thai-Burma border have been in existence since 1984, and Palestinians have been living as refugees since 1948.4 Levels of insecurity within a conflict situation fluctuate, forcing people to endure the ebb and flow of battle and resulting in recurrent episodes of flight and return. Darfur, Sudan, is a current example of an ongoing, unstable conflict setting. Humanitarian crises do not progress from one phase to the next in a linear fashion, and different scenarios may coexist in various regions of a single country. Consequently, IRC’s health programming is adapted across contexts. Table 1 describes a range of scenarios and relevant health objectives to guide interventions in such settings.

The provision of humanitarian relief is intended as a short-term input to alleviate the effects of crisis. As soon as feasible in any phase of a crisis, the emphasis of our programming shifts from provision of direct care to strengthening of local health institutions that will be able to provide for the good health of the population in the longer term.

### HUMANITARIAN CRISIS AND HIV: UNCERTAIN LINKS

The factors influencing the HIV epidemic in humanitarian crises are complex. HIV thrives in situations of poverty and inequality, which are endemic in conflict, but there is evidence as well that certain realities of conflict and displacement have had a protective effect against the proliferation of the epidemic. Our overview of the intersection

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<th>Table 1. Health Objectives in Various Phases of Humanitarian Crises (IRC)</th>
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<td><strong>Humanitarian crisis scenario</strong></td>
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| Acute crisis | Reduce excess mortality  
Sustain life with dignity |
| Protracted crisis:  
- Stable: long-term camps  
- Unstable: ongoing or intermittent insecurity | Increase access to essential health services in displaced and host communities  
Build capacity of displaced health staff and host community staff  
Prepare for further acute emergencies |
| Durable solutions:  
- Repatriation/internal resettlement of internally displaced persons  
- Local integration  
- Third-country resettlement | Provide support to facilitate return or resettlement  
Ensure information and coordination between origin and destination  
Ensure access of returnees to health services |
| Reconstruction | Restore health services  
Reconstruct and develop sustainable health systems |

Source: International Rescue Committee.
between HIV transmission and situations of armed conflict reflects Paul Spiegel’s work with the United Nations High Commissioner for Refugees (UNHCR) in exploring this question.10

One factor in conflict settings that favors the transmission of HIV is the disruption of communities that results in altered sexual networks. When a community is hit by conflict, the social structure is fractured as people follow various paths to seek safety—neighbors turn against one another to ally with opposing ethnic or political sides, and people flee in whatever direction holds the most promise. Family units are broken as some are killed, some join fighting forces, some flee, and some are separated during flight. Having fled with only the clothes on their backs and absent traditional social and family support, women, girls, and young boys may exchange sex for survival—a reality that carries with it the risk of HIV transmission.11 Another factor contributing to HIV transmission is the lawlessness that is inherent in conflict, which results in increased incidence of sexual violence. Rape has been associated with violent conflict for centuries, both as a weapon of war and as opportunistic exploitation in situations where law and order have broken down.12 Forced sexual intercourse traumatizes delicate tissues and increases the likelihood that HIV transmission will occur.13 A third factor supporting HIV transmission in conflict settings is the destruction of infrastructure and disruption of health services. People no longer have access to preventive HIV programming such as health education, care for sexually transmitted infections, safe blood transfusions, prevention of mother-to-child transmission of HIV services, or even condoms. The aftermath of conflict is also a period of increased vulnerability to HIV transmission as populations emerging from extended periods of instability have been shown to lack basic information about HIV,14 and reopened access routes bring truck drivers, migrants, and humanitarian workers from higher prevalence settings into areas previously isolated from HIV.

While several risk factors are present, other circumstances mitigate HIV transmission. Conflict zones are insecure areas where normal commerce stops and populations are isolated from exposure to external sources of the virus. Refugees benefit from humanitarian agencies that provide health information and services, including treatment of sexually transmitted infections and access to antiretroviral drugs. Returnees have better knowledge of HIV and adopt less risky behaviors than the nondisplaced.15 Isolation of populations in refugee camps or insecure areas and reduced mobility to high-prevalence urban settings also limit interactions with higher prevalence sexual networks, thereby limiting exposure to the virus.

The awareness of increased risk of HIV transmission among people affected by conflict has led to the assumption of rapid rises in HIV prevalence among people affected by conflict. However, evidence in this regard is mixed. Clearly the HIV epidemic flourished during the years of civil conflict in Uganda and declined after peace was restored to most of the country. On the other hand, despite the increased risk of HIV transmission at the individual level during rape, there is as yet no evidence that widespread incidence of rape results in increased HIV prevalence at the population level. Additionally, research in sub-Saharan Africa showed lower HIV prevalence among the camp residents in 9 out of 12 camps studied as compared with the surrounding host population (two others had a similar prevalence and one a higher prevalence).16 For example, Angolan refugees living in Namibia and Zambia were found to have a much lower HIV prevalence (5%-10%) than their host populations (25% and 15% in the areas surrounding the camps), but higher rates than in Angola (which had a prevalence of 1%-4% in areas of return).17
Although the relationships between conflict, displacement, and HIV transmission are multifaceted and require further study, key factors that influence the spread of HIV in displaced populations include HIV prevalence in country or area of origin, HIV prevalence in communities hosting the displaced population, and the degree of interaction between displaced population and surrounding communities.\textsuperscript{10}

**CHALLENGES AND OPPORTUNITIES IMPLEMENTING HIV-RELATED INTERVENTIONS**

Challenges to implementing HIV-related interventions in the setting of a humanitarian crisis have much in common with the challenges that are present in resource-limited settings generally. These include lack of sufficient numbers of qualified human resources; lack of infrastructure, equipment, and supplies; lack of financial resources; lack of leadership and accountability among public servants; and enduring denial, stigmatization, and discrimination.

Settings of conflict and displacement do, however, present some unique challenges. Staffing shortages are exacerbated as health workers are injured or killed when violence erupts. Additionally, skilled health workers, like other community members, flee the conflict and seek employment outside the conflict zone. Recruitment and retention of qualified staff who are willing to work in isolated, insecure environments is an ongoing challenge for humanitarian agencies, and governments engaged in internal conflict routinely impose bureaucratic obstacles via visa and work-permit requirements.

Shortage of financial resources dedicated to HIV programming presents a significant obstacle to addressing the disease in conflict settings. When war threatens a government, it is common to divert funding from health or other social services to shore up military forces. External donor funding for health services in humanitarian crises is provided in six-month to one-year grants—unrealistic timing for risk-behavior and stigma-reduction activities. Such short-term funding aims to deliver urgently needed minimum services but fails to respond to the reality of protracted crises where conflict and insecurity continue for a decade or more.

Logistics are another challenge, as insecurity, remote location, and ever-deteriorating road conditions impede the provision of necessary medicines and supplies.

Language and cultural differences between humanitarian staff and beneficiary populations present another notable challenge. The presence of various national, ethnic, religious, and linguistic groups in one camp requires diverse approaches to HIV-related services within a single program. For example, the population of Kakuma Refugee Camp in northern Kenya consists of Sudanese, Somalis, Rwandans, Burundians, and Ethiopians, representing Muslim and Christian beliefs as well as several languages.

The breakdown of social structures also hinders HIV care as the loss of family members results in a lack of support for people living with HIV.

For too long the assumption that HIV-positive people affected by conflict would not adhere to their drug regimen held up their access to antiretroviral (ARV) medications. At the Barcelona AIDS conference in 2002, Médecins Sans Frontières (MSF) dispelled this myth by presenting evidence of good ARV adherence by a cohort of refugees.\textsuperscript{18} Another argument for denying refugees access to ARVs was the expectation that they would likely someday return to a location where treatment was not available. However, efforts by the U.S. Bureau for Population, Refugees, and Migration along with UNHCR and IRC have built upon MSF’s work to make ARVs available to refugees worldwide. The challenge of repatriation is to provide refugees with sufficient medication for the transition period and
ensure that they are able to access HIV services at their destination point.

Despite the many challenges, HIV programming is being undertaken in humanitarian crises. In 2003, the United Nations Inter-Agency Standing Committee produced guidelines on addressing HIV in emergencies. Governments and international organizations do provide financial, technical, and direct assistance to conflict-affected populations. Humanitarian health agencies offer free health services, allowing access for people previously unable to afford care.

The presence of nongovernmental organizations (NGOs) improves the situation in other ways. Besides funding, NGOs bring technical expertise and logistical capacity. NGO programs include capacity-building activities for refugee and host country staff, thus helping to develop the health workforce. Collaboration among NGOs and government services improves the quality of care for both displaced and host populations.

Humanitarian crises can provide unique opportunities for HIV interventions. Camp populations are clearly defined, basic population data are available, and people are logistically easier to reach. The enclosed environment facilitates health education, access to services, client follow-up, and partner notification. Also, high-risk groups, such as members of the military and sex workers, may be more accessible in a crisis setting than they in a non-militarized, stable situation. During postconflict reconstruction, infrastructure and services that were inadequate before the crisis can be upgraded for the benefit of some of the most underserved people in the world.

**CASE STUDIES**

In this section we describe two of IRC’s experiences implementing HIV programs serving people affected by years of conflict in Sudan.

**Case Study One: HIV Programming during the Reconstruction Phase in Southern Sudan**

The IRC works collaboratively with returnee, IDP, and host populations in Southern Sudan striving to rebuild war-torn communities. Decades of conflict have left Southern Sudan with a dearth of qualified health workers, extremely poor transportation and communication systems, and a limited range of HIV control activities. While visiting IRC sites in Rumbek and northern Bahr el Ghazal in Southern Sudan in 2007, Susan Purdin (IRC’s health advisor for Sudan and a co-author of this chapter) helped facilitate a workshop with teachers and high school students in preparation for World AIDS Day. Participants eagerly discussed all aspects of HIV and AIDS, including voicing opinions that revealed persistent denial and stigma within the community. One teacher denied that HIV existed in the country at all, and other participants (teachers and students) suggested that HIV-positive people should be isolated from the rest of the population. While voluntary counseling and testing was being promoted, with significant numbers of people being tested, support services for people who test positive were limited. Because of intense stigma, people often disappeared after receiving positive results, and no one was participating in post-test support activities. Figure 1 shows the number of people tested in Rumbek and the cumulative total of those who tested HIV-positive from 2005 to 2007.

Unfortunately, at the time of this visit, the HIV project was funded only for prevention activities, and treatment was not available in Rumbek for those who tested positive. And, while previously offered, the supply of nevirapine for use in prevention of mother-to-child transmission of HIV had run out.

On the positive side, condoms were in high demand, and new, locally fabricated boxes dispensing free condoms were distributed widely. Education on HIV prevention was being offered through many
The IRC has provided health services in Kakuma Refugee Camp since 1992 and as of 2008 was serving more than 60,000 refugees. The camp is populated primarily by Southern Sudanese, with smaller populations from seven other countries, representing a total of 40 ethnic groups. The IRC HIV program provides a comprehensive HIV prevention, care, and treatment package. As of February 2007, more than 100 people were receiving antiretroviral therapy (ART) through the IRC clinic in Kakuma camp. HIV-positive people are referred to partner agencies for additional services such as nutritional and livelihood support.

In the interest of equity, IRC also includes the host population in HIV interventions. Initially, the community’s nomadic lifestyle and insecurity in the district made provision of services difficult.

Lessons learned in this program include the following:

- Even in a setting long-isolated by conflict, community education programs can promote the uptake of testing services despite deep-seated stigma and denial.
- In a postconflict setting, extraordinary attention is required to maintain a reliable drug supply, which is essential for sustained implementation of prevention of mother-to-child transmission programs.

Case Study Two: HIV Interventions in a Protracted Emergency—Kakuma Refugee Camp, Kenya

The IRC has provided health services in Kakuma Refugee Camp since 1992 and as of 2008 was serving more than 60,000 refugees. The camp is populated primarily by Southern Sudanese, with smaller populations from seven other countries, representing a total of 40 ethnic groups. The IRC HIV program provides a comprehensive HIV prevention, care, and treatment package. As of February 2007, more than 100 people were receiving antiretroviral therapy (ART) through the IRC clinic in Kakuma camp. HIV-positive people are referred to partner agencies for additional services such as nutritional and livelihood support.

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<table>
<thead>
<tr>
<th>Program Area / Intervention</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Prevention</strong></td>
<td></td>
</tr>
<tr>
<td>Behavior change communication (BCC)</td>
<td>Mass media campaigns, Community outreach</td>
</tr>
<tr>
<td>Condom distribution</td>
<td>Provision of male and female condoms</td>
</tr>
<tr>
<td>Gender-based violence (GBV) prevention and response</td>
<td>Advocacy against violence and exploitation and promote awareness of gender rights, Training of staff in codes of conduct, Ensuring health-care services for survivors of GBV, Establishment of a coordination mechanism for GBV prevention/response</td>
</tr>
<tr>
<td>Medical transmission</td>
<td>Universal precautions, Blood transfusion safety</td>
</tr>
<tr>
<td>Postexposure prophylaxis (PEP)</td>
<td>HIV prophylaxis for occupational and nonoccupational exposure (including survivors of rape)</td>
</tr>
<tr>
<td>Testing and counseling</td>
<td>Client-initiated testing and counseling, Provider-initiated testing and counseling</td>
</tr>
<tr>
<td>Prevention of mother-to-child transmission</td>
<td>Provider-initiated testing and counseling for pregnant women and partners, Antiretroviral prophylaxis for mother and infant, Infant feeding support</td>
</tr>
<tr>
<td>Comprehensive management of sexually trans-mitted infections</td>
<td>Syndromic management with counseling, condom provision, partner notification, and referral for HIV testing and counseling</td>
</tr>
<tr>
<td><strong>HIV Treatment, Care, and Support</strong></td>
<td></td>
</tr>
<tr>
<td>Comprehensive care package</td>
<td>Antiretroviral therapy, Prevention and treatment of opportunistic infections, Psychosocial support, Palliative care, Provision of nutritional support, bed nets, safe water, and sanitation, Socioeconomic support, Care and support of orphans and other vulnerable children</td>
</tr>
<tr>
<td><strong>Laboratory Infrastructure</strong></td>
<td></td>
</tr>
<tr>
<td>Laboratory infrastructure</td>
<td>Development and strengthening of laboratory facilities to support HIV/AIDS activities</td>
</tr>
</tbody>
</table>

(continued on next page)
Lessons learned from the Kakuma Refugee Camp are as follows:

- The prospect of refugee return is not a reason to limit access to ART for displaced people. Proper planning and communication ensures that returnees will be able to continue treatment.
- Working with local organizations can improve access to mobile populations and insecure areas.
- Extending services to the host community diffuses tensions between refugee and host populations and is effective in reducing the spread of HIV that results from interaction between the two populations.

IRC has worked around these challenges by funding local organizations that can more easily access insecure locations and by providing ARVs to trained members of the nomadic community for distribution to HIV-positive individuals as they travel together.

One of the challenges facing the program is the expected repatriation to Southern Sudan and the need for returnees receiving ART to continue their treatment. Efforts have been made to identify locations within Southern Sudan where ART can be accessed and this information has been provided to refugees on ART.

<table>
<thead>
<tr>
<th>Program Area / Intervention</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategic Information</td>
<td></td>
</tr>
<tr>
<td>Monitoring and evaluation</td>
<td>Development of indicators with clear definitions and targets for each program activity</td>
</tr>
<tr>
<td></td>
<td>Use of appropriate data collection tools</td>
</tr>
<tr>
<td></td>
<td>Development of flowcharts from raw data collection to analysis, utilization, and dissemination</td>
</tr>
<tr>
<td>Policies and Systems</td>
<td></td>
</tr>
<tr>
<td>Coordination</td>
<td>Development of mechanisms of coordination among sectors and organizations, e.g., BCC participants</td>
</tr>
<tr>
<td>Organizational Policy and Strategy</td>
<td>Dissemination of standardized guidelines and policies</td>
</tr>
<tr>
<td>HIV/AIDS in the Workplace</td>
<td>Prevention, treatment, care, and support among staff</td>
</tr>
<tr>
<td>Capacity Building</td>
<td>Training and mentoring of staff, partners, and communities</td>
</tr>
<tr>
<td></td>
<td>People living with HIV and community participation in program design, implementation, and evaluation</td>
</tr>
<tr>
<td>Advocacy</td>
<td>Use of quantitative and qualitative information to illustrate achievements and needs</td>
</tr>
<tr>
<td></td>
<td>Involve people living with HIV/AIDS</td>
</tr>
<tr>
<td></td>
<td>Promotion of best practices</td>
</tr>
</tbody>
</table>
Preparedness and a comprehensive response. These guidelines are currently undergoing revision, primarily to update them to include the provision of ART, an intervention that should not be withheld from any medically eligible person, regardless of the setting.

Conclusion

The factors affecting HIV in conflict-affected populations are varied and complex, and the humanitarian aid associated with crisis situations brings unique opportunities to prevent the spread and mitigate the effects of the HIV epidemic. The challenge for humanitarian organizations is to understand the context, take measures to reduce the risks, and seize opportunities to provide information and services.

An effective approach to HIV in humanitarian crises involves adaptation of interventions to suit the emergency scenario, cultures of the displaced and host communities, levels of awareness of HIV, existing state of health-care systems, availability of human and financial resources, and anticipated time frame of the intervention. Experience has shown that, even with limited resources and challenging settings, quality interventions to provide HIV prevention, care, and treatment are possible and, indeed, imperative.

### A Framework for HIV Interventions in Humanitarian Crises

IRC’s HIV interventions across the various phases of humanitarian crises include a continuum of activities within a comprehensive framework. Specific activities should be introduced according to the particular phase of the crisis (see Table 2). Cutting across the framework are three key considerations: addressing the needs of survivors of gender-based violence, promoting youth-friendly services, and including people living with HIV in the planning and provision of services.

### International Standards

Despite the diversity of contexts, there are internationally agreed-upon guidelines for HIV interventions in emergency settings. The Sphere Project has published internationally recognized minimum standards of disaster response. These include minimum standards for the control of HIV (Box 1).

Mentioned previously, the Inter-Agency Standing Committee Guidelines for HIV/AIDS Interventions in Emergency Settings present cross-sectoral HIV-related interventions for both emergency preparedness and a comprehensive response. These guidelines are currently undergoing revision, primarily to update them to include the provision of ART, an intervention that should not be withheld from any medically eligible person, regardless of the setting.

### Box 1. Sphere Project Key Indicators for the Control of HIV/AIDS

The following indicators are from the Sphere Handbook, which contains recommendations for minimum standards in disaster response.

<table>
<thead>
<tr>
<th>Key Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>People have access to the following essential package of services during the disaster phase:</td>
</tr>
<tr>
<td>- free male condoms and promotion of proper condom use</td>
</tr>
<tr>
<td>- universal precautions to prevent iatrogenic/nosocomial transmission in emergency and health-care settings</td>
</tr>
<tr>
<td>- safe blood supply</td>
</tr>
<tr>
<td>- relevant information and education so that individuals can take steps to protect themselves against HIV transmission</td>
</tr>
<tr>
<td>- syndromic case management of sexually transmitted infections</td>
</tr>
<tr>
<td>- prevention and management of the consequences of sexual violence</td>
</tr>
<tr>
<td>- basic health care for people living with HIV/AIDS</td>
</tr>
</tbody>
</table>

Plans are initiated to broaden the range of HIV control services in the postdisaster phase.

*Source: The Sphere Project, 2004.*

International Standards

Despite the diversity of contexts, there are internationally agreed-upon guidelines for HIV interventions in emergency settings. The Sphere Project has published internationally recognized minimum standards of disaster response. These include minimum standards for the control of HIV (Box 1).20

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18. Médecins Sans Frontières. Presented at: 
14th World AIDS Conference; July 7-12, 2002; 
Barcelona, Spain. Poster TuPeB4660.

19. Inter-Agency Standing Committee (IASC). 
Guidelines for HIV/AIDS interventions in 
emergency settings. Geneva, Switzerland: 
WHO/IASC; 2003.

20. The Sphere Project. Humanitarian charter 
and minimum standards in disaster response. 
There is little doubt that Sub-Saharan Africa is in the midst of an HIV/AIDS emergency; children, women, and men are all caught in the crossfire of this relentless epidemic. Much attention has been paid to the impact of the epidemic in this region on women, sex workers, young people, and other vulnerable populations; but research and interventions targeting men who have sex with men (MSM) have been conspicuously absent. According to a 2007 report from the International Gay and Lesbian Human Rights Commission entitled “Off the Map,” there are a number of troubling explanations for this lack of response on the part of key HIV/AIDS stakeholders, including homophobic stigma and denial; restrictive international reproductive health policies; the mixed record of international and domestic nongovernmental organizations with regard to responding to the needs of same-sex-practicing people; the lack of sufficient skills and resources among lesbian, gay, bisexual, and transgender organizations in Africa; and the lack of political space in which to effectively advocate for access to HIV-related services and other health-related human rights at the domestic, regional, and international levels.¹

At a meeting of Schorer (the Dutch gay and lesbian health service provider) in September 2007, a number of civil society organizations, policymakers, and researchers came together to highlight the absence of appropriate research targeting MSM (and women who have sex with women, WSW) in the context of HIV/AIDS. The questions that arose were not only concerning the absence of data on HIV infections among these categories of vulnerable populations, but also the absence of an understanding of appropriate, evidence-based preventive measures. Similar questions emerged at an international meeting of key stakeholders working in the area of gender, same-sex sexuality, service delivery, and health in Pretoria, South Africa, in May 2007.²

No discussion of HIV/AIDS is possible without consideration of the issues that shape its interpretation and meaning, such as sex, sexuality, and disease. These related concepts are themselves often subject to a variety of misconceptions and stereotypes. The brief discussion presented here offers some perspective on these issues (within the context of HIV/AIDS) as well as the concept of homossexuality as it relates to the HIV epidemic in sub-Saharan Africa.
TERMINOLOGY: SEX, SEXUALITY, AND DISEASE

Sexuality, while viewed by many as an intimate, personal domain, is in actuality regulated and policed by many powerful external forces, including culture, politics, law, religion, and commerce. Activism related to sexuality is primarily in response to political will being exerted over people’s expression of their sexuality, a common struggle in many countries around the world. For instance, the drive to decriminalize certain sexual orientations or sexual practices in Africa and elsewhere has given rise to a number of organizations to promote sexual diversity and the human rights of lesbians and gays (e.g., the Lesbian and Gay Equality Project in South Africa, the Gay and Lesbian Coalition of Kenya, and Rainbow Project in Namibia).

Sex, broadly defined, is a way of categorizing humans that “divides them into biologically based categories—male or female.” Sexuality, in turn, is defined as “a set of social processes that produce and organize the structure and expression of desire.” When the abstract concept of sexuality moves toward tangible expression—that is, through sexual acts, sexual behaviors, and sexual choices—social constructs begin to take shape. Today we increasingly witness the impact of HIV/AIDS on how we negotiate our sexuality and our sexual activity. For instance, the emergence of HIV/AIDS has resulted in the resurgence of associations of sexuality with disease. Consequently, the medical community’s interest in sexuality is expanding to new areas beyond the traditional specialties of sexually transmitted infections, obstetrics and gynecology, and psychiatry.

HOMOSEXUALITY

Much like race, sexuality is a marker of fundamental differences. The feminist movement’s critique of patriarchy, the gradual liberation of gay and lesbian people around the world, and the impact of HIV/AIDS have all contributed to an understanding of sexuality as less of a social and moral “line in the sand” than a continuously debated source of identity and meaning.

In South Africa for example, homosexuality has enjoyed a renewed acceptance since the fall of Apartheid. The transition from the criminalization of homosexuality under the Apartheid government to the equal rights of gays and lesbians under the constitution created by the ruling African National Congress represents a considerable step in the right direction. Yet despite these protections (known as the “Equality Clause”) of individuals against unfair discrimination due to their sexual orientation, it remains to be seen whether these clauses will be fully supported by governmental action.

One issue that is emerging in many different political and social contexts is the consideration of sexuality as a human rights issue. Sexual difference, and in particular, homosexuality, has been used as the basis for criminalization, exclusion, and marginalization around the world. Often discrimination of homosexuality has been fueled by its relation to HIV/AIDS, as was seen in the early years of the epidemic and continues to be the case in many countries (e.g., Namibia, Botswana, and Zimbabwe) where a lack of access to information, along with discrimination in provision of basic services, puts lesbian, gay, bisexual, and transgender people in the region at particular risk both of contracting HIV/AIDS and of suffering disproportionately from its medical consequences.

HIV/AIDS AND MEN WHO HAVE SEX WITH MEN

First identified in the early 1980s by doctors who were seeing homosexual men dying without explanation, AIDS was initially termed GRID (gay-related immunodeficiency). Only in 1984 was the term AIDS (acquired immune deficiency syndrome)
HUMAN RIGHTS AND HIV CARE

officially taken up by the medical establishment. Despite this early correction, the myth that AIDS is a gay-related disease still prevails in many settings.

The phrase MSM, while not new, is certainly new to many parts of the world. This phrase broadly describes men who lead different lives in different contexts. Like any label, it is not an inconsequential designation; it has a history, makes assumptions, and conveys complex suggestions about how sexuality is framed by those who use it. Essentially, it is used to focus attention on sexual acts, providing a way to communicate about or speak about safe sex practices, without committing to culturally coded identities (e.g., gay, lesbian, bisexual).

In sub-Saharan Africa, there are virtually no programs to combat HIV/AIDS and violence specifically among MSM and WSW. This is at least in part due to the tenuous legal situation of MSM in many African countries, several of which have laws criminalizing same-sex conduct, often termed “sodomy laws” (Figure 1). Because data on MSM and WSW populations are sparse, governments, donors, and civil society organizations need to develop policies and programs for all sexual minorities (not just those who self-identify as gay, lesbian, or bisexual).

Although there is a great need for interventions targeting these often marginalized or hidden populations, many obstacles stand in the way of progress. HIV prevention programs for MSM are hindered by many factors, including (1) denial at all levels that same-sex relations take place; (2) stigmatization and/or criminalization of MSM; (3) inadequate or unreliable epidemiological information on HIV transmission through male-to-male sex; (4) difficulty reaching MSM, especially those who do not self-identify; (5) lack of awareness or sensitivity among health facility staff about the existence or needs of MSM; (6) reluctance on the part of donor agencies to support prevention programs among MSM; and (7) lack of attention in national AIDS strategies to the needs or existence of MSM. (It should be noted that the government of South Africa, after much lobbying and advocacy, finally included vulnerable groups such as MSM in its current National Strategic AIDS Plan.)
Innovative approaches to overcome these barriers are essential so that informed, qualitative research on MSM can assist in better addressing the needs of this population.

Some issues to consider regarding the conducting of research with MSM are as follows:

- MSM are a diverse group, and there is diversity in expression and organization of homosexuality. In order to develop effective interventions, there is a need to understand the diversity that exists within this population.
- HIV risk cannot be understood and effectively addressed without taking other issues into account (e.g., stigma, discrimination and violence, alcohol and drug use, socioeconomic and cultural circumstances).
- Effective research requires involvement of affected communities; outcomes of research should be shared with the community in the appropriate format.
- The usefulness and efficacy of MSM as a concept may change over time.

**Prevalence of HIV Infection Among MSM**

It is difficult to know the prevalence of HIV infection among MSM in developing countries for a number of reasons. First, due to a number of causes including lack of political support, very little research has been done that focuses on the prevalence of HIV infection in this population and the characteristics of infected or at-risk men. Second, there are methodological challenges: It is practically impossible to recruit representative samples of men who engage in same-sex relationships. This implies that when prevalence data are reported for this population, it is always important to examine how the men were recruited into the study (i.e., is participation based on self-selection or a somewhat random recruitment strategy). Eligibility criteria for participation in the study must also be looked at carefully—did

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men have to self-identify as gay, or was a wider net cast and was involvement in homosexual sex the criterion? Also, it is important to know the channels that were used for recruitment and to what extent these channels promoted diversity among men in the sample or whether homogeneity was a factor. Yet despite these considerations, valuable research can be conducted. Baral and colleagues reviewed available studies and showed that in Kenya, Senegal, Sudan, and Egypt the observed prevalence of HIV in MSM was 1.6 (Kenya) to 108.9 (Egypt) times as high as in the general population. Van Griensven concluded that the high HIV prevalence among MSM from Kenya, Senegal, and Sudan was remarkable: While adult HIV prevalence in Kenya recently declined to an estimated 6.1%, and adult HIV prevalence in Senegal and Sudan is estimated to be 0.9% and 1.6%, respectively, the prevalence observed among MSM in these countries was 10.6% (Kenya), 21.5% (Senegal), and 9.3% (Sudan). Although


**International Gay and Lesbian Human Rights Commission (IGLHRC) calls upon the governments of African nations to—**

- Repeal all laws that criminalize same-sex consensual conduct in keeping with international human rights law. These laws contribute to HIV vulnerability for same-sex-practicing people by driving them underground and supporting their marginalization. End arrests, harassment, and persecution of people on the basis of sexual orientation in countries that have no antihomosexuality laws.
- Prosecute physical and verbal attacks, expulsion from schools and housing, and other forms of harassment, persecution, and abuse of same-sex-practicing people. Extend the equality provisions of national constitutions to include sexual orientation. End impunity of law enforcement officials and private individuals for homophobic discrimination and violence.
- Build relationships with local lesbian, gay, bisexual, and transgender (LGBT) and sexual rights organizations and provide funds for the scaling-up of successful HIV prevention, voluntary counseling and testing, treatment, and care programs for same-sex-practicing people through direct government grants and contracts. Work collaboratively with organizations that have experience implementing such programs.
- Make condoms, dental dams, and latex-compatible lubricants available in jails and prisons; offer comprehensive HIV prevention education to people who are incarcerated.

**IGLHRC calls upon the United States government to—**

- Launch requests for applications in Africa specifically for HIV prevention, care, and treatment programs for men who have sex with men and women who have sex with women. Ensure that successful applicants have experience implementing similar programs, preferably in Africa, and that they partner with local LGBT organizations.
- Fund a comprehensive study of HIV transmission between women and the HIV vulnerabilities of same-sex-practicing women in Africa.
- Stop the exportation of homophobia by removing restrictions on international reproductive health funding that increase stigma against sexual minorities. Rescind the Mexico City Policy (Global Gag Rule) and the requirement of the Prostitution Pledge. Modify the implementation of the ABC approach to eliminate the supremacy of abstinence-only until marriage programs. Promote comprehensive HIV-risk-reduction education.
- Include lubricants and dental dams as supplies that can be funded under the President’s Emergency Plan for AIDS Relief and other U.S. funding programs. Ensure that condoms are readily available for distribution by governments and nongovernmental organizations (NGOs) without complicated warnings of their supposed ineffectiveness.
### Box 1. Summary of Recommendations from the 2007 International Gay and Lesbian Human Rights

**IGLHRC calls upon the United States government to (cont.)**
- Create a small grant fund with which African LGBT organizations can implement HIV pilot projects; provide organizational and programmatic capacity building in the form of training and technical assistance to increase the success of these initiatives. Use these projects to gather information on the effectiveness of various techniques and strategies for decreasing HIV transmission among same-sex-practicing people.

**IGLHRC calls upon foreign governments, foundations, and corporate donors, including the United States, to**
- Increase funding to African government agencies and international and local organizations ready to implement programs for same-sex-practicing people in Africa. Encourage grantees implementing broad-based HIV public education campaigns to investigate the needs of same-sex-practicing people and adjust their approaches to be more inclusive.
- Refrain from funding any project or organization that openly discriminates against LGBT people or preaches hate against anyone due to their membership in the social categories protected by the International Covenant on Civil and Political Rights.
- Fund a comprehensive study of HIV transmission between women and the HIV vulnerabilities of same-sex-practicing women in Africa.

**IGLHRC calls upon private voluntary organizations working against HIV/AIDS in Africa to**
- Undertake appropriate consultations with LGBT organizations and leadership in Africa, as quickly as possible, in order to jointly launch HIV prevention, treatment, and care programs that specifically target same-sex-practicing people.
- Ensure that same-sex-practicing people are not excluded from the messages contained in generalized HIV/AIDS public education programs. Promote images of individuals and their relationships that are representative of the broad spectrum of human sexuality.
- Work with country-level staff to develop policies that promote equality and respect for same-sex-practicing people who access programs and services.
- Staff programs that target same-sex-practicing individuals with self-identified same-sex-practicing people. Make training opportunities available to help these individuals to adequately fulfill their roles. Offer them adequate and appropriate support to withstand the homophobia they are likely to face from within and outside the organization.

**IGLHRC calls upon domestic AIDS service organizations working against HIV/AIDS in their countries to**
- Develop policies that promote equality and respect for same-sex-practicing people who access programs and services.
- Ensure—through invitations, advertising, community fora, promotional materials, and other means—that same-sex-practicing people are welcome participants in organizational programs and events. Reach out!
- Assist LGBT organizations in designing and managing AIDS prevention, care, and treatment programs to serve their own communities. Partner with LGBT organizations to access funding and implement HIV programming for same-sex-practicing people and LGBT communities.
- Increase the availability of condoms, including female condoms. Ensure that latex-compatible lubricants and dental dams are part of standard “safer-sex kits” available to all recipients.


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seroprevalence studies in South Africa are still under way, preliminary findings suggest that HIV prevalence among MSM is in the same range as the general population. What these studies also show is that same-sex sexuality is part of the sexual repertoire of African men, regardless of its legal status.

**SUMMARY**

A number of possible strategies to better address HIV among MSM have been identified (see Box 1). It is up to all stakeholders to help move us toward a more inclusive model of HIV/AIDS programming that takes the needs of all affected populations into account, regardless of how marginalized or “hidden” they may be. Although legislation protecting the rights of individuals, regardless of sexual orientation, and the rescinding of laws criminalizing same-sex conduct are steps in the right direction, they are only the first step. As has been observed in South Africa and elsewhere, additional steps must be taken to ensure that appropriate actions are taken by both government and nongovernment actors to enforce and protect the rights of MSM and other marginalized groups. Only in this way will we succeed in conducting meaningful research and developing interventions that can succeed in combating the epidemic among MSM and other same-sex-practicing people.
REFERENCE LIST


Noerine Kaleeba in front of her home in Uganda.
IN THE STORIES OF THE breakthroughs in the AIDS fight, Uganda is often cited as a birthplace of change. But in 1986, when Noerine Kaleeba’s husband, Christopher, learned he was HIV-positive, even their closest friends shunned them.

Kaleeba remembers one Sunday that year when she, her husband, and their four young girls—ages 8, 7, 5, and 3—slid into their regular pew at All Saints Church in Kampala, the nation’s capital. Just as they sat, others around them stood and left.

“It’s very difficult to believe that happened in Uganda, but it did happen,” Kaleeba said.

That affront, still remembered clearly more than two decades later, propelled Kaleeba onto a path of activism. Her husband died the next year. She remained HIV-negative, surprising her doctor, who had never before heard of a discordant couple—

written by John Donnelly
photographs by Dominic Chavez
with one partner infected, the other not. Kaleeba remembered the doctor telling her at the time, “We don’t know what’s going on. The virus doesn’t seem to show up in your blood.”

That same year, Kaleeba, a physiotherapist by training, helped start a support group in Uganda for those infected and affected by the virus. The group became The AIDS Support Organization, or TASO, which grew so surely and strongly that it soon was a model for the rest of the continent and beyond.

She sees all her work growing out of how she initially reacted to rejection. “It was an act of self-preservation because we were so stigmatized and so alone,” she said. “When I met other people going through the same problems, I knew I was not isolated, and I decided I will not take this lying down. I decided I will set up a visible process where people could be cared for and have their health restored and have their dignity restored.”

Kaleeba, now 56, had ambitions outside Uganda. After eight years as TASO’s executive director, she joined UNAIDS in Geneva as partnership and community mobilization adviser. Organizations bestowed awards and honorary degrees upon her. Groups corralled her to sit on their boards. She became known internationally for not mincing words about problems facing fellow Africans. But in 2005, she was ready to return to her African roots, first to Malawi and then to her native Uganda, to work on issues affecting women and children.

She seemed happy to be back in Africa. “I love being with people,” she said outside her Malawi office. “I love sitting with them as they do their planning, day by day, walking the journey with them.”

In Uganda, friends call her Mama Kaleeba. It fits her well. In 2007, she was supporting 38 children, almost all of them orphans.

“For us, to lament the plight of orphans, to talk about it, to write about it, and not doing something concrete—well, for us, that is not an option,” she said.

Her new mission, though, has been trying to slow the tide of children orphaned by AIDS deaths. “You can provide school fees and food for orphans, but if you ask the children what they want, they want Mom and Dad. So my part is to keep the parents alive. As long as they are alive, those children are not orphans.”

“To lament the plight of orphans, to talk concrete—well, for us, that is not an option.”
Q: What are the current challenges now in the fight against AIDS?
“I have always believed the response to HIV/AIDS should center on the people impacted the most. For Africa, it means the poor, the women, and the children. When you look at the programs, it doesn’t focus on that. We still are planning very generalized responses. We are not addressing the root causes of the problem. One of them is that women don’t have sufficient education. We are not addressing the central issue of poverty. A woman who has no access to money will not be able to take a bus to a clinic. It doesn’t matter how much money we pour into the clinic if women can’t get there.”

Q: How would you change the programs?
“I would put more resources and efforts with the village chief, the traditional healer, the small Christian or Muslim leader—the ones we know reach grassroots. I also would get better information to the local health worker. On an international level, we have even glamorized the work they do, but we haven’t put any effort into really teaching them. In many communities in Africa, the health workers are still churning out the same old false stories about HIV that they did 20 years ago.”

Q: What will be the biggest challenge in five years?
“The challenge will be still to work toward a day when there is community conversation about the impact of HIV, when there are basic conversations in a village. Now we talk about AIDS in AIDS workshops, in a meeting somewhere. Only rarely do women talk about it when they fetch water from a well. This silence in villages fuels HIV, and the feelings of shame and stigma that go with it.”

Q: How do you get people to talk about HIV at a waterhole?
“From my experience it’s a combination of things. There has to be a high degree of political openness arising from the political leaders, the heads of state. You should also have openness at the community level, in households. You need to get traditional leaders, people living with HIV, or families affected by HIV/AIDS to begin articulating their own issues and how AIDS has impacted them. And lastly, you also need international solidarity. Uganda would not have been able to do what it did without international solidarity. It’s not just about money, but it’s also about starting scientific studies that educate us. All of that leads to reduced stigma and learning more about the path of this virus.”
“I feel happy to see this photo. These children didn’t refuse when I asked if I could take a picture of them. It made me laugh, which does me good.”

About the Artist
Cecilia lives with her grandmother and older brother; their parents died of AIDS when Cecilia was very young. Her brother, Serge, runs a small business, providing the family with some income. Contributions from Reencontro, a local NGO, also help make ends meet.

Cecilia loves school. She walks 30 minutes each way to school every day and hopes to be a director of a school when she grows up. Many of her concerns are with her family and home because the roof of the house leaks when it rains and she worries about her grandmother’s health.
I feel happy to see this photo. These children didn’t refuse when I asked if I could take a picture of them. It made me laugh, which does me good.

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BUILDING COMPREHENSIVE HIV/AIDS CARE
PROGRAMS IN RESOURCE-LIMITED SETTINGS

LAYING A STRONG FOUNDATION

- Workforce Capacity
- Laboratory and Pharmacy Services
- Monitoring, Evaluation, and Quality of Care
- Human Rights and HIV Care

EDITED BY
RICHARD G. MARLINK AND SARA J. TEITELMAN
ESTABLISHING A FRAMEWORK FOR SUCCESS

Volume 2

ESTABLISHING A FRAMEWORK FOR SUCCESS

- Science and Treatment of HIV Infection
- Opportunistic Infections, Cancers, and Coinfections
- Prevention and Management of Tuberculosis
- HIV Prevention, Counseling, and Testing
- Prevention of Mother-to-Child Transmission of HIV
- Pediatric and Adolescent HIV Care

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BUILDING COMPREHENSIVE HIV/AIDS CARE PROGRAMS IN RESOURCE-LIMITED SETTINGS

ELIZABETH GLASER
Pediatric AIDS Foundation
About the Artist
Funeka Nceke is 28 years old and lives in the Cape Town township of Khayelitsha in a makeshift home with no electricity or running water. She lives with her two children (ages 12 and 8 months), her niece, and her niece’s boyfriend. She learned that she was HIV-positive in 2003. Funeka wants people to see that those who are HIV-positive can be “fresh and healthy” and enjoys taking photos of her house, her happy children, and TAC (Treatment Advocacy Campaign) marches.
from the ground up

BUILDING COMPREHENSIVE HIV/AIDS CARE PROGRAMS IN RESOURCE-LIMITED SETTINGS
VOLUME I: LAYING A STRONG FOUNDATION

VOLUME II: ESTABLISHING A FRAMEWORK FOR SUCCESS

VOLUME III: DEVELOPING PATHWAYS AND PARTNERSHIPS
FROM THE GROUND UP:
Building Comprehensive HIV/AIDS Care Programs in Resource-Limited Settings

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Introduction to Volume II: Establishing a Framework for Success

It is essential that HIV/AIDS programs are based upon the most up-to-date, sound clinical and scientific evidence and practical experience. There are numerous, and often disparate sources of information to be drawn from in the field of HIV/AIDS, often making it hard to ensure that programs are thoroughly evidence-informed. Yet we must always strive for the highest possible standard of care, while ensuring that we take into account the wide spectrum of services that constitute a truly comprehensive approach. The AIDS pandemic represents a formidable challenge for the medical, nursing, and allied health communities, one that we will not conquer for some time. Yet the numerous brilliant minds dedicated to this cause have taken us further than was previously thought possible, giving us remarkably effective treatments and preventive interventions, and providing insight into the most complex facets of this disease.

This second volume starts off with the section “Science and Treatment of HIV Infection,” which provides a brief overview of the characteristics of HIV infection and the basics of antiretroviral treatment. Here we will learn about the geographic variations of the virus, as well as the immune response and the effect of antiretroviral treatment on this response. We are also reminded that when we treat someone living with HIV, we are treating the whole person, not just one disease. Therefore we must take into account a range of other health needs, such as treatment for tuberculosis, malaria, and hepatitis. Two sections in this volume, “Opportunistic Infections, Cancers, and Coinfections” and “Prevention and Management of Tuberculosis,” discuss the identification and management of these and other life-threatening conditions in HIV-positive individuals, and how the associated heightened risks from coinfection and co-treatment can be minimized.

A largely unmet need also exists for psychosocial support for people living with and affected by HIV. Counseling is a powerful tool at our disposal that can be used to both prevent new infections, and to support those living with and affected by HIV. The chapters in the section “HIV Prevention, Counseling, and Testing” show us that it is within our power to equalize the balance between prevention and treatment in order to stem the tide of new infections. Prevention has lagged behind treatment, a trend that must be reversed in order for us to make headway in combating the global pandemic. Some of the methods proposed by the authors in this section include greater integration of prevention into care and treatment programs, the creation of prevention interventions targeting people living with HIV, and the use of innovative counseling and testing strategies.

Rounding out this volume are the sections “Prevention of Mother-to-Child Transmission of HIV” and “Pediatric and Adolescent HIV Care”. These two sections outline the critically important steps we can take to stop the spread of disease to newborn infants, and to manage infection in young people—a highly vulnerable and often overlooked group. Chapters focus on a range of important issues, from drug selection for prevention of mother-to-child transmission and methods of early infant diagnosis, to experiences establishing youth-friendly health services.
Ultimately the success of our programs will be measured not only by how many people we enroll into care and treatment, but also by our ability to prevent new infections and provide quality services to all those in need, especially the hardest-to-reach populations. If there is one theme that runs throughout the diverse chapters featured in this volume, it is that no health condition can be managed in isolation, and no individual, regardless of age or gender, can attain long-term health without receiving a comprehensive range of services that respond to their medical as well as their psychosocial needs. Based on this assertion, it could be said that true success will be conditioned upon our ability to apply a programmatic framework that encompasses, and is able to link together, all of these disparate but inextricably linked services at all levels of care—from the health facility to the community.

Michel Kazatchkine

Michel Kazatchkine, M.D., executive director of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, has spent the past 20 years fighting AIDS as a leading physician, researcher, administrator, advocate, policymaker and diplomat. Throughout his career, Dr. Kazatchkine has been closely involved with national and international NGOs working in the field of health and development. He is a long standing member of Médecins du Monde and a founding member of Nova Dona, an NGO providing services to drug users in Paris.
SAM PHIRI GREW UP in a rural village in Malawi among farmers who scratched out a living from the land. That was what people did there, generation after generation. There was little in his upbringing that would suggest he would move beyond secondary school. But Phiri, who is executive director of the Lighthouse Clinic, Malawi’s first AIDS treatment center, was driven to do community service. And he found that he had a strong interest in medicine.

He said his religious upbringing also guided him. His mother, he said, taught him that their Christian faith meant “we should be caring for others.”

“Even now, my mother and I do not talk about what exactly that I do,” Phiri said. “Instead, she says to me, ‘Son, do you make sure your skills as a Christian are assisting your patients?’”

The son always tells his mother he is. Phiri, a
DR. PHIRI TENDS TO ONE OF HIS PATIENTS AT THE LIGHTHOUSE CLINIC IN LILONGWE, MALAWI.
“With ARVs coming in, we finally have treatment. But scale up strategies on behavior change.”

medical clinician who is working on his PhD at the London School of Hygiene and Tropical Medicine to become a clinical epidemiologist, has been treating AIDS patients since 1993. For many years, the situation seemed hopeless; hospitals were swamped with AIDS cases—one 1997 study in Malawi found that 73% of the adults hospitalized with a fever were HIV-positive—and treatment options were all poor.

Many times, over several years, Phiri and his colleagues despaired at the rate of death from AIDS. “The corridors of the hospital were full, the verandas were full, and then they would leave the hospital very, very sick,” he said. “We had no way of following up on these patients who returned to their homes. I’m sure most of them died.”

In 2002, he helped found the Lighthouse, which would not only usher in an era of antiretroviral medicines to people infected with HIV, but also give those patients specialized care that was lacking in hospitals. Phiri and several friends chose the name Lighthouse because to them it represented a “beacon of hope—even though Malawi is a landlocked country,” he said, laughing.

In his job, Phiri, 42, has mostly served as an administrator, although he saves one day a week to see patients. “I am a clinician at heart,” he said. “I don’t want to lose that because it is so satisfying to see a patient, manage their care, and watch them improve.”

The Lighthouse has grown steadily in its first years, and by the end of 2007, it was overseeing the antiretroviral treatment of 5,000 patients. The clinic also was counseling and testing roughly 2,000 people a month. And it is helping train a new cadre of health workers in Malawi to treat people with HIV. Nearly three-quarters of Malawi’s health workers who see AIDS patients were trained at the Lighthouse. Sitting in his office at the clinic, Phiri reflected on the beginnings of the Lighthouse and its future.
Q: What was the genesis of the Lighthouse?
“I remember it well—it was 1996. I was working in the central hospital (in Lilongwe), and the adult wards were really full. I said to myself, ‘What is really going on? Isn’t there anything I can do?’ We had a problem with the drugs, and a lot of people were dying. On top of that I lost some friends in the medical department.”

Q: Do you recall one death in particular?
“Yes, it was the death of one of my colleagues—a close friend. He opened up quite late, that he had AIDS. By the time he confided in me, he was really not well. But there was more to it. He had meningitis and we did not have the best medicine for it. I said then that we really could have done better.”

Q: When did you know that the Lighthouse was going to work?
“Just after we opened it in 2002, we had a group education session for many patients. We wanted to give them general HIV information. Stigma was very high. People didn’t talk about having AIDS. But at that meeting, I was shocked that people stood up and said, ‘I found out I was with HIV and I was told I could come here to be assisted. How can you help?’ I knew then that the clinic was going to be busy, and that it was going to be hard work.”

Q: For a while, the number of patients began to overwhelm staff. How did you deal with that situation?
“By 2005, we were seeing over 250 people a day. We decided to limit that to 180 patients. It was difficult, but we had to do it. It was first come, first served. By 7 a.m., we were registering 180 patients. Then we adjusted our system: nurses took care of some patients, and patients who were well would come every two months, not every month.”

Q: What are the challenges you’ll face in the next five years?
“We will not have a problem in finding enough people to put on treatment. The problem is how we cope with the demand. The government’s goal in Malawi is to have 245,000 patients around the country on treatment by 2010. With more people on treatment, we’ll also have more side effects, and more resistance. So doctors may need to do more clinical work with individual patients. That means we will have to focus on capacity building and improving service delivery.

“The other big change deals with prevention and behavior change. With ARVs [antiretroviral drugs] coming in, we finally had treatment. But now people may go back to loose behaviors. We need to scale up strategies on behavior change.”
SCIENCE AND TREATMENT OF HIV INFECTION
HUMAN IMMUNODEFICIENCY VIRUS types 1 and 2 (HIV-1 and HIV-2) are members of the Lentivirus genus of the Retroviridae family of RNA viruses and are 50% similar at the genetic level. HIV-2, although more closely related to the simian immunodeficiency virus (SIV), is the second human immunodeficiency virus and constitutes the closest known human virus related to the prototype AIDS virus, HIV-1. HIV-2 shares many virologic and biologic features with HIV-1. Like other retroviruses, both HIVs induce lifelong infection, with permanent integration of viral genetic material into the host cell's DNA. The enzyme responsible for viral replication, reverse transcriptase, is error-prone, which results in considerable genetic variation. This variation is more pronounced in the genes that encode the outer envelope regions compared with the polymerase (pol) and group-specific antigen (gag) genes, which are more genetically constrained from variability. Both HIV-1 and HIV-2 enter susceptible cells via the same primary receptor, the CD4, but secondary co-receptors may differ between the two viruses. As a result of these similarities in cell receptors, both viruses are transmitted by the same routes and infect the same cell types in people.

HIV-2
Although HIV-1 and HIV-2 are highly related lentiviruses, they maintain some distinct epidemiologic and biologic characteristics. HIV-2 is largely confined to West Africa, while HIV-1 infection is prevalent worldwide and accounts for approximately 95% of all HIV infections globally. Importantly, disease progression to AIDS occurs much more slowly in HIV-2. In comparison to HIV-1, these biologically relevant characteristics of HIV-2 infection in vivo appear to model those of an attenuated HIV infection. To date, the precise mechanisms responsible for this attenuated phenotype of HIV-2 remain unclear. However, HIV-2, like HIV-1, causes AIDS, although more slowly, and it was based on these initial similarities that some believed that HIV-2 might cause a second worldwide AIDS epidemic. Now, 23 years after the discovery of HIV-2, no such epidemic has occurred. Rather, research studies conducted both in the laboratory and in HIV-2-infected people in West Africa have highlighted distinct biological differences between these related viruses.
History and Distribution of HIV-2 in Africa

It is now recognized that HIV and closely related viruses in primates, termed SIVs, exist. The close antigenic relatedness of both SIV and HIV-2 to the prototype HIV-1 virus prompted both the discovery and further classification of these related viruses.\(^3\)\(^-\)\(^5\) When sera from West African female sex workers were screened for antibodies to HIV-1 antigens, the antibodies revealed extensive cross-reactivity for the virus gag antigens but minimal antibody binding reactivity for the HIV-1 envelope.\(^3\) Yet, when the same West African human sera were assayed on SIV antigens, they reacted strongly with the envelope proteins as well as the gag antigens, suggesting infection with a virus that was more closely related to SIV than to HIV-1. As more sequence data became available from various HIV-2 and SIV strains, it has also become apparent that no branching order of divergence can be identified and that HIV-2 and SIV most probably share a common ancestor.\(^6\)\(^-\)\(^7\) Therefore, it is well recognized that HIV-2 is more closely related to SIV than to HIV-1. As estimated that the HIV-1 and HIV-2/SIV groups of viruses might have diverged from each other as recently as 50–60 years ago.\(^8\)\(^-\)\(^9\)

The discovery of HIV-2 in Senegal, West Africa, in the mid-1980s prompted numerous studies to determine the geographic distribution and biological significance. Through the use of type-specific serology assays, we now recognize that HIV-2 is prevalent in most West African countries, surprisingly a distinctly different worldwide distribution compared to that of HIV-1.\(^10\)\(^-\)\(^12\) In most other countries of West Africa, such as Burkina Faso, Ghana, Ivory Coast, Nigeria, and Mali, infection with HIV-1 is more prevalent than infection with HIV-2, ranging from a 3- to 24-fold rate ratio (HIV-1 versus HIV-2).\(^13\)\(^-\)\(^18\) Although recent national serosurveys have not distinguished these virus types, it is widely considered that HIV-2 prevalence rates are diminishing. This supports the hypotheses raised by Anderson and May, who analyzed the available biological and epidemiological data on HIV-1 and HIV-2 and used simple mathematical models to study the competition between the two viral types.\(^19\) The mathematical model of the concomitant transmission of the two viruses within the same sexually active population suggested a positive association between pathogenicity and reproductive success, indicating that HIV-1 would competitively displace HIV-2 in the long term. In our study of both viruses in Dakar, Senegal, over the past 20 years, we have also observed the decrease of HIV-2 prevalence in registered sex workers and a concomitant increase in HIV-1.\(^20\)

Outside West Africa, sporadic reports of HIV-2 infection have been previously made in Portugal, Mozambique, Angola, southwestern India, and Brazil; these events are all related to the former ties Portugal had with West Africa.\(^21\) Portugal itself appears to have low but stable rates of HIV-2 prevalence in the population.\(^14\) The other countries once shared common historical-political ties, with some economic trade relationships existing even today. As noted, HIV-2 has been detected in some large cities in southwestern India,\(^22\)\(^,\)\(^23\) perhaps because of exchange with the former Portuguese colonies of Africa. Goa, a former Portuguese colony, situated south of Bombay on the western coast, has reported 4.9% HIV-2 and 9.8% HIV-1 infection rates in patients with sexually transmitted infections (STIs).\(^22\) To date, significant HIV-2 infection has not been reported in other parts of Asia.

HIV-2 Laboratory Diagnosis

The close relationship of HIV-2 to HIV-1 on a genetic and antigenic level has necessitated the development and use of type-specific assays in order to diagnose and distinguish these related viruses. The same methodologies and technologies...
for HIV-1 serologic testing, virus culture, and genetic diagnostics such as polymerase chain reaction (PCR) have been modified for HIV-2 diagnosis and improved over the years. Because most of the original HIV antibody tests were developed using HIV-1 antigens, the degree of cross-reactivity and specificity for HIV-2 was highly variable. Most of the first-generation tests used whole virus antigens, where antigens such as p24gag and pol proteins (p66/p51) were well represented. These antigens are more strongly cross-reactive between HIV-1 and HIV-2 compared to the envelope antigens, especially the external envelope protein, the gp120. In the early 1990s, most European nations, followed by the United States, incorporated HIV-2 testing into blood bank screening. The antibody tests used were Enzyme-Linked ImmunoSorbent Assays (ELISAs) with combined antigens of HIV-1 and HIV-2. Confirmation of HIV-2 serostatus requires an HIV-2-specific immunoblot (Western blot) or specific peptide assays. Immunoblots demonstrating a profile of major structural gene product recognition are typically used to confirm HIV-1 and HIV-2 diagnosis using standard criteria. HIV-2-specific diagnosis by immunoblot requires antibody reactivity to env + gag + pol antigens. In the absence of reactivity to gag or pol antigens, the presence of reactivity to two envelope antigens is required (gp120 and gp32, transmembrane protein).

Various investigations have focused on identifying type-specific antigens to allow confirmatory tests that will distinguish between HIV-1 and HIV-2. Most have been made as synthetic peptides, but some were larger bacterially expressed peptides which vary in sensitivity and specificity. As most were selected for specificity, one might expect that sensitivity could be compromised. Thus, although appropriate for type-specific confirmation, they may not be as useful as larger HIV-2-specific antigens for initial screening.

The various type-specific assays can yield a result of HIV-1 and HIV-2 positive status. The HIV dual antibody profile is characterized by antibodies with strong reactivity to the env antigens of both HIV-1 and HIV-2 by immunoblot and/or radioimmunoprecipitation analysis (RIPA). This may result from the extensive cross-reactivity that exists between the viruses and the lack of type-specificity of the assay employed. Several possible biologic explanations for this phenomenon can also be entertained, including dual infection by both viruses or infection with a recombinant virus. When human serum samples were tested in places such as Ivory Coast, Senegal, and Burkina Faso, a disproportionately large fraction of the samples often tested as “dual positive” because they appeared reactive on both HIV-1 and HIV-2 confirmatory tests. These sites have significant rates of both HIV-1 and HIV-2 infection, and distinction of viruses and designation of dual reactivity remains a diagnostic challenge for the typical HIV laboratory in geographic locales where both viruses are circulating. When rates of HIV-2 virus infection in a region or study have been low or absent, it is generally considered that the finding of dual HIV-1/HIV-2 infection is erroneous and likely due to cross-reactivity from HIV-1 infection alone.

**Lowered Sexual and Perinatal Transmission Rates**

Although HIV-1 and HIV-2 are thought to be transmitted through human populations by the same modes of transmission, the epidemiologic distribution suggests that the rates of these transmissions may be distinct. In West Africa, the spread of HIV-1 has exceeded that of HIV-2 over the past two decades. During an eight-year period of follow-up in Senegal, there was a 26-fold increase in HIV-1 infection rates, whereas HIV-2 infection rates remained relatively constant. These studies indicated that HIV-2 may have been in the human
population in Africa at least as long as HIV-1, and in West Africa, HIV-2 has apparently been present considerably longer. The relative lack of significant HIV-2 prevalence in Europe, North America, and Asia in the face of HIV-1 expansion also supports the general notion that HIV-2 is spread less efficiently than HIV-1.21,42-48

HIV-2 infection transmitted by blood and blood products has been reported in case reports; however, widespread HIV testing in blood bank settings has most probably limited the risk of this mode of transmission.45,50 The most common modes of HIV transmission in HIV-2-endemic areas are perinatal and heterosexual transmission; since most West African countries have been afflicted with both HIV-1 and HIV-2 infections, direct comparison of transmission rates between the two viruses has been possible. In Senegalese female sex workers followed over an 11-year period, the annual incidence of HIV-1 dramatically increased, with an 18-fold increase in risk per year and a 13-fold increase in risk over the entire study period. By contrast, the incidence of HIV-2 remained stable, despite higher HIV-2 prevalence.10,41 In this high-risk group, the heterosexual transmission of HIV-2 was significantly slower than that of HIV-1, which strongly suggests differences in the heterosexual transmission potential of these two related immunodeficiency viruses.

Gilbert et al performed a modeling study of HIV-2 and HIV-1 to compare transmission potentials, where new nonparametric competing-risks failure-time methods were used, which minimized modeling assumptions and controlled for risk factors for HIV infection. Observing 1,948 women followed from 1985 to 1999, we compared the male-to-female transmission probability of HIV-1 and HIV-2 per infectious sexual exposure. The HIV-1 versus HIV-2 infectivity ratio over time was estimated by nonparametric kernel smoothing of the HIV-1/HIV-2 infection hazard ratio in sex workers adjusted by an estimate of the relative HIV-1 versus HIV-2 prevalence in the partner population. HIV-1 was found to be significantly more infectious than HIV-2 throughout the follow-up period (P<.0001). The HIV-1/HIV-2 infectivity ratio was inferred to be approximately constant over time, with an estimated ratio of 3.55.51

Maternal or perinatal transmission of HIV-2 also appears to be less efficient than for HIV-1.52-57 Perinatal transmission of HIV-2 and HIV-1 has been studied in Guinea Bissau, Ivory Coast, France, and Senegal, with all demonstrating extremely low rates of perinatal transmission of HIV-2 (0%–3.7% transmission) in contrast to that of HIV-1 (15%–45% transmission).52,53,57-59 In studies that measured perinatal transmission of both viruses, the rate of HIV-1 transmission was 10- to 20-fold higher than that of HIV-2 (see Table 1).

**HIV-2-Related Disease and Differences in Disease Progression**

Early case reports described HIV-2-infected people with disease consistent with an AIDS diagnosis.60-62 The disease characteristics, including tuberculosis, chronic diarrhea, and *Candida* infections, were similar to diseases seen in HIV-1-associated AIDS in the same settings.62-64 Central nervous system involvement has also occasionally been described in HIV-2 AIDS cases.65,66 However, classical African AIDS comorbidities, such as tuberculosis, often have had only a weak epidemiological association with HIV-2, even in HIV-2-endemic areas.67-69

In Dakar, Senegal, our prospective studies conducted in a registered female sex worker cohort have provided the unique opportunity of measuring the infection and progression rates of both HIV-1 and HIV-2 infections.67,68,70,71 Importantly, these prospective studies have compared disease progression in individuals with known times of infection, and the cohort has now been observed for more than 22 years, representing one of the
alterations in T-cell subsets evaluated prospectively showed similar results, where immunosuppression was significantly slower to develop in HIV-2-infected people than in those infected by HIV-1 and could not be demonstrated in all subjects.68,73 Skin-test anergy to various antigens was also less pronounced in HIV-2 infection.68,73 Together, these studies of HIV-2 infection in populations in West Africa conducted in the 1990s demonstrated that the rate of immunosuppression and development of AIDS was significantly slower when compared with HIV-1 infection.

These distinct differences in pathogenicity provide a unique opportunity to identify viral and host immune mechanisms involved in a closely related and relevant virus system that is predicted to have a significantly slower course of progression. Evidence for a lower viral burden in HIV-2-infected individuals has been reported from both virus-isolation and PCR studies.76-82 The isolation rate of HIV-2 from peripheral blood mononuclear cells or plasma of asymptomatic HIV-2-infected individuals was lower than the isolation rate for HIV-1.80 At lower CD4 lymphocyte counts, virus isolation was equally efficient in both infections.

In our prospective study of HIV-2-infected individuals, we also identified individuals who fit a definition of long-term nonprogression and could determine a rate of this phenotype in the study population,68,71 also noted by others.72 Using a definition of long-term nonprogression of greater than or equal to eight years of infection in the absence of AIDS or related symptoms and stable CD4 (T4) lymphocyte counts greater than 500 cells/mm³, we found that 39 of 41 women (95%) could be classified as long-term nonprogressors.

Since it is well recognized that progression to AIDS correlates with clinical immunosuppression, studies to evaluate the level of immunocompromise with HIV-2 infection have been conducted to further define the clinical significance of HIV-2 infection. In cross-sectional studies, T4 lymphocyte counts and T4:T8 ratios appeared reduced in HIV-2-infected subjects, but less dramatically than in HIV-1-infected subjects.68,73-75 Similarly, alterations in T-cell subsets evaluated prospectively showed similar results, where immunosuppression was significantly slower to develop in HIV-2-infected people than in those infected by HIV-1 and could not be demonstrated in all subjects.68,73

Table 1. Key differences between HIV-1 and HIV-2

<table>
<thead>
<tr>
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<th>HIV-1</th>
<th>HIV-2</th>
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<tr>
<td>Geographic Distribution</td>
<td>Worldwide</td>
<td>West Africa</td>
</tr>
<tr>
<td>Heterosexual Transmission</td>
<td>15%-45%</td>
<td>0%-5%</td>
</tr>
<tr>
<td>Perinatal Transmission</td>
<td>7-10 years</td>
<td>10-25 years</td>
</tr>
<tr>
<td>Time to AIDS</td>
<td></td>
<td>NNRTIs* ineffective</td>
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<tr>
<td>Treatment</td>
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*Non-nucleoside reverse transcriptase inhibitors

longest HIV natural-history studies in the literature. The Kaplan-Meier analysis of HIV-2-infected individuals indicates that 85% (95% CI, 50%-96%) remain AIDS-free after 8 years of HIV-2 infection.68 These differences in survival probabilities between HIV-2 and HIV-1 were also seen for Centers for Disease Control and Prevention (CDC) stage IV disease and CD4 lymphocyte counts below 400 cells/mm³ and below 200 cells/mm³, as outcomes.

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reverse transcriptase–polymerase chain reaction to measure HIV-2 viral load and determined levels of plasma virus in the cohort of registered commercial sex workers in Dakar, Senegal.\textsuperscript{77} HIV-2 viral RNA was detectable in 56% of all samples tested; the median load was 141 copies/mL. Levels of HIV-2 viral RNA in the plasma were inversely related to CD4 cell counts. HIV-2 and HIV-1 viral loads were compared among newly infected women in the cohort; the median viral load was 30-fold lower in the HIV-2-infected women (\(P<.001\), Wilcoxon rank-sum test), irrespective of the length of time infected. This suggests that plasma viremia is linked to the differences in the pathogenicity of the two viruses.\textsuperscript{77} Similar findings have also been described in Gambia and Guinea Bissau.\textsuperscript{78,83}

Levels of virus in the plasma are closely related to the pathogenicity of HIV-1, and infection with HIV-2 leads to a significantly lower plasma viral load. To further identify the source of this difference, we measured both viral RNA and proviral DNA in matched samples from 34 HIV-2-infected individuals. The median level of HIV-2 RNA for the group was 189 copies/mL. Levels of HIV-2 RNA were below the limit of detection in nearly half the women, consistent with what we have previously reported in this population.\textsuperscript{76} Levels of HIV-2 proviral DNA were similar to those of HIV-1 but failed to correlate with levels of viral RNA. Thus, it appears that significant differences occur upon expression, release, and/or maintenance of virions in the bloodstream. Our laboratory has gone on to demonstrate that HIV-2 is able to establish a stable, integrated proviral infection in vivo, but that accumulation of viral mRNA is attenuated in HIV-2 infection, relative to HIV-1. The differences in viral mRNA are consistent with the differences in plasma viral loads between HIV-1 and HIV-2, and suggest that lower plasma viral loads, and possibly the attenuated pathogenesis of HIV-2, can be explained by lower rates of viral replication in vivo.\textsuperscript{44} Further comparative studies of both viral and host factors that may affect expression will be useful for understanding the differences between HIV-1 and HIV-2 pathogenesis.

Since slower disease course appears to be common in HIV-2 infection, we reasoned that certain subsets of the population would possess host characteristics that might predispose them to a more rapid disease course. We conducted a case-control study investigating possible associations between human leukocyte antigen (HLA) and the risk of disease progression in HIV-2.\textsuperscript{85} The HLA class I status was molecularly typed in female sex workers from the Dakar, Senegal, cohort; HLA B35 was associated with lack of p26 antibodies (\(P<.05\)) and higher risk of disease progression. The same association was found for the class I haplotypes B35-Cw4 and A23-Cw7 (\(P<.05\)), similar to the association with HIV-1.\textsuperscript{86} Our data show that certain HLA molecules are associated with risk of disease progression in HIV-2; some of the alleles and haplotypes involved in susceptibility to disease are similar for both HIV-1 and HIV-2. Therefore, certain genetic factors may be shared by HIV-1 and HIV-2 with respect to susceptibility to enhanced disease progression.

**HIV-2 Treatment**

It is generally assumed that drugs that have efficacy against HIV-1 will be effective against HIV-2. However, with the exception of a few in vitro analyses,\textsuperscript{87} most HIV-1 drugs have not been thoroughly tested for activity against HIV-2. In addition, experience with antiretrovirals (ARVs) has been largely confined to the developed world, where HIV-1 non-B subtypes and HIV-2 are rarer. Hence, it is still not clear that current ARV therapeutic regimes will be as efficacious given differences in virus subtype or type. Further, the natural history of HIV/AIDS in the developing world does differ from the disease in the developed world, where distinct...
endemic opportunistic infections, common infectious disease agents, and clinical standards of care may contribute to these differences. This suggests that certain aspects of HIV clinical management in developing-world settings will also require additional consideration. Antiretroviral therapy (ART) is directed at lowering in vivo virus replication. Clinical management and treatment decisions have been difficult in the absence of a commercially available HIV-2 plasma viral load assay.

We have had limited experience in the therapy of HIV-2 patients in the United States, where it appears that standard combination ART can readily reduce viral load levels below detection. To date, only case series and reports have evaluated the efficacy of HIV-1 ART regimens for the treatment of HIV-2 infection; clearly, clinical trials are needed in the future. Through a case series of 10 HIV-2-treated patients in the United States, Mullins et al reported that HIV-1 regimens have a reduced efficacy in the treatment of HIV-2 disease. From the few published studies, including our own, we are not able to adequately assess the clinical utility of the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of antivirals as a treatment option for HIV-2, although in vitro data suggest that this class of drugs may be ineffective for treating HIV-2. Similar to our observations, it appears that HIV-2 differs from HIV-1 in the risk of disease progression at any given CD4 cell count and may therefore have different implications for the timing and management of ARV therapy.

The reverse transcriptase (RT) and protease genes from 12 HIV-2-infected individuals who had been treated with ARVs were examined for the presence of drug-resistance mutations. Four individuals carried virus genotypes with amino acid substitutions potentially associated with resistance to nucleoside analogues: two at codon 70 (K→R) and two at codon 184 (M→V); the latter two patients harbored a codon Q151M mutation, which has been associated with multidrug resistance in HIV-1. Substitutions associated with resistance to protease inhibitors at codon 46 were observed in all individuals. Moreover, minor resistance mutations, as well as new ones, were often seen in the protease gene. Thus, in limited studies, amino acid changes in the HIV-2 RT and protease genes, which could be associated with drug resistance, seem to occur at positions identical to those for HIV-1.

**HIV-1 SUBTYPES**

In the early 1990s, molecular techniques to sequence and classify HIV viruses became more available. These advances allowed for further characterization of HIV infections worldwide, with particular emphasis on Africa, which bears the highest rates of infection. It soon became apparent that genetic variation in HIV-1 led to distinct strains, subtypes, or clades. The genetic variability of HIV has been attributed to the lack of proofreading ability of the RT enzyme, the rapid turnover of virions, recombination of viruses, and selective immunologic pressures. Three distinct groups within HIV-1, M, N, and O, have been identified based on phylogenetic analysis of env and gag sequences from various geographic regions. Most HIV-1 sequences belong to group M (major). A divergent subset of viruses identified in Cameroon in 1994, which did not cluster with group M viruses, were classified as group O (outlier), and in 1998, another set of viruses, which did not cluster with group M or O viruses, were termed group N viruses. It is thought that the three groups were introduced by three independent SIVcpz transmissions into the human population in the early part of the 20th century. Interestingly, the earliest available HIV-1 isolate was sampled in the Democratic Republic of Congo in 1959, and molecular clock analyses estimate the timing of the most recent common
ancestor of HIV-1 group M to the 1930s\textsuperscript{100,101} and that of group O to the 1920s.\textsuperscript{102}

Prior to 1992, HIV-1 strains were classified based on their geographic origin, as European / North American versus African strains, because early phylogenetic analyses indicated that viruses from Europe and North America clustered separately and distinctively from viruses isolated in Africa.\textsuperscript{103-105} As more viruses from around the world were sequenced and analyzed, it became obvious that the original classification scheme was insufficient. Further analyses of env and gag gene sequences indicated the presence of multiple phylogenetic clusters, or clades, that were equidistant from one another.\textsuperscript{106} These clades were termed subtypes, which are defined as groups of viruses that closely resemble each other more than they do other subtypes.\textsuperscript{94,105,106} The viruses originally classified as European / North American were reclassified as subtype B, while the African viruses were
divided between subtypes A through F, excluding E. Subsequently, subtypes G, H, J, and K were also classified\(^\text{105}\) (Figure 1). To date, nine subtypes and 34 circulating recombinant forms (CRFs) have been described. In North America and Europe, the most prevalent form is the subtype B. However, in Africa, where the disease is the most prevalent, non-B subtypes predominate, with all nine subtypes and many CRFs described across the continent.

In addition to groups and subtypes, some group M subtypes have been further divided into subsubtypes.\(^\text{104}\) Based on full-length sequence data, subtype A has been subdivided into A1–A4,\(^\text{103,107,108}\) and subtype F into F1 and F2.\(^\text{109,110}\) It has also been suggested that the group of viruses designated as subtype K should actually have maintained the name F3, but for historical reasons it has been left as a separate subtype.\(^\text{104}\) Similarly, subtypes B and D should have been classified as related subsubtypes but have been maintained as separate subtypes as well.\(^\text{104,111}\)

At the nucleotide level, genetic distances between subtypes range from 15% to 22% in the gag gene, and from 20% to 30% in the env gene,\(^\text{103,104,112-114}\) while the genetic distances between subsubtypes range from 7% to 12% in the gag gene and 11% to 16% in the env gene.\(^\text{102-104,107,112}\)

Over the years, with the increasing use of full-length sequencing, it has become obvious that a number of intersubtype recombinants are also circulating in human populations. Recombination occurs when RT switches between two genomic templates during replication at an estimated rate of three recombination events per replication cycle.\(^\text{115}\) Recombination is usually preceded by dual infection of a cell with different viruses. The recombinants formed are of two varieties. They are either CRFs, which are widely spread in populations and usually have been found in at least three epidemiologically unlinked individuals, or unique recombinant forms (URFs), which do not attain epidemiological significance. CRFs are defined as recombinants that share an identical mosaic structure, indicating that they are descendants of the same recombinant event(s).\(^\text{104,111}\) As of February 2009, there were 43 CRFs listed in the Los Alamos HIV Sequence Database.\(^\text{115}\) There have also been reports of intergroup recombinants, composed of a mosaic of group M and group O viruses.\(^\text{116-118}\) Thus far, though dual infection with HIV-1 and HIV-2 has been shown in a number of studies, there has been no in vivo evidence of an HIV-1/HIV-2 recombinant.\(^\text{119,120}\)

**Geographic Distribution of HIV-1**

**Group M Subtypes**

Phylogenetic classification of HIV strains has assisted in tracking the diversity of the globally circulating strains. Subtypes C and A viruses account for most of the current HIV-1 infections worldwide, and they are followed by subtype B and the inter-subtype recombinants CRF01_AE and CRF02_AG. While subtype B viruses are primarily found in Europe, the Americas, and Australia, subtype C dominates in southern Africa and India\(^\text{94,103,121-123}\) (Figure 2). Subtype D viruses are predominantly found in central and eastern Africa, with a few cases sometimes appearing in southern and western Africa.\(^\text{20,103,124}\) Though a pure subtype E virus has never been found, it is part of the CRF01_AE recombinant form. CRF01_AE has been identified in Thailand, the Philippines, China, and central Africa. Subtype F has been found in central Africa, South America, and eastern Europe. Subtype G has been reported in western and eastern Africa as well as central Europe. Subtype H has been found only in central Africa. Subtype J was identified in Central America, and subtype K was found in the Democratic Republic of Congo and Cameroon. The recombinant virus CRF02_AG is the most prevalent virus in West Africa.\(^\text{20,94,122,125-132}\)

Despite the geographically specific distribution of some of the HIV-1 subtypes, we continue to see
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Factors. Primarily, it is believed that founder viruses were introduced into given populations, and once they adapted, they rapidly diversified. It has been hypothesized that the coexistence of different subtypes in a given population is determined by the biological characteristics of the subtype, in particular transmissibility and virulence, as well as by interactions and cross-infections between different risk groups. While the rate of HIV spread is not uniform across the globe, there appears to be an inverse correlation between the rate of disease spread and the variety of subtypes in a population. More specifically, in areas where the rate of spread has been relatively slow and stable, such as central Africa, we see a number of circulating subtypes in the population, as opposed to southern Africa, which has witnessed an explosive epidemic but has one predominant subtype. It has been speculated that the large variety of subtypes in central Africa

Figure 2. Worldwide distribution of major HIV-1 subtypes and HIV-2

It is difficult to interpret the variations seen in the distribution patterns of the various subtypes. As more than two decades have elapsed since the beginning of the HIV epidemic, the global patterns of spread are a result of a long period of evolution, which is nearly impossible to reconstruct. It seems likely that the geographic distribution of the different subtypes has been determined by a number of shifts in certain subtypes as the world becomes more of a global community. As immigration and travel increase, we have seen a shift in subtype distributions, and it has been estimated that anywhere from 25% to greater than 40% of the new infections in Europe are non-B variants of African and Asian origin. We are also witnessing an increasing number of non-B infections in the United States. For example, in a report on a well-studied military cohort, 6% of all new infections were due to non-B subtypes.

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has been due to the relatively low spread of HIV-1 in the population. Furthermore, it is believed that a number of subtypes can continue to coexist, potentially because of the low crossover between networks of risk groups.103

**HIV-1 Subtypes and Correlates of Disease and Pathogenesis**

In addition to the distinct epidemiologic patterns exhibited by various HIV-1 subtypes, differing biologic properties have been identified across some subtypes. There is evidence suggesting a relationship between subtype and modes of transmission. Studies in Cape Town,136 Finland,137 Thailand,138 Australia,139 and Chile140 found that most subtype B strains were associated with homosexual transmission while non-B strains were associated with heterosexual transmission. Similarly, in a study of U.S. military personnel, Brodine et al135 found that people infected with non-subtype B HIV were more likely to report heterosexual contact than those with subtype B infection.

Infection with certain subtypes has also been associated with increased risk of vertical transmission. A study conducted on mother-infant pairs in Tanzania revealed that mothers infected with HIV-1 subtype A, subtype C, and intersubtype recombinants were more likely to transmit to their infants than were mothers infected with subtype D.141 In an earlier related study, for perinatally transmitted C/D recombinant viruses, the V3 regions (env) were always from subtype C and never from subtype D, suggesting that viruses containing subtype D-V3 have a reduced fitness as compared to those with subtype C-V3.142 Conversely, a study conducted in Kenya indicated that women infected with viruses that contained some subtype D sequence were more likely to transmit than were women who had any other sequence combinations in the env and gag.143 Finally, a study of injecting drug users in Thailand found a significantly higher transmission probability associated with subtype E as compared to subtype B.144

Various studies have demonstrated significant differences between subtypes with regard to disease progression. We have described how Senegalese women infected with a non-A subtype were eight times more likely to develop AIDS than were those infected with subtype A.70 Studies from Uganda and Tanzania revealed that subjects with subtype A had a slower progression to disease than those with subtype D.145,146 Further research indicated that these differences might be explained by the fact that subtype D viruses are more likely than subtype A viruses to utilize the CXCR4 co-receptor for viral entry.147,148 Conversely, a study conducted in London, comparing HIV-1 disease in African immigrants and non-African Londoners, found no difference in progression by subtype. However, it should be noted that this study used a cross-sectional design and measured disease progression starting from when the HIV-1-infected person presented at the clinic.149

Clinical and immunological differences have also been found between subtypes. In Kenya, where subtypes A, C, and D were all co-circulating within the same population, it was found that high plasma RNA levels and low CD4 counts were significantly associated with subtype C infection.150

In a prospective study conducted at a methadone treatment clinic in Thailand, people infected with CRF01_AE were found to have higher viral loads in early infection than those infected with subtype B.151 However, this difference decreased over time, such that the viral loads were similar at 12, 18, and 24 months post-seroconversion.151 Similarly, a study in our laboratory indicated that women infected with CRF02_AG had a significantly higher viral load during the early stage of infection than did women not infected with CRF02_AG.152 Infection with multiple subtypes has also been associated with higher viral loads and
lower CD4 T-cell counts. Another study revealed that subjects infected with subtype D had lower average CD4 T-cell counts over the period of follow-up than did those infected with subtype A. Conversely, a study conducted in Thailand found no major differences with regard to the degree of immunosuppression or rates of opportunistic infections between people infected with subtype B' (Thai B) or CRF01_AE. However, it must be noted that this study was cross-sectional and that the analyses of lymphocyte counts did not take into account the time since seroconversion or the disease stage for any of the subjects assessed when comparing across the groups.

A few recent studies have identified structural and functional differences across subtypes. An in vitro study showed that viruses expressing a subtype C Vpu protein replicate with a lower efficiency than those expressing a subtype B Vpu; furthermore, when these viruses containing subtype C Vpu were injected into macaques, there was a more gradual CD4 T-cell decline as compared to macaques injected with viruses containing subtype B Vpus. Subtype B viruses also were shown to have longer gag proteins than non-subtype-B viruses; this variation could potentially affect protein structure and function. Preliminary data evaluating nef protein sequences revealed that insertions and deletions found in subtype C nef, which are not found in subtype B, might be associated with a slower disease progression. Finally, subtypes have been shown to differ in their propensity to recombine with other subtypes or CRFs; a recent in vitro study indicated that subtype C viruses were more likely than subtype B viruses to recombine with CRF01_AE.

Variation in subtype has also been associated with different levels of interaction with HIV-2. Sarr et al showed that the in vivo interaction between HIV-1 and HIV-2 was influenced by HIV-1 subtype. They found that the prevalence of CRF02_AG viruses was significantly higher in dually infected individuals compared with women who were singly infected with HIV-1.

A number of recent studies looking at resistance mutations have revealed differences in mutation patterns across subtypes. A study in Brazil suggested that subtype C viruses have a lower rate of accumulation of mutations conferring resistance to ARV than do subtype B viruses. ART-experienced patients infected with subtype A had a lower prevalence of K65R and Y181C than those with subtypes B or C. M89I/V was significantly more frequently observed in protease-inhibitor-treated patients with subtypes C, F, or G infection than in those with subtype B. Some studies found that HIV-1 subtype can influence selection and fading of HIV-1 variants with specific drug-resistance mutations after antiretroviral drug exposure. Following administration of single-dose nevirapine (sdNVP) for prevention of mother-to-child transmission (PMTCT), NVP-resistance mutations were higher in subtype-D-infected patients than in those with subtype A. The differences could be explained by the finding that Y181C faded from detection at a greater rate in women with subtype A, and K103N accumulated at a greater rate in women with subtype D. Additional studies showed that NVP resistance is highest in subtype C patients, followed by those with D and finally those with subtype A.

Some cross-sectional studies have failed to demonstrate biological or clinical differences in genetically diverse viral strains. A recent study found no difference in the rate of CD4 decline, clinical progression, or plasma HIV-1 RNA levels between individuals infected with subtypes A, B, C, or D. Laurent et al found no difference in survival, clinical disease progression, or CD4 decline between those infected with CRF02_AG and those infected with other strains of the virus. In addition, in a study comparing differences between subtypes...
A and D in mother-to-child transmission, subtype did not appear to influence infant survival.167

Impact of HIV-1 Subtypes on Vaccine Development

One of the major challenges to the development of an effective HIV vaccine is the genetic diversity of the virus. As a result, the role of HIV-1 subtype variation must be seriously considered—particularly given the geographic distribution of HIV-1 viruses, with Africa and Asia harboring the largest proportion of HIV-1 variants or subtypes. To date, it is not yet known the degree to which HIV-1 subtypes, subsubtypes, and circulating recombinant forms may be important in the design of an effective HIV vaccine.95

Whether or not a candidate vaccine against HIV-1 should be based on the dominant subtypes in a given region is unclear and the subject of much speculation and debate. In order to appropriately address the issue, one must consider the relationship between the HIV-1 genetic subtypes and immune responses. Since the most effective neutralizing antibodies appear to be effective across genetic subtypes, it has been argued that a vaccine targeting the humoral immune response focused on genetic subtypes would not be necessary; some support the approach of targeting more conserved regions of the genome, and that is likely to yield cross-protective immunity. Evaluation of cellular immunity by subtype has also indicated that cross-recognition across subtypes may be possible, at least in natural infection.168,169 As Moore et al105 point out, given that subtype designations were not made based on the antigenic or immunogenic properties of the virus and they do not correspond to neutralization serotypes, it might not make sense to be concerned with generating a subtype-specific vaccine, rather one that is broadly cross-reactive. Furthermore, the issue of superinfection and recombination begs the question of whether or not a vaccine generated against a single subtype will be cross-protective against other subtypes of virus.170

Nonetheless, there are many researchers who are still interested in generating clade-appropriate vaccines for given regions. The belief is that a subtype-specific vaccine candidate might increase the number of potentially cross-reactive epitopes by augmenting the level of similarity between the vaccine and the population. For those designing subtype-specific vaccines, there are two major approaches: isolate-based, or consensus- or ancestral-sequence-based vaccines.171 The first approach involves the selection of an isolate from the geographic region to which the vaccine is directed, while the second approach requires the construction of either a consensus or ancestral sequence using all available sequence data and an evolutionary model.171 When considering the possibility of using an isolate-based vaccine, the question arises as to where the representative isolate should be chosen from. Given the great diversity within subtypes and the fact that the geographic restrictions of viruses are slowly disappearing, this is a difficult choice. One solution is to use a polyvalent vaccine containing isolates as well as a group M consensus sequence.171

Overall, even though many recommend against generating subtype-specific vaccines, it is important to test the vaccines for all the subtypes to make sure that they are equally effective, as it has been found that, when used individually, the broadly neutralizing antibodies 2F5, 2G12, and IgG1b12 were not effective against a subtype C primary isolate but were effective when used in combination.172

CONCLUSION

In summary, HIV’s propensity for genetic diversification has resulted in two closely related HIV types, HIV-1 and HIV-2. These viruses have a distinct geographic distribution, with HIV-2 predominating in West Africa. Current epidemiologic trends suggest that HIV-2 is unlikely to result in a global
pandemic like HIV-1 and may in fact be decreasing in endemic regions. Major differences in the biologic properties between HIV-1 and HIV-2 suggest a more ancestral history to HIV-2 with adaptation to the human host and relative attenuation. This has resulted in lowered transmission potential and decreased pathogenicity. The diversification of HIV-1 appears to be more recent and less well understood. HIV-1 subtypes, subsubtypes, and recombinant forms demonstrate a unique geographic distribution, even within the African continent. Current studies suggest that the epidemiology of these variants is dynamic, particularly within Africa. In the future, it will be important to molecularly characterize HIV subtypes in order to accurately map the molecular epidemiologic timeline. This may indicate important differences in the transmission and pathogenic properties of HIV subtypes and determine their impact on HIV infection and potential immune correlates. Finally, it seems clear that the quest for an effective HIV vaccine will need to determine the impact of HIV diversity on the ability to provide protection. Further research—particularly in Africa, where these diverse HIV types, subtypes, and recombinant forms exist—will be critical to our ability to integrate this information in effective therapeutic and prophylactic interventions.
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During the course of viral infections, many viruses are not eradicated from the human host but are rather held in a state of containment by the host immune response, leading to a persistence or latency of the viral infection. A consequence of this viral persistence is the likelihood of reactivation of the infection if immune control ceases. This reactivation may occur during a state of immunodeficiency, perhaps accompanied by either a symptomatic or an asymptomatic viral reactivation. Prime examples of this phenomenon occur among viruses belonging to the Herpesviridae family, such as herpes simplex virus (HSV), cytomegalovirus (CMV), varicella-zoster virus (VZV), or Epstein-Barr virus (EBV). Immunodeficiency allows viral escape to take place, and varying forms and severity of reactivation disease may occur. These latent/persistent viruses are held in check by various components of the immune system.

OVERVIEW OF THE IMMUNE SYSTEM
There are two basic components of the immune system: the innate system and the adaptive system.

Innate Immune System
A wide range of innate immune mechanisms operate as a first line of defense upon exposure to infection. The physical barriers to infection include skin, mucous secretions, ciliary action, lachrymal tears, gastric acid, and the antagonistic effect of normal microbial flora. If penetration occurs, bacteria are destroyed by soluble factors, such as lysosomal enzymes, and through ingestion by phagocytic cells. The main phagocytic cells are polymorphonuclear leucocytes and macrophages. Once engulfed by phagocytic cells, these organisms are destroyed by a number of microbicidal mechanisms, including reactive oxygen intermediates or the synthesis of nitric oxide, which is released within cytoplasmic granules. The complement system, which is a multicomponent system, is triggered to attract phagocytic cells. Following activation of the complement system, with the accompanying activation and attraction of phagocytic cells and neutrophils, an inflammatory response occurs. There is also an elaboration of other acute phase proteins, such as C-reactive and mannose-binding proteins, which augment the inflammatory response.
Extracellular killing of virally infected cells can be carried out by natural killer (NK) cells. NK cells, an important component of the innate immune system, participate in early responses against infected or transformed cells either through the production of cytokines or by direct cytotoxicity. These responses are mediated through interactions involving killer cell immunoglobulin-like receptors (KIRs), which are found on the cell’s surface. Various KIR isotypes promote stimulation of NK cell activity, whereas others cause inhibition of activity. KIR isotypes function in close association with human leukocyte antigen (HLA) molecules. The KIR allele KIR 3DS1, in the presence of HLA-B BW4-80ILE, has been shown to delay HIV disease progression. Lysis by NK cells can also take place against cells recognized by host antibodies through binding of immunoglobulin to fragment constant (Fc) receptors on the NK cells.

Toll-like receptors (TLRs) play a key role in the response to microbial infections. TLRs recognize structurally conserved molecules derived from microbes and activate an immune response once these molecules have breached physical barriers, such as skin or intestinal tract mucosa. TLRs are believed to be a crucial component of the innate immune system and appear to be one of the most ancient, conserved components of the immune system. TLRs, which are a type of pattern-recognition receptor, recognize molecules that are broadly shared by pathogens but that are distinguishable from host molecules, collectively referred to as pathogen-associated molecular patterns (PAMPs).

During acute primary HIV infection, there is an acute depletion of CD4 cells in the intestinal mucosa, leading to compromise in the integrity of mucosal epithelium. A consequence of this is the translocation of microbial products from the lumen. These products include lipopolysaccharide (LPS), peptidoglycan, and bacterial 16sDNA, which all interact with TLRs and have the capacity to cause intense immune activation of a broad range of T cells. Upon engagement with the TLR, the T cells enter the cell cycle but fail to complete division and instead die by apoptosis. Further evidence of the role of the TLRs’ response to microbial products suggests that there is a direct correlation between LPS in plasma and the individual’s state of immune activation. The highest levels of LPS were found in progressive disease, whereas the lowest levels were found in long-term nonprogressors. Levels of bacterial products were also correlated with the state of activation of T cells and CD4 lymphocyte levels.

Cellular Factors

The recently identified protein called APOBEC3G has both an antiviral and an antiretroviral effect. This protein is from the APOBEC family of cytidine deaminases, which hypermutate retroviral genomes and render them unstable. These proteins are expressed in the natural target cells for HIV infection, namely CD4 lymphocytes and macrophages. When the virus infects these cells, APOBEC3G is packaged into the viral particle. When the virus subsequently infects a new cell, the APOBEC3G within the viral particle hypermutates the nascent viral complementary DNA (cDNA), which is then degraded. The vif gene product of HIV attempts to overcome this innate antiviral response by binding to the protein and overcoming its effect. TRIM5alpha is another cellular factor shown to have activity against HIV-1. This cellular protein interacts with the viral capsid and interferes with the uncoating process through which viral RNA is released into the cytoplasm of an acutely infected cell.

A feature of the wide range of innate immune responses is that they are not amplified by repeated exposures to infection (in contradistinction to the adaptive system). Recovery from viral infections can be assisted by interferons.
THE CLINICAL FEATURES OF ACUTE primary infection develop days to weeks after acquisition of HIV infection. The manifestations are protean and include a nonspecific influenza-like illness, infectious mononucleosis-like illness, or an acute neurological presentation, often with acute aseptic meningitis. It is important to take a good clinical history, as symptomatic primary infection occurs in the majority of cases. Generalized lymphadenopathy may be present, which more commonly involves the cervical nodes. In sub-Saharan Africa, clinical diagnosis may be made more difficult by the high burden of acute febrile illnesses.

**Diagnosis of Acute Primary Infection**
Routine laboratory testing may provide clues to aid in the diagnosis of acute primary infection. Hematological abnormalities are frequently noted, including thrombocytopenia, anemia, leucopenia, lymphopenia, and monocytosis, and atypical lymphocytes may be present on a blood film. CD4 counts are usually decreased, and there is a reversal of the CD4:CD8 ratio.

Tools used to detect primary infection in the absence of seroconversion include p24 antigen assays and nucleic acid testing. Assays for p24 antigen are widely available and relatively inexpensive. However, the sensitivity of this assay is often suboptimal due to antibody that has formed a complex with the antigen. The assay’s sensitivity can be enhanced by using an immune complex dissociating step before performing the assay.

Where resources are available, the test of choice is the polymerase chain reaction (PCR) test for HIV-1 RNA. During acute infection, the HIV RNA levels are typically greater than 10,000 copies/mL of plasma. Levels lower than 10,000 copies/mL warrant further investigation.

**Adaptive Immune System**
The primary cells of the adaptive immune system are lymphocytes, which are derived from pluripotent cells in the bone marrow. The lymphocytes undergo serial proliferation and differentiation, ultimately leading to the development of a cellular and humoral immune response (Figure 1).

**Cellular Response**
Bone marrow–derived lymphocytes actively divide in the thymic cortex and then migrate to the medulla, where they are induced to differentiate into cells that will eventually participate in cellular immune responses. The thymus gland is very active in infants and is responsible for the selection of T cells in the body that will provide protection throughout life. During a person’s lifetime, the thymus gland atrophies and becomes smaller; until recently, it was thought that the gland became inactive after the third decade of life. Recent evidence suggests, however, that the gland retains activity throughout a person’s life, but that the thymic reserve declines with age. These emigrant naive T cells migrate to the secondary lymphoid tissues, such as the inner cortex of the lymph nodes, the periarticular sheaths in the lymph nodes, and the Peyer’s patches in the gut, tonsils, and appendix. Once at these sites, the thymic-dependent T lymphocytes become immunologically competent.
T cells only recognize antigen when it is on the surface of a body cell. Accordingly, the T-cell surface receptors recognize antigen when it is presented in conjunction with another surface marker belonging to a group of molecules known as the major histocompatibility complex (MHC). When this occurs, a naive T cell is introduced to an antigen and becomes “primed” and activated as an effector cell. There is a constant movement of naive, effector, and memory cells from the blood circulation to the lymphatic circulation and lymph nodes. Antigen-primed T cells migrate to tissues where HIV replication occurs; in these tissues, clonal expansion and recruitment of other effector cells takes place, leading to hyperplasia of the tissue, which manifests as lymphadenopathy, a condition often seen in early phases of HIV infection.
Cytotoxic T lymphocytes (CTLs) bear the CD8 molecule and are a major immunological mechanism in the control of viremia. They inhibit viral replication in at least two distinct ways. In the first instance, direct killing of infected cells takes place. When a virus invades a cell, a proteolytic degradation of viral proteins takes place. These proteins are then transported into the endoplasmic reticulum, where they form a complex with a developing MHC class-1 molecule and are transported to the cell surface. The presence of the viral protein (usually 8–10 amino acids in length) within the protein-binding cleft of the class-1 molecule acts as an immunological signal to CTLs. This event activates the CTL to kill the infected cell through a direct recognition mediated by the T-cell receptor (TCR) on the CTL. This cell killing is carried out through the production of granzymes and perforins by the CTL. Although most cytolytic activity is mediated through this route, CD8 cells expressing Fas ligand can also bind to Fas (CD95) on the surface of target cells, thereby inducing apoptotic cell death. At the same time, activation of the CTL leads to the release of soluble antiviral factors, which inhibit progeny viruses from entering target cells. These antiviral factors include the beta chemokines RANTES (regulated on activation normal T cell expressed and secreted), MIP1α (macrophage inflammatory protein 1α), and MIP1β. These chemokines prevent HIV from entering cells by competing for binding to certain co-receptors and promoting internalization of the HIV co-receptor. RANTES, MIP1α, and MIP1β are active against macrophage-tropic chemokine receptor 5 (CCR5, or R5) viruses; other soluble factors are active against CXC chemokine receptor 4 (CXCR4, or R4) viruses.

Recent studies have reported additional antiviral factors that are produced by CD8 cells but that are clearly not chemokines. A group of defensins produced by neutrophils and CD8 cells have a similar action. This compound is probably one constituent of soluble antiviral factors loosely termed CD8 antiviral factor (CAF). These factors act by inhibiting viral transcription and appear to have an action that is distinguishable from chemokine- or defensin-mediated viral suppression. CD8-mediated responses may be related to progression of HIV disease and disease outcomes.

All T lymphocytes bear the CD3 molecule and the T-cell receptor. The major T-cell subset bears the CD4 molecule, and these T cells are responsible for coordinating and helping the immune response—hence, the name T-helper cells. They promote CD8 cell activity and support B cells in the production of antibodies.

In addition to CTLs, the cellular immune response also relies on virus-specific T-helper cells. T-helper cells bear the CD4 molecule, and these T cells are responsible for coordinating and helping the immune response. The T-helper cells become activated and drive immunological signals to other categories of immune cells by direct cell-to-cell interactions and by the release of soluble factors. In this instance, the viral peptides that serve as targets for the T-helper response tend to be larger and are often 12–15 amino acids in length. A hallmark of progressive HIV infection is the lack of strong HIV-specific T-helper cell responses, which are lost early in the infection; this loss often occurs during acute primary infection. There are interesting clinical correlates of this phenomenon. In patients who have strong T-helper responses, viral suppression is good. This is also seen in so-called elite controllers, where T-helper responses are optimal.
antigen receptors and as identification markers. Upon stimulation, these cells undergo blast transformation, proliferation, and differentiation, eventually becoming plasma cells that produce antibody. The majority of antibodies in HIV infection are nonneutralizing and are often directed against virion debris rather than against conformational epitopes on intact virions. Neutralizing antibodies are directed against a number of different epitopes, including antibodies that prevent entry of virus into cells (directed against the V3 loop) and into CD4 binding (CD4-binding-site antibodies). Some antibodies are directed against linear portions of the viral envelope, whereas others are directed against conformational structures.

Some potent neutralizing antibodies do not prevent binding of glycoprotein 120 (gp120) to CD4; instead, they interact with the viral–receptor complex, thus preventing the necessary conformational change that allows entry to be mediated by gp41. Neutralizing antibodies as a means of immune control have been problematic in that they tend to be weak and lack broad cross-reactivity. The viral envelope displays considerable adaptability, with the capacity to revise its glycosylation sites, resulting in a changed three-dimensional configuration that allows it to escape antibody-mediated neutralization. Lack of capacity to neutralize new strains arising within an individual results in an expansion of the viral “quasi species.” The relationship of autologous neutralizing antibody responses to disease progression has been studied. Studies comparing the strength and breadth of neutralizing antibodies in long-term nonprogressors and rapid progressors (see definitions later in this chapter) showed that responses in “controllers” was significantly greater than responses in “progressors.”

As with the cellular immune responses, the humoral responses are often disregulated and are characterized by paradoxical hyperactivation and hyporesponsiveness. Hyperactivation is reflected by polyclonal hyperglobulinemia, only a portion of which is directed against HIV antigens. Other features of the hyperactivation include bone marrow plasmacytosis, heightened expression of activation molecules on B lymphocytes, and the presence of autoreactive antibodies in plasma. The humoral hyporesponsiveness is manifested by a decrease in protective antibody responses to antigens and after immunization with protein or polysaccharide vaccines.

Other Important Components of the Immune System

**Macrophages**

Infection of monocytes/macrophages occurs via the CD4 receptor, which is expressed on the cell surface; however, this infection is in smaller numbers as compared with CD4 lymphocytes. Because macrophages do not undergo lysis, these cells become significant reservoirs of HIV. Monocyte migration from the blood to tissues takes place continuously, facilitating the transport of the virus to various tissues and anatomical compartments. Both monocytes and macrophages are antigen-presenting cells that stimulate T- and B-lymphocyte responses; they are also primary effector cells. They both have an extensive array of antimicrobial, antifungal, chemotactic, and secretory functions, including the production of proinflammatory cytokines. Although many of these functions are preserved in HIV infection, many others are not. One of the most important functional impairments relates to the decreased killing of mycobacteria, which is significant due to the high burden of mycobacterial disease in developing countries, where the majority of HIV infections occur.

**Dendritic Cells**

Dendritic cells (DCs) are an important group of antigen-presenting cells that are derived in the bone marrow from precursor CD34 stem cells and
that act as a primer of the immune response. DCs, which are found in lymphoid tissue and in non-lymphoid tissues (e.g., lungs, skin, and brain), trap antigens and migrate to lymphoid tissue, where the antigens are presented to immunocompetent cells. There is also a concentration of DCs within lymph nodes; these DCs form part of the follicular dendritic network. Over the course of HIV disease, there is a loss of the follicular dendritic network, presumably due to a loss of interactive signals with immunocompetent cells and to a disturbance in the tissue's cytokine milieu.36

DCs are thought to play an important role in the early events of HIV infection. The major pathway of viral transmission is by cell-associated virus, which is taken up by interdigitating dendritic cells (Langerhans cells) situated in the cervical, vaginal, and rectal mucosa. These cells are characterized by the expression of CD1a and the presence of Birbeck granules. Virus has been shown to be carried on dendritic cells by way of DC-SIGN (dendritic cell-specific ICAM-grabbing non-integrin) to the regional lymph nodes, where a bridgehead of infection is established. Two populations of DCs can be identified in blood: myeloid dendritic cells (characterized by expression of CD11c) and plasmacytoid dendritic cells (CD123). Circulating numbers of these cells tend to be diminished in HIV infection, and this may occur early in primary infection.37,38

The Role of Cytokines
CD4 cells communicate with other cellular components of the immune system by either cell contact or the elaboration of soluble factors known as cytokines. There are a number of different cytokines, each having different and distinct actions. A bipolar Th1/Th2 concept was originally described in the mouse model, in which there was a division of CD4 cells into Th1 and Th2 cells based on the cytokine production from the respective cells.39,40 Due to the enormous complexities of the human immune response, this model is not directly applicable to humans. However, relevant features can provide some insights into immunopathogenesis during the course of HIV infection. Th1 cells secrete cytokines that will drive a cell-mediated immunity effected predominantly by CD8 cells. Examples of these cytokines are IL-1, IL-2, IL-6, IL-12, IL-15, tumor necrosis factor alpha (TNF-α), and interferon-γ. A Th2 response drives a humoral immune response and will stimulate B cells. Th2 cytokines include IL-4, IL-5, and IL-10. Th1 and Th2 cells are derived from a precursor Th0 cell that is thought to be a naive cell capable of secreting a broad range of cytokines. It is postulated that the differentiation into a Th1 or Th2 response is a function of the type of antigen initially encountered and the immunological environment predominating in the tissue at that time (Figure 2). There is a cross-regulation between these distinct responses, as well as a synergism in the differing modes of action. During HIV disease progression, CD4 cell loss leads to a progressive decline in the Th1 responses and therefore to a progressive decline in cell-mediated immunity, with a switch to Th2-type immunity in late-stage disease.

There is also a group of CD4 cells, classified as T-regulatory (Treg) cells, that serve a regulatory function. These cells, which bear the CD25 marker, are able to inhibit both Th1 and Th2 responses.41 The Treg cells express cytokine IL-10 and transforming growth factor beta (TGFβ). Some contrasting effects have been attributed to Treg cells, including impairment of HIV-specific responses on the one hand and suppression of immune activation on the other.42

Recent research has demonstrated the possible importance of Th17 cells, which elaborate a cytokine IL-17. IL-17 is important in host defense against extracellular pathogens, such as bacteria and fungi. Th17 cells are profoundly depleted in
levels of immune activation have been shown to be a feature in HIV-negative subjects in Africa when compared with their European counterparts, suggesting that environmental factors may be responsible for this observed difference. Some investigators speculate that hyperimmune activation demonstrated in Africans may be a contributing factor in the pathogenesis of AIDS in Africa. This immune activation has the potential to create a situation where HIV can be more readily acquired and, if acquired, can lead to a more rapid progression of disease.

The gut mucosa of HIV-infected individuals and in pathogenic models of simian immunodeficiency virus (SIV) infection. With the loss of Th17 cells, bacterial commensals within the gut lumen may gain access to deeper tissues and contribute to the events involving the gut-associated lumen tissue (GALT) in primary infection, leading to immune activation and CD4 cell loss. The proinflammatory cytokines, particularly TNF-α, can upregulate HIV replication and drive high viral loads, as was seen in a cohort of HIV-infected African patients during and after treatment for tuberculosis. Abnormal


**NATURAL HISTORY OF HIV INFECTION**

Figure 3 outlines the events occurring in the typical course of HIV infection. The sections that follow provide a detailed description of immunological events occurring at points A through E.

**Point A**

Point A represents the time of acquisition of HIV infection. At this time, the immune system's status is normal (as represented by the CD4 count, which in adult subjects lies between 800 and 1200 cells/mm³). This is followed by a rapid burst of viral replication, during which very high levels of virus are often recorded. The replication of virus takes place in CD4 lymphocytes, leading to a loss of CD4 cells. Although destruction of CD4 cells occurs throughout the body, it is particularly profound in the gut’s mucosa-associated lymphoid tissue.

**Point B**

Point B represents the curtailment of the burst of HIV replication. The control is initially brought about by a cellular immune response, predominantly in the form of CD8 cytotoxic lymphocytes.⁴⁶,⁴⁷ Animal models have also demonstrated the importance of CD8 T-cell responses in the control of viremia during primary infection with SIV.⁴⁸ Although antibodies are detected at this time, they do not contribute meaningfully to the curtailment of viral replication, because they are nonneutralizing. Antibodies are, however, useful in the clinical context in that they can be detected by various test systems (usually serological) for identifying HIV infection. The interval between point A and point B is referred to as the window period, during which the patient is antibody negative even though viral replication can be detected. The appearance of the immune response at point B is often accompanied by
a clinical illness, which can take various forms and is known as the seroconversion illness. This illness often resembles an acute mononucleosis syndrome, similar to that seen in acute EBV infection. In both HIV and EBV infection, the clinical syndrome is caused by the immune response to the respective virus. Viral levels are suppressed, and, depending on the quantity and quality of the immune response, a level of virus in the body is reached that is unique to each individual. This “viral set point” has prognostic significance, in that patients with lower viral set points enjoy a survival advantage.

**Point C**

Although there is some recovery in CD4 levels in the peripheral blood at point C, premorbid levels are not regained. The maturation of the immune response may take several months, and it is only then that an effective viral set point is reached. The patient then enters the period of clinical latency (point D).

**Point D**

Point D may last for a number of years. During this period, the patient is usually asymptomatic or at most mildly symptomatic. Viral levels (i.e., viral load) remain remarkably constant, with occasional periodic “viral blips.” These blips are due to upregulation of viral replication, often brought about by the immune activation surrounding an intercurrent infection or immunization. When the immune activation ceases, the viral levels fall back to previous set-point levels. During this clinical latency, however, there is a progressive and gradual loss of CD4 cells brought about by various pathogenetic mechanisms.

With the decrease in CD4-cell functionality, particularly in regard to the help they offer CD8 cells, viral escape from the immune system takes place, accompanied by increasing viral levels and expansion of the viral quasi species. Numerous studies have shown that CTL responses decline with disease progression; this decline is probably related to the number and functionality of virus-specific T-helper cells.

The architecture of lymphoid tissue is also altered over time, resulting in progressive loss of the follicular dendritic cells (FDCs). During the early phases of disease, lymph nodes are hyperplastic, with trapping of virus within the FDC network and continual presentation of antigens to the immune system. With the disintegration of the lymphoid tissue, however, the virus is no longer trapped, resulting in a spillover of virus into the peripheral blood. This spillover contributes to the high blood levels of virus seen in the later stages of HIV disease.

**Point E**

When the amount of CD4 cells reaches critically low levels (usually less than 200 cells/mm³), symptomatic disease and other opportunistic events are likely to occur. At this time, various virological and immunological events have taken place. With the loss of immune control comes an expansion of the viral quasi species and a change in the tropism of the virus from a macrophage-tropic virus, which utilizes the CCR5 molecule for viral entry (R5 virus), to a lymphocyte-tropic virus, which utilizes the CXCR4 molecule as a co-receptor (R4 virus). Monitoring of CD4 counts and viral load is important at all stages of infection, as it is used to help clinicians determine when to commence preventive chemotherapy for opportunistic infections and when to commence antiretroviral therapy (ART). Both of these therapies attempt to halt and, to an extent, reverse the immunological damage that has taken place. In recent years, the timing of ART initiation has undergone modifications in an attempt to strike a balance between protection of the immune system and prevention of the long-term effects of ART.
During the course of HIV infection, there is a switch from R5 to R4 viruses (Figure 4). Studies have shown that subtype-C viruses almost exclusively utilize CCR5 for viral entry and that individuals who are homozygous for a deletion of the gene coding for CCR5 (CCR5Δ32) are resistant to HIV infection. The mutant CCR5 allele is most commonly detected in Caucasian populations. Individuals who are heterozygous for the CCR5 deletion have a slower progression of disease. To date, the mutant allele has not been detected in African or Asian populations. There have been conflicting reports on the influence of the 64I allele of CCR2 on disease progression, with some studies showing delayed progression and others showing no influence of the mutant allele. Notably, among a cohort of sex workers in Kenya who showed resistance despite repeated high-risk exposures to HIV-1, resistance was not related to any of the above polymorphisms in the chemokine receptors.

**Chemokines**

Chemokines are soluble proteins that attract white blood cells to sites of infection or inflammation in the body. They are expressed in a wide range of cell types and tissues in the body and are classified into two subfamilies: CXC or α-chemokines and CC or β-chemokines. HIV utilizes the chemokine receptors on CD4 cells as a co-receptor, an interaction necessary for viral entry. Macrophage-tropic HIV-1 viruses are nonsyncitium inducing (NSI) in culture systems and utilize the CCR5 receptor for viral entry (R5 viruses). Almost all new infections are due to macrophage-tropic viruses. The β-chemokines MIP1α, MIP1β, and RANTES are the normal physiological ligands for CCR5. These agents prevent entry of HIV into cells. T-cell-tropic viruses, which are syncitium inducing (SI), utilize CXCR4 for viral entry (R4 viruses). The normal physiological ligand for CXCR4 is stromal-derived factor 1 (SDF1).
MECHANISMS OF CD4 CELL LOSS
A hallmark of HIV disease is the functional impairment of CD4 lymphocytes, as well as their loss in lymphoid tissue. A sequential loss of immune responsiveness to recall antigens, followed by alloantigens and then mitogens, has been described.\(^\text{36}\) The depletion of CD4 cells appears to result from factors other than the direct cytopathic effect of HIV itself. Destruction of CD4 cells by various mechanisms, diminished production of CD4 cells, and the sequestration of CD4 cells in lymphoid tissue all appear to contribute to the decrease in circulating CD4 cells. CD4 T cells have a key role in mediating immune responses through the production of immunomodulatory cytokines; the loss of these cells and the failure of the remaining cells to function adequately lead to a critical impairment of immune responses.

Diminished Production
In HIV disease, the output of lymphocytes from the bone marrow is impaired. This impairment may arise from diminished functionality of progenitor CD34 cells, which appear to be susceptible to HIV infection,\(^\text{61,62}\) or from the replacement of bone marrow tissue due to mycobacterial infection or lymphoma in more advanced disease. T lymphocytes undergo maturation and differentiation in the thymus gland, where T cells with very high avidity for host HLAs that bind endogenous peptides are deleted, thus reducing the risk of autoimmune reactivity. Also eliminated are T cells with a low avidity for the host HLAs, thus ensuring that the remaining cells are potentially capable of recognizing host HLAs that bind foreign peptides. The population of antigen-naive T lymphocytes that emerges contains a diverse distribution of T-cell receptors capable of recognizing a broad array of peptide antigens. Although thymic activity is greatest during early development and childhood, there is evidence that thymic function still occurs in adults.\(^\text{8}\) There is also evidence that HIV can infect thymic stromal cells and that R4 viruses can infect thymocytes, thus interfering with thymic function.\(^\text{63}\)

The role of the thymus in HIV disease is complex. Thymus size is often preserved in HIV-infected adults and can also be evident in older subjects;\(^\text{64,65}\) there is also indication that thymic output is maintained in HIV-uninfected people.\(^\text{66}\) Other evidence indicates that thymic size decreases after viral suppression with ART, suggesting that thymic
epitope can abolish CTL recognition. Failing CTL function is an important correlate of HIV disease progression. A study of HIV-positive mothers who transmitted virus to their children showed that CTL escape played an important role in the transmission of virus. HIV-positive children who expressed HLA B27, an allele usually associated with viral control in adults, failed to have adequate viral control and had higher viral loads. Investigation revealed that mothers who expressed HLA B27 also transmitted a CTL escape variant to their children, such that the dominant B27-restricted Gag epitope could not be targeted. In contrast, children who inherited HLA B27 from their fathers and received virus from their mothers (who had not been under B27-restricted selection pressure) were able to mount a vigorous CTL response and achieve better viral control.

Apart from the viral escape mutation mechanism that interferes with the cytotoxic activity of CD8 cells, it has been shown that CD8 cells may become dysfunctional. This dysfunction may be due to reduced lytic activity, poor proliferation in vitro, or decreased expression of signaling molecules that mediate T-cell receptor activation.

Neutralizing Antibodies
There is a rapid evolution of immune escape directed against the predominant viruses circulating in the blood. Escape occurs mainly through mutations in glycosylation sites in the envelope protein. A new generation of antibodies then evolves to deal with this “new” mutant virus, and the process is repeated. Unfortunately, these responses are type specific, and there is limited cross-reactivity.

Viral Diversity
HIV is a retrovirus with an inherent capacity to develop viral mutations because of an error-prone reverse transcriptase enzyme and the lack of a corrective proof-reading mechanism. This capacity
is further fueled by high levels of viral replication and the effect of the immune system's selection pressure. Even a single mutation in a defined CTL epitope is sufficient to impair CTL recognition.81

Establishment of a Viral Reservoir

Most T cells exist in the resting state, with approximately half being naive cells that have not yet responded to an antigen. The remainder of the resting T-cell population consists of memory T cells, which have encountered antigen and have been programmed to react to that specific antigen in the future. When these memory cells encounter the antigen a second time, they become activated, undergo blast transformation, and carry out that cell's specific immunological function. After the immunological event, a small number of these cells revert back to the resting memory cell state. HIV preferentially replicates in activated CD4 cells, which are typically destroyed in the process. However, some cells become infected when reverting to the resting state. When this occurs, HIV becomes integrated into long-lived-memory CD4 cells, a situation known as postintegration latency. These events begin early in infection, creating over time a reservoir of latently infected cells. These cells are sheltered from the immune system; because they are transcriptionally inactive, they are not eradicated by current ARTs.

The molecular mechanisms involved in the establishment of latency have not been fully elucidated. Although it is generally believed that the virus exists in a transcriptionally silent state, recent work indicates that although the “latent” genome is transcriptionally active, the viral transcripts are retained in the nucleus.82 Certain conditions within resting T cells inhibit HIV gene expression—for example, some of the host transcription factors (NF-κB and nuclear factor of activated T cells) necessary for gene expression are absent. Recent evidence also indicates that exposure of quiescent cells to certain cytokines can induce those cells to move along the cell cycle to the G1 phase, thus removing barriers to reverse transcription. Such cells are therefore susceptible to HIV infection but do not undergo full activation and cell cycling. Infection of quiescent cells may thus establish a repository of infected cells, maintaining a reservoir of HIV that exists for many years.83,84 Infected individuals harbor approximately one latently infected cell per million resting CD4 cells. Although the size of the infected cell pool is relatively small, it has the capacity, upon activation, to become transcriptionally active and to release virions into the lymphocyte circulation. The frequency of these cells tends to remain stable for years and is minimally affected by ART.85,86

Monocytes and tissue macrophages are also considered to be important cellular components of viral persistence and latency.87,88 The general consensus is that macrophages within the central nervous system serve as a reservoir of HIV infection. It is unclear, however, whether the reservoir comprises long-lived HIV-infected microglial cells or whether the reservoir is continually replenished by infected monocytes migrating from the periphery. Other potential reservoirs of infection include sites within the genital tract89,90 and possibly the kidney.91

Research has shown that neither the prolonged use of ART nor strategies to activate expression of virus from these reservoirs (by activating T cells through the T-cell receptor or with IL-2) have been successful in eradicating virus from the reservoirs, though the amount of virus may decrease slightly.92-94 An added concern is that mathematical modeling and limited experimental evidence suggest that pharmacologically induced high-level T-cell stimulation not only is unlikely to eliminate the T-cell reservoir but could potentially result in T-cell depletion as well.95
**CORRELATES OF DISEASE PROGRESSION**

The majority of HIV-infected individuals remain asymptomatic and maintain good viral control for a number of years before CD4 cell loss allows viral escape and opportunistic disease. This situation occurs in 85% of individuals; without ART, a period of 7 to 10 years passes before full-blown AIDS occurs. A smaller percentage of individuals (5%–10%)—a group known as “rapid progressors”—display poor viral control, rapid loss of CD4 cells, and rapid disease progression. At the other end of the disease spectrum is a group that displays a slow progression to disease. This latter group, comprising 5%–10% of infected individuals, is referred to as “long-term nonprogressors” (LTNPs) or “elite controllers.”

**FACTORS INFLUENCING THE IMMUNE RESPONSE**

The immunological events that take place at various stages of HIV disease were discussed in the preceding sections. The following section covers factors that influence the immune response at the various stages of disease.

**Host Genetic Factors**

Differences in host genetic composition may also affect the immune response and, consequently, the rates of disease progression. Polymorphisms in the chemokine co-receptors necessary for viral entry have been associated with differing rates of disease progression. These polymorphisms are seen in people who are heterozygous for the delta-32 base pair deletion in the CCR5 open reading frame. These individuals are characterized by decreased expression of cell surface CCR5, lower viral load, and slower disease progression. Viral peptides are presented to the immune system for recognition in association with HLA alleles, and certain HLA alleles may vary in their efficiency of antigen presentation. It has also been shown that even a single substitution in an HLA molecule can determine peptide binding and presentation. Certain HLA class-1 alleles have been associated with a greater risk of disease progression, such that patients with a greater heterozygosity in HLA class-1 alleles have demonstrated better outcomes. In essence, this would imply that patients with a broader immune response enjoy a better prognosis. Certain HLA backgrounds have been associated with protection against HIV infection; these backgrounds have been described in seronegative partners of HIV-infected individuals and in certain groups of sex workers who have been resistant to infection (see later in this chapter). For instance, a study of seronegative sex workers in South Africa found a clustering of HLA-A24 that was not found in HIV-infected women, suggesting that this allele may confer protection. Certain HLA molecules (e.g., HLA-B27 and HLA-B14) are associated with an immunodominant state, which results in a slower progression to AIDS. In these cases, the slow disease progression results from the HLA recognition of immunodominant epitopes, leading to a restriction in the viral diversity within the viral quasi species and thus in greater immune control. This, in turn, leads to a lower viral set point. In contrast, HLA-A29 and HLA-B22 are significantly associated with rapid progression to AIDS, possibly a result of limited antigen presentation. A persuasive example of the influence of the HLA system on the immune control of HIV infection is seen among LTNPs, or elite controllers, among whom there is a significant association with HLA-B*57.

**Immune Activation**

As stated earlier, immune activation plays a key role in the pathogenesis of HIV infection, as seen in resource-limited settings, in particular in sub-Saharan Africa. Activation of the immune system is a necessary component of the body’s response
to invading organisms. However, if the immune activation is excessive or prolonged, a number of negative consequences may occur. This excessive immune activation occurs in HIV infection because of the ongoing mutation and evolution of the virus within the quasi species. The negative effects of excessive immune activation include upregulation of HIV replication, driven by proinflammatory cytokines and leading to CD4 cell loss; integration of unintegrated viral RNA; apoptosis of uninfected cells; and polyclonal stimulation of B cells, with production of high levels of immunoglobulins.103,104

The immune activation noted in HIV-infected individuals is probably multifactorial in nature. The first factor is the direct effect of HIV on T cells. The interaction between gp120 and the CD4 or CCR5 molecule can induce intracellular signaling.105 The second factor inducing systemic immune activation is the host immune response to HIV. This activation is likely to be initiated at the innate immune system level, involving plasmacytoid dendritic cells through TLR stimulation, resulting in adaptive HIV-specific humoral and cellular responses.106 A further mechanism of immune activation relates to the translocation of intestinal microbial products from the intestinal lumen to the systemic circulation, where they can cause immune activation by binding to TLRs.4,107 Other pathogens, including opportunistic pathogens, play an additive role in promoting immune activation.108 It has also been shown that helminth infections, which cause immune activation, may result in enhanced disease progression.109 Another potential factor is the non-antigen-specific bystander activation of T and B lymphocytes caused by increased stimulation of proinflammatory cytokines. This activation results in these cells becoming prone to activation-induced cell death.110,111

At the molecular level, there is an increase in the number of CD8 cells bearing activation markers such as CD38 and HLA-DR. High expression of these activation markers is seen at the time of seroconversion. High levels of CD8/CD38 expression has been noted in the presence of high viral loads and serve as an independent prognostic marker.112-114 A further measure of the state of immune activation is reflected in the levels of inflammatory cytokines in HIV-infected subjects. Plasma levels of TNF-α, IL-1, and IL-6 are often elevated in later stages of HIV infection, and both TNF-α and IL-6 levels are directly correlated with plasma HIV RNA levels.115 With the administration of ART, measures of immune activation decrease, further supporting the hypothesis that the activation is related to viral replication.

States of immune activation are more commonly encountered in African populations than among populations in developed countries.116 This is due to the high levels of immune system activation seen in settings where there is a high burden of endemic infectious diseases, such as tuberculosis, respiratory infections, schistosomiasis, and various sexually transmitted infections (STIs).117 In the case of STIs, activated lymphocytes are found both systemically and at the site of infection and are associated with genital ulceration, which facilitates the acquisition and dissemination of HIV infection. Helminthiasis has also been associated with significant immune activation in African subjects.

With the introduction of ART, a significant and rapid decrease in activation markers occurs. A drop in the viral load is associated with a decrease in CD38/HLA-DR+, CD38/CD45RO+, and HLA-DR+CD45RO+. In this instance, the RO surface marker refers to the marker that identifies memory cells, and the CD45+ marker is found on all leucocytes.

**Viral Subtype**

The proinflammatory cytokines have been shown to upregulate HIV replication due to the binding of nuclear factor kappa B (NF-κB) to a consensus sequence in the core enhancer region of HIV’s long
terminal repeat (LTR). Studies have shown that the NF-κB enhancer configuration and copy number differ among subtypes. In subtypes B and E, one or two NF-κB consensus sequences are present in the viral LTR’s core enhancer region. In subtype C, however, three or more NF-κB consensus sequences have been reported. Thus, in subtype C, the potential exists for greater cytokine-driven viral replication. The resultant higher viral loads could, in turn, result in greater disease progression.

During primary HIV infection, a massive depletion of CD4 memory cells occurs in the GALT. In simian HIV (SHIV)-infected macaque monkeys, the viral RNA of the SHIV chimera bearing the subtype-C promoter predominated in feces and serum during primary infection. The subtype-B promoter, however, was found predominantly in peripheral blood mononuclear cells. Viral RNA in the feces reflects viral production in GALT. The action of cytokines, such as IL-2 and IL-15, in the intestinal environment can upregulate HIV replication by interaction of these cytokines with the NF-κB binding sites. This interaction may translate into differences in disease progression due to higher viral loads. It has been noted that there is a slower disease progression in subtype-A infections, with significant differences observed in viral load at peak viremia during acute primary infection, and at the viral set point.

**Malnutrition**

Malnutrition, an endemic problem in resource-limited settings, is an important underlying cause of childhood deaths, as well as an aggravating factor in a number of infectious diseases among adults. Malnutrition alters all defense mechanisms, including anatomical barriers, cell-mediated responses, phagocytic and microbicidal functions, and humoral functions (both antibody and complement). A reduction in the opsonic capacity of serum, diminished avidity of antibodies, inhibition of neutrophil and macrophage migration, and reduced intracellular killing capacity of phagocytic cells have also been recorded in individuals suffering from malnutrition. Secretory immunoglobulin A (sIgA) levels in these individuals are also decreased, which can lead to increased bacterial colonization of the respiratory epithelium.

The cellular immune defects observed in malnourished children include involution of the thymus gland, with a decrease in thymus-derived lymphocytes, leading to an impairment of T-dependent antibody responses and an imbalance of the Th1/Th2 axis. HIV infection, in turn, also causes several metabolic disturbances, including changes in whole-body protein turnover, increased urinary nitrogen loss, and skeletal muscle breakdown, which further compromise the nutritional deficit.

A feature of HIV infection is a depletion of micronutrient status. These micronutrients include selenium, zinc, magnesium, vitamin E, cyanocobalamin, vitamin C, folic acid, and niacin. All of these factors play a key role in various immune processes, as well as in the functional and structural integrity of epithelial tissues. They are also involved in DNA synthesis, hemopoiesis, and decreasing oxidative stress in tissues.

**Age at the Time of HIV Infection**

Data from a number of cohort studies indicate that the risk of disease progression and mortality can be correlated with age, after adjusting for CD4 counts and plasma HIV RNA levels.

**Interaction between HIV and Malaria**

The interaction between HIV and malaria has important public-health implications in resource-limited settings, particularly in sub-Saharan Africa, where there is a high prevalence of both infections. HIV infection impairs the cell-mediated immunity that is crucial for antimalarial responses. In areas of stable malaria transmission, such as Uganda,
malaria infection rates and frequency of clinical illness appear to be increased in HIV-infected adults, particularly those with low CD4 counts. For instance, a study in urban Malawi found an increasing incidence of clinical malaria with significant parasitemia when CD4 counts decreased, suggesting an inverse relationship between parasite density and CD4 count. Studies suggest that HIV-associated immunosuppression interferes with parasite control and a loss of specific protection against malaria-driven disease.

In regions of unstable malaria transmission, HIV-infected adults are at an increased risk of complicated and severe malaria and death. This is significant because more than half of the global burden of malaria is in hypendemic and mesoenemic regions. For instance, studies in South Africa have reported a doubling of the risk of complicated malaria and a fivefold increased risk of death in HIV-infected adults. An additional factor is the prolonged clearance times for parasitemia following malaria treatment in HIV-infected adults. A study in Malawi, examining the effect of malaria on HIV disease, demonstrated up to a 10-fold increase in HIV viral load among patients with malaria. This effect was correlated with the level of parasitemia and clinical severity of disease. Such increases in viral load will lead to CD4 cell loss, which is likely to influence the progression of HIV disease.

LESSONS LEARNED FROM SPECIAL GROUPS

Highly Exposed, Persistently Seronegative Individuals

In most settings, highly exposed, persistently seronegative (HEPS) individuals have been identified who, despite repeated exposures to HIV, have remained seronegative. The immune response among HEPS may provide important clues regarding the dominant correlates of immunity that could potentially assist vaccine development. The mechanisms of protection among HEPS remain unclear, and there may be more than one possible pathway. For instance, in some individuals, there is evidence that an abortive infection has occurred, while in others, there may be a true resistance to infection.

Low levels of CD8 cells reactive to HIV peptides have been found in groups of high-risk seronegative individuals. A study from Gambia among a group of sex workers reported that detectable CTL responses were seen in three of six HEPS individuals, suggesting that infection had occurred but had been cleared. Another study in Nairobi demonstrated the presence of mucosal anti-HIV CTLs in individuals who remained seronegative, despite repeated high-risk exposures. Humoral responses have also demonstrated immunological memory to HIV. Specifically, mucosal immunoglobulin A (IgA), capable of cross-clade HIV binding and neutralization, has been found in genital secretions of some high-risk uninfected individuals. It has also been postulated that some exposed seronegative individuals may actually harbor low levels of virus or that repeated exposures continually boost these immunological responses, hence promoting ongoing protection. The latter hypothesis may be supported by findings from a group of sex workers who ceased commercial sex work for a period of time and then became infected once they recommenced their high-risk exposures.

Earlier experiments provide compelling evidence that CTLs from HEPS individuals provide protection. In a series of experiments, CTLs that were transferred to severe combined immunodeficiency (SCID) / beige mice provided protection to subsequent HIV challenge. Yet not all HEPS individuals display these CTL responses, suggesting that protective factors are also at work.

Genetic influences also play a protective role, such that individuals who are heterozygous for
the deletion of the CCR5 gene are relatively resistant to infection. Just as certain HLA backgrounds have been associated with HEPS sex workers, they may also play a role in protection. For instance, an increased frequency of HLA-B18 and HLA-A11 have been found in sex workers in Thailand. Increased frequency of HLA-B18 has also been found in the Nairobi, Kenya, HEPS cohort. In KwaZulu-Natal, South Africa, a higher frequency of HLA-A68 was noted in uninfected or HEPS individuals.\textsuperscript{135}

**Long-Term Nonprogressors**

LTNP, or elite controllers, make up approximately 5%–10% of HIV-infected individuals.\textsuperscript{20(pp301-330),143} This group also provides important insights into the correlates of immune control of HIV and can thus inform HIV vaccine design. The LTNP, as a group, are fairly heterogeneous, with the following common characteristics:

- Have had HIV infection for 10 years or longer
- Are asymptomatic
- Are not on ART
- Have normal or stable CD4 counts
- Have strong cellular immune responses
- Have good neutralizing antibody responses
- May have genetic profiles associated with delayed progression

**ADDITIONAL CONSIDERATIONS**

**Superinfection**

For a long time, it was assumed that individuals infected with one strain of HIV would be resistant to infection from another strain. Yet the ever-increasing number of circulating recombinant forms (CRFs) provide ample proof that “superinfections” are not a rare curiosity, but rather a more frequent phenomenon than was previously realized. These superinfections hold important implications for the clinical management of disease, as well as for vaccine design.

**Monitoring of Immune Status**

The hallmark of HIV disease is the destruction of CD4 lymphocytes. Thus, the most commonly used test for measuring individual immune status is the CD4 count, which clinicians use to define the stage of HIV infection; to determine when to initiate chemoprophylaxis against opportunistic infections (e.g., *Pneumocystis jiroveci* pneumonia) and to commence ART; and to monitor response to treatment. The AIDS diagnosis is made in individuals with a CD4 count of 200 cells/mm\(^3\) or less or a CD4 percentage of less than 14%. There is considerable variation among patients in the loss of CD4 cells, with an accelerated loss seen in patients with higher viral loads or in patients with coexisting morbidities (e.g., tuberculosis). CD4 percentages are less variable than are CD4 counts and are important to take into account when assessing immune function, particularly when comparing results performed on different platforms or by different laboratories.

The gold standard for measuring CD4 cells is flow cytometry, a technique that is often beyond the reach of facilities in resource-limited settings because of its high cost and the need for trained laboratory personnel. Simpler, lower-cost strategies for CD4 testing in resource-limited settings are currently being developed. Total lymphocyte count (TLC) has been used, with limited success, as a surrogate for CD4 counts. However, the reference ranges used for CD4 and CD8 counts are currently being developed. Total lymphocyte count (TLC) has been used, with limited success, as a surrogate for CD4 counts. However, the reference ranges used for CD4 and CD8 counts are often based on analysis of samples from healthy individuals in developed countries, and there is a paucity of reports containing reference ranges from African countries, where it is thought these parameters may differ.\textsuperscript{144} This theory is supported by a study in Abidjan, Côte D’Ivoire, in which the absolute CD4 counts of HIV-infected individuals were found to be higher than in HIV-infected patients in France.\textsuperscript{144} Similar discrepancies have been noted in other African populations when compared with their counterparts in Europe or North America.\textsuperscript{145}
A number of factors influence CD4 counts, including age, sex, diurnal variations, exercise, and certain drugs. In pediatric populations, CD4 percentages are used for clinical management decisions due to the wide variation in absolute CD4 counts in this age group. In summary, it is important to establish local CD4 and CD8 reference ranges based on local or regional data, rather than simply using the potentially inappropriate ranges provided by test kit manufacturers.

**Immune Reconstitution Following Commencement of Antiretroviral Therapy**

When viral suppression is achieved after the initiation of ART, reconstitution of the immune function is possible. This reconstitution may manifest as the disappearance of opportunistic infections and the restoration of delayed-type hypersensitivity (DTH) to recall antigens. The capacity for more optimal immune restoration relies on antiretrovirals (ARVs) being initiated before the immune system has sustained advanced viral damage. Sustained viral suppression is associated with a decrease in activation markers (i.e., CD38 and HLA-DR+ cells) and a progressive increase in CD4 cells. There is a biphasic increase in CD4 cells, with the initial increase being related to a release of memory cells from lymphoid tissues bearing the CD4/CD45RO+ marker. This is followed by a slow and steady increase in naïve CD4 cells that display CD4/CD45RA+ markers.

Current guidelines for developing countries suggest that initiation of ART should take place when an individual has a CD4 count below 200 cells/mm$^3$ and/or an AIDS-defining condition. However, an ever-increasing body of evidence suggests that in these settings, earlier initiation of treatment will lead to more comprehensive restoration of immune function. For instance, a recent study showed that patients commencing ART at baseline CD4 counts higher than 350 cells/mm$^3$ regained nearly normal CD4 counts after six years of therapy.147,148

**Immune Reconstitution Inflammatory Syndrome**

The suppression of HIV replication following ART allows for recovery of the immune system and restoration of pathogen-specific immune responses. In some cases, this is accompanied by immunopathological reactions and clinical deterioration.149,150 This condition is termed immune restoration disease, or immune reconstitution inflammatory syndrome (IRIS), and has been reported in relation to a number of pathogens and autoimmune phenomena. In states of severe immunodeficiency, pathogens are not eradicated from tissues; instead, they remain latent or dormant and do not elicit an inflammatory response. Restoration of pathogen-specific immunity causes either local or generalized inflammatory changes. IRIS has been reported with mycobacterial infections, cryptococcal disease, hepatitis B and C, cytomegalovirus infections, varicella zoster, herpes simplex, and pneumocystis infections.

Tuberculosis (TB) is the most common opportunistic infection of HIV-infected individuals in sub-Saharan Africa. There are two distinct forms of IRIS associated with TB.150,151 Paradoxical IRIS occurs in individuals who have had a diagnosis confirmed and who are receiving (or have completed) anti-TB treatment. In this form, shortly after commencing ART, there is a paradoxical worsening or recurrence of TB symptoms, signs, or radiological features. The other form of IRIS, called “unmasking IRIS,” occurs when an unrecognized TB infection is revealed after the patient is initiated on ART. In this instance, TB is occult and unrecognized because of profound immunodeficiency. Once ART is commenced, the immune restoration leads to the unmasking of TB.
AIDS Vaccine Development

In this third decade of the AIDS pandemic, the goal of developing an effective preventive vaccine remains elusive. Traditional viral vaccines allow the respective virus to enter the body of vaccines, and then the vaccine-generated immune processes deal with the invading organism. In HIV infection, however, the integration of HIV into the genome of the target cells within the mucosa or adjacent lymphoid tissues allows a very limited window of opportunity for vaccine-induced immune responses to be protective.

Efforts to develop a vaccine initially focused on the HIV viral envelope, which is the target of neutralizing antibodies in HIV-infected people. It was hoped that neutralizing antibodies would be generated that could bind to the envelope, neutralize the virus, and clear the infection before it became established. Yet when these vaccines were tested, they failed to protect healthy subjects from HIV infection. One reason for this was that the gp120 protein undergoes significant conformational change on interacting with the CD4 receptor, thus exposing hypervariable regions. In this scenario, it is easy for escape mutants to be generated, resulting in a loss of protection.

With new insights into the pathogenesis of HIV, attention was drawn to the effect of cellular mechanisms that control viral replication. Although there is a considerable body of evidence regarding the role of CD8 CTLs in controlling viremia, there has been no observed effect on the latently infected CD4 reservoir, which escapes immune surveillance.

If the goal of a preventive vaccine remains elusive, then the question of whether partial protection offered by a vaccine could potentially alter the course of HIV disease must be answered. A lower viral set point is known to confer a survival advantage. In addition, it is possible that pre-existing immune responses may provide protection from the devastating GALT CD4 cell loss that occurs during acute primary infection. In addition to the benefit to the individual, there may also be a public-health benefit from a partially protective vaccine. For instance, the HIV epidemic is driven by transmission of virus by individuals who are in the early phases of disease progression, a period associated with high viral loads. If a vaccine were successful in reducing the viral loads of HIV-infected individuals during the early acute phase of infection, this might, in turn, confer some protection to the general population.

A number of vaccine trials are currently underway that use priming immunization with a vector approach to stimulate cellular immunity, followed by booster immunizations to promote antibody production. However, a recent setback occurred when the HIV Vaccine Trials Network studies HVTN 502 and 503 (Phambili study, South Africa), based on the Merck candidate vaccine MRKAd5 HIV-1 gag/pol/nef construct, had to be prematurely discontinued. The vector used was an attenuated adenovirus, which is normally responsible for the common cold. The randomized, double-blind, placebo-controlled Phase IIb study was halted prematurely because the Data Safety and Monitoring Board, upon reviewing the preliminary data, found that the HIV infection rates were similar in both the test and the placebo groups. The viral load estimations in both groups were also found to be similar.153
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Immunology of HIV-1 and the Host Response in Children

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The majority of children living with HIV-1 (hereafter abbreviated as HIV) acquired the infection perinatally via mother-to-child transmission. Because the host in this scenario has an immature and developing immune system,\textsuperscript{1} the virological and immunological characteristics of HIV infection in infants and young children differ significantly from those in older children and adults. Persistence of HIV viremia occurs at high levels during the first years of life and, in many infants and children, rapidly causes a profound failure of the young child’s immune system.

Before the introduction of combination anti-retroviral therapy (ART), roughly 20% of HIV-positive infants living in Europe suffered a serious CD4 T-cell loss and clinical deterioration within the first year of life, resulting in severe HIV-related manifestations; nearly 30% of infected children died before the age of five years.\textsuperscript{2} A recent analysis of the clinical course in more than 3,000 untreated HIV-positive infants from different countries in sub-Saharan Africa showed an even worse prognosis, with a mortality rate greater than 50% by two years of age. Infants with early perinatal infection acquired before the age of four weeks appeared to have a particularly great increase in mortality risk.\textsuperscript{3} This finding was confirmed by other researchers, who reported that 85% of intrauterine- and intrapartum-infected infants showed a rapid decline in CD4 T cells and met the criteria for initiating ART within six months after birth.\textsuperscript{4} In contrast, some perinatally HIV-positive children live for more than 10 years without serious clinical manifestations. The mechanisms behind these differential disease patterns have not yet been elucidated, but both virological and immunological characteristics appear to be relevant.\textsuperscript{5,6}

This chapter provides an overview of the current knowledge on the constitution of the immune system and host responses toward HIV and common microorganisms in HIV-positive children before and after starting ART.

CD4 and CD8 T cells in healthy infants and children

Physiologically, newborns have much higher absolute numbers and percentages of CD4 T lymphocytes than do older children and adults. A gradual decrease in CD4 T cells is observed during the first six years of life.\textsuperscript{7} Infants up to three months of age have a median CD4 T-cell percentage of 52%, and this decreases to a median of 37% by age 6 to 12
It has been demonstrated that absolute CD4 T-cell numbers vary more with age than do CD4 percentages. CD8 T lymphocytes also change markedly during the first years of life. An increase from a median of 16% at age three to six months to a median of 26% at age 12 to 18 years has been reported.7,8

During infancy, fresh naive T cells are continuously released from the thymus, and since children constantly encounter new antigens in their first years of life, the compartment of previously activated CD4 and CD8 T cells and memory T cells increases progressively.7 T-cell receptor excision circles (TRECs) can provide insight into the replicative history of T cells. TRECs are stable circular DNA fragments that are formed as by-products during T-cell receptor gene rearrangements in the thymus. They are not replicated upon further division of cells but pass to one of the two daughter cells. Thus, the TREC content of T lymphocytes has been used as a marker of T-cell proliferation.9 Several studies have found that the TREC content per lymphocyte decreases with age.10,11

Various reports indicate that race-related differences and environmental factors may influence the levels of these immunologic parameters. Total lymphocyte numbers and CD4 and CD8 subset values were generally found to be lower in healthy black children than in healthy white children.12-15 And in comparison with black children living in Europe, black children living in Uganda had lower CD4 T-cell values, whereas no significant differences were found between their CD8 T-cell and total lymphocyte values.4 Lower CD4 T-cell counts and especially lower naive CD4 T-cell counts also have been reported in healthy Ethiopians.16,17 However, in a group of Ethiopian infants and children it was documented that these differences were not yet present at birth, but rather developed over time. A recent study sheds light on this remarkable finding. It was demonstrated that the numbers of CD4 and CD8 T cells at birth in Ethiopian neonates were similar to those in Dutch neonates. Moreover, no differences at birth were found for the TREC content of lymphocytes, or the number of naive T cells. However, significant differences developed between Ethiopian and Dutch children already at a young age and persisted into adulthood. These age-dependent differences were associated with a higher baseline level of activated T cells in the Ethiopian individuals. It was hypothesized that the higher level of immune activation was caused by a higher antigenic exposure (e.g., to parasites) occurring in Ethiopians shortly after birth and well into adulthood.18

The mounting evidence that CD4 T-cell values differ between populations living in different environments complicates the use of this marker as the main immunologic parameter for starting and monitoring HIV treatment, emphasizing the need for population-specific baseline values for this and other childhood parameters.

**Immune System During HIV Infection in Infants and Children**

The hallmark of HIV infection, in both adults and children, is depletion of CD4 T cells. The progressive loss of CD4 T cells, key coordinators of the immune function, undermines both the humoral and cellular arms of immunity. As in adults, various patterns of CD4 T-cell loss and clinical disease progression have been observed among children. It has been postulated that CD4 depletion in the periphery is caused by persistent immune activation during the HIV infection, which results in continuous proliferation of T cells, thereby exhausting the naive T-cell pool. It is well known that CD4 depletion occurs more rapidly in infants and children than in adults. This finding is remarkable in light of an active thymus present in infants and young children that can produce naive T cells and may therefore be expected to be well equipped.
to compensate for the loss in naive T cells at the periphery. However, studies on the dynamics of naive and memory T cells in healthy and HIV-positive children demonstrated that healthy children had an age-related increase in the total body numbers of naive and memory T cells, whereas absolute numbers of TREC’s remained stable.\textsuperscript{19} The proportion of dividing naive T cells was high, especially in younger children, which indicated that the expansion was the result of proliferation, in addition to antigen-mediated naive T-cell activation leading to the formation of memory T cells.

On the basis of these results, it was concluded that the expansion of the naive T-cell pool after birth was more dependent on T-cell proliferation than was previously recognized.\textsuperscript{19} In untreated children infected with HIV, total body numbers of T cells and TREC’s were significantly reduced compared to the levels in healthy children. In contrast, T-cell division levels of both naive and memory T cells were much higher than those in healthy children. This indicated that, similar to HIV infection in adults, continuous activation of naive T cells significantly contributes to the erosion and exhaustion of the naive T-cell pool and progressive loss of CD4 T cells during HIV infection in children.\textsuperscript{19}

These events take place during the growth of the infant body, which, under normal conditions, is already in need of both a continuous supply of new T cells from the thymus and an active proliferating peripheral T-cell pool to meet the requirements for control and defeat of commonly encountered microbes and other antigens. Moreover, as will be discussed, immune control by the effector cells of the immune system, which is important for limiting HIV replication, is not yet fully developed, and thus these cells are unable to limit the constant and vigorous activation of the CD4 T cells by HIV itself. Altogether, this may explain the more rapid loss of CD4 T cells in infants and young children.

**HOST IMMUNE RESPONSE TO HIV-1 AND OTHER PATHOGENS**

**Antibody Responses: HIV-Specific Antibodies**

Following acute infection, neutralizing antibodies against various HIV gene products are generated in older children and adults. These antibodies have been detected from day 28 on, but they are unable to control the HIV infection.\textsuperscript{20-21} In fact, a poor correlation between neutralizing antibody response and disease progression has been found.\textsuperscript{23,24} This may be explained by the continuous emergence of neutralizing escape mutants as a result of selective pressure by the potent neutralizing antibody response.\textsuperscript{21,22}

Moreover, neutralizing antibodies do not arise prior to the fall in plasma viral load as occurs in acute HIV infection. It was suggested that envelope-binding antibodies, generated before the appearance of neutralizing antibodies, may play a role in reducing the viral load by effector functions other than direct neutralization.\textsuperscript{25}

IgG antibodies actively pass through the placenta during pregnancy, and vertically infected infants have maternally derived, specific HIV antibodies. Active production of functional antibodies, however, starts only after one year of age.\textsuperscript{26}

A few studies in children have evaluated the association between the presence of neutralizing antibody levels and the clinical course. In some studies, a better clinical condition was found in the infants of mothers with higher levels of neutralizing antibodies.\textsuperscript{27,28} The same association was found for antibodies mediating cellular cytotoxicity.\textsuperscript{27}

**Antibodies to Other Microbes and Vaccination Antigens**

As in adults, HIV infection in children is characterized by high levels of immunoglobulins (hyper IgG, hypergammaglobulinemia). This phenomenon
probably results from a continuous antigen-driven stimulation of naive B cells, leading to a state of hyperactivation with the production of low-avidity antibodies (i.e., antibodies that interact only weakly with their antigen). In contrast, B-cell function becomes defective and the ability to produce specific antibodies is impaired.

The production of specific antibodies requires a smooth interaction between various components of the immune system: antigen-presenting cells, B lymphocytes, and T lymphocytes. Dendritic cells, as all antigen-presenting cells, initiate T- and B-cell activation by processing antigens and presenting them on their surface for recognition by specific CD4 T cells. The percentage of plasmacytoid dendritic cells was shown to be decreased in children infected with HIV, and the function of these cells, as measured by their ability to produce interferon alpha, was also profoundly impaired.

To be able to mount an adequate antibody response to the majority of antigens, B cells require the help of CD4 T cells. Cytokines produced by CD4 T cells stimulate the B cells to differentiate into immunoglobulin-producing B cells or memory B cells. Thus, CD4 T-cell depletion due to HIV infection results in insufficient B-cell activation and differentiation. This explains why pathogens against which antibodies play a crucial role in defense can potentially cause serious infections in HIV-positive children and adults.

It has also been demonstrated that the response of HIV-positive children against various vaccination antigens is decreased as compared to healthy children. Moreover, during the course of the HIV infection, the responsiveness toward various vaccination antigens wanes with time. This phenomenon has been demonstrated for diphtheria, tetanus, measles, mumps, rubella, pneumococci, and Hemophilus influenzae type B. In addition, antibodies to naturally occurring pathogens, such as varicella zoster virus (VZV) and cytomegalovirus (CMV), also decrease. Loss of CD4 T helper cell function, as well as loss of memory B cells by apoptosis, appears to be responsible for this phenomenon.

CURRENT IMMUNIZATION PRACTICES IN HIV-POSITIVE CHILDREN

Although the ability to mount antigen-specific immune responses to vaccination antigens may be suboptimal in HIV-positive children, and especially in those with a more advanced stage of immunodeficiency, these children may still benefit from routine vaccinations. The World Health Organization (WHO) advises routine vaccinations for HIV-positive children, with modifications for those with symptomatic HIV infection. Asymptomatic children can be safely immunized with diphtheria, tetanus, poliomyelitis, and hepatitis B vaccine, consisting of inactivated components, and also with measles, oral poliomyelitis, and yellow fever vaccine, consisting of live attenuated viruses. For measles, the first vaccination is usually administered at the age of 9–12 months, but for HIV-positive children, an extra dose at the age of 6 months is advised to provide protection at a younger age.

WHO advises the administration of BCG (bacille Calmette-Guérin) vaccine at birth to all infants in countries with high TB exposure rates, but cautions that this vaccination should be withheld for infants suspected to be HIV-positive in countries where there is a low risk of acquiring TB. Symptomatic children should not receive yellow fever vaccine.

The U.S. Advisory Committee on Immunization Practices (ACIP) recommends against the use of BCG and yellow fever vaccine in all HIV-positive children, whether asymptomatic or not, and also recommends against administering the measles
vaccine to children with CD4 T-cell levels less than 15%. Moreover, ACIP recommends the use of inactivated poliomyelitis vaccine rather than the oral vaccine containing live virus.44

**ROLE OF THE INNATE IMMUNE SYSTEM**

Insight into the contribution of the innate immune system in controlling HIV infection is only beginning to emerge. This part of the immune system is the first to come into action after HIV transmission, and observations in adults indicate that the innate immune system combats HIV at different levels during the disease.45,46 In healthy newborns, the innate immune mechanisms have been found to be impaired. For example, the production of pro inflammatory cytokines and the response of macrophages to interferon gamma (IFN-γ) were found to be deficient.47

Studies evaluating the different components of the innate immune system in HIV-positive children have been sparse. Conflicting data have been reported on the association between mannose binding lectin (MBL), a circulating pattern-recognition molecule, and disease progression. One study found no relation between low MBL levels and disease stage, while another reported MBL deficiency to be more frequent in a group of children with an advanced stage of HIV disease.48,49

A study on natural killer (NK) cells observed that the cytolytic function of neonatal NK cells may depend on the characteristics of the target cells. For example, decreased cytolytic NK cell activity was found for target cells infected with herpes simplex virus (HSV) or CMV, whereas the direct killing capacity of neonatal NK cells for HIV-infected cells was similar to that of adult NK cells.50-52 However, antibody-dependent NK-cell-mediated cytotoxicity of HIV-infected cells was inferior.52 During HIV infection, decreased levels of NK cells, in particular the subset of mature NK cells, were measured in HIV-positive adults as well as children.31,53

Plasmacytoid dendritic cells are also part of the innate immune system. These cells belong to the primary line of defense and are extremely important in initiating an immune response. As stated previously, both the percentage and function of these dendritic cells were decreased in children infected with HIV.31 It is therefore likely that the lack of proper innate immune mechanisms contributes to the inability to control HIV infection after vertical transmission.

**ADAPTIVE CELLULAR IMMUNE RESPONSE: CYTOTOXIC T CELLS**

Antigen-specific cytotoxic T lymphocytes (CTLs) play an important role in clearing acute viral infections and containing chronic viral replication in humans. In healthy infants, the function of these effector cells of the immune system may be deficient or deviant, which explains why some acute viral infections run a severe clinical course while other viral infections (such as hepatitis B and HIV) tend to establish an ongoing chronic disease in infants after perinatal transmission.54

In adults, HIV-specific CTLs usually emerge during the first weeks of HIV infection and appear to play a crucial role in limiting infection and disease progression by partial immune control.55 The level of CD8 T-cell activation in early infection is an independent predictor of the rate of CD4 T-cell decline in adults.56 Several earlier studies have reported on the function of cytotoxic CD8 T-cell responses in children. Cytotoxic T-cell responses were weaker or absent in almost all infants younger than six months of age, whereas CTL responses in older children were comparable to those in adults.57-59 Evaluation of specific cytotoxic responses against HIV proteins in a group of vertically infected children demonstrated that the majority of asymptomatic children had detectable cytotoxic
were less pronounced in HIV-positive adults and children.\textsuperscript{64,65}

The mechanisms behind these weaker and different cytotoxic T-cell responses against HIV in infants have not yet been elucidated, but could be due to partial HLA (human leukocyte antigen) compatibility between mother and child. HIV antigens are processed by infected cells, and fragments are presented on the surface of the cells by HLA class I molecules for recognition by CTLs. It has been shown that CTL escape can occur during HIV infection, leading to a decrease in CTL responses against the HIV mutant variant either because the HLA molecule cannot bind the antigen of the HIV variant anymore, and thus it cannot be presented, or because the HIV variant interferes with CTL recognition.

As children’s HLA is at least 50% identical to maternal HLA, and as the virus has been under maternal CTL immune pressure, transmission of an HIV CTL escape variant may hamper the development of proper immune responses. A study elegantly showing this was performed by Goulder et al in which mother-to-child transmission was studied in the setting of HLA-B27 expression.\textsuperscript{66} HLA-B27 expression is associated with prolonged immune containment of HIV infection in adults, whereas a mutation in a dominant and highly conserved B27-restricted epitope of HIV resulted in a loss of HLA presentation, in failure to present the epitope to CTL, and in disease progression. The researchers showed that in mothers expressing HLA-B27 who transmitted HIV to their infants, viruses encoding for CTL escape variants in this dominant HLA-B27-restricted epitope were specifically transmitted. Instead of being able to recognize the normally susceptible wild-type epitope, CTLs of these infants targeted an otherwise subdominant HLA-B27-restricted epitope but subsequently failed to contain HIV replication.\textsuperscript{66} This mechanism may explain why HIV causes the persistent
high levels of viremia and rapid disease progression seen in a significant proportion of infants. In addition to preferential transmission of already escaped viruses, it was shown that additional viral escape mutants may also arise within the infants early after perinatal infection for HLA alleles that are not present in the mother. Mutations of an HLA-B57-restricted epitope were shown to arise in HLA-B57-positive infants, born to HLA-B57-negative mothers, further contributing to lack of viral control.

**CLASSIFICATION OF IMMUNODEFICIENCY IN HIV-POSITIVE CHILDREN**

The failing immune system in HIV-positive children allows microorganisms to flourish and cause disease. This results in aggravation of the common diseases of childhood, such as respiratory tract infections, and in opportunistic infections.

To define the stage of HIV infection and the need for ART, an age-related classification staging system and age-related therapy guidelines have been developed by WHO and by the Centers for Disease Control and Prevention (CDC). Both guidelines use CD4 T-cell percentages as a marker for the severity of immunodeficiency. The WHO classification system is the most widely used system in resource-limited settings (Table 1). It is important to note that a child’s CD4 T-cell values may vary in association with intercurrent illnesses. Serial CD4 T-cell measurements provide a more realistic view of the child’s immune status, and CD4 T-cell values should be determined at least twice before a decision to initiate ART is taken.

Threshold CD4 T-cell values for severe immunodeficiency are based on longitudinal data of HIV-positive infants and children in resource-rich settings. For children older than one year of age, these values correspond to a 12-month mortality risk of 5% or less. Younger infants, and especially those under the age of six months, have an increased mortality risk, even with higher CD4 T-cell percentages.

As discussed before, baseline immunologic parameters differ between populations. Whether the chosen threshold values are also appropriate for HIV-positive children in resource-limited settings is not yet clear, and this needs to be evaluated.

The WHO immunologic classification system also provides age-related total lymphocyte

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**Table 1. CD4 T-Cell Levels in Relation to the Severity of Immunosuppression**

<table>
<thead>
<tr>
<th>Level of Immunosuppression</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤11 months</td>
</tr>
<tr>
<td>Not significant immunosuppression</td>
<td>&gt;35%</td>
</tr>
<tr>
<td>Mild immunosuppression</td>
<td>30%–35%</td>
</tr>
<tr>
<td>Advanced immunosuppression</td>
<td>25%–29%</td>
</tr>
<tr>
<td>Severe immunosuppression</td>
<td>&lt;25%</td>
</tr>
</tbody>
</table>

Source: WHO.68

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Source: WHO.68
values, indicative for immunodeficiency (Table 2).68 Several studies have indicated that the total lymphocyte count is a powerful predictor of the risk of disease progression. As such, it is a valuable marker that may be used to determine eligibility for ART in resource-limited settings where CD4 determination is not yet available.71,72

RESPONSES OF THE IMMUNE SYSTEM IN CHILDREN LIVING WITH HIV AND ON ART

Recovery of CD4 T Cells
Most children respond well to ART, and even children with advanced immunodeficiency generally show a rapid recovery of CD4 T cells and an improvement in their clinical condition, growth, and development.73-77 However, a recent study from Zambia of nearly 5,000 HIV-positive children, of whom almost 60% received ART, also indicated that an earlier initiation of ART than currently is recommended by WHO may be needed (especially in infants younger than 18 months) to prevent mortality in the first three months after the initiation of ART.77

Studies have found that total CD4 T-cell numbers and naive CD4 T cells increase more, and take place more rapidly, in younger children than in older children and adults. This phenomenon is attributed to the fact that younger children still have a functional thymus, whereas thymic output decreases after early childhood.78-80 However, it has also been shown that the relative gain of naive and total T-cell numbers is independent of age when numbers are normalized for age-matched controls.79,81 It is important to note that even children who start ART with a low baseline CD4 T-cell count generally recover to levels similar to those of age-matched controls, and often do so within the first year of therapy.82

Whether full recovery of CD4 T-cell counts could be achieved in all age groups has been debated for a long time. Recent data demonstrated that recovery of the total number of CD4 T cells is indeed possible in HIV-positive children and adults on long-term ART with sustained viral suppression.82 However, a difference was seen between adults and children with regard to naive CD4 T cells. While all the children had normalized numbers of naive CD4 T cells, this was not the case for adults who had started ART with low baseline CD4 T-cell counts.82 This finding indicated that recovery of the T-cell compartment may nevertheless be expected in children who have a more advanced level of CD4 T-cell depletion. Although this could be used as an argument to postpone ART to prevent adverse events associated with long-term use of antiretrovirals, it is obvious that decreasing CD4 T-cell levels are associated with an increasing risk of (opportunistic) infections. Thus, in order to prevent serious morbidity and mortality, early diagnosis of HIV infection is important, and ART should be initiated before serious immunosuppression occurs.

Table 2. Total Lymphocyte Values Indicating Severe Immunosuppression

<table>
<thead>
<tr>
<th>Age</th>
<th>Age</th>
<th>Age</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤11 months</td>
<td>12–35 months</td>
<td>36–59 months</td>
<td>5–8 years*</td>
</tr>
<tr>
<td>Total lymphocyte count</td>
<td>&lt;4,000 cells/mm³</td>
<td>&lt;3,000 cells/mm³</td>
<td>&lt;2,500 cells/mm³</td>
</tr>
</tbody>
</table>

*Data in children older than 8 years of age are limited.

Source: WHO.68
Recovery of Functional Immunity

In contrast to the excellent recovery of T-cell numbers in children, several studies indicate that the reconstitution of functional immunity may still be impaired. While being treated with ART, HIV-positive children still showed an increased loss of protective antibodies against vaccination antigens and, to a lesser extent, of antibodies against natural antigens. In 40% of children, declining antibodies against measles, mumps, and rubella (MMR) antigens were observed, while 21% of children lost antibodies against VZV and 7% against CMV. This is in contrast to findings in longitudinal studies of vaccinated healthy children, in whom antibodies against MMR could be detected in 86%-100% of children after 9-15 years of follow-up.83,85

Moreover, after stimulating the immune system with booster vaccinations, an adequate immune response was observed in only a portion (60%-85%) of the HIV-positive children. This is in agreement with other studies, in which HIV-positive patients who received tetanus toxoid booster vaccinations showed a moderate antibody response and subsequent waning of antibody titers in the following years.86,87

Different response patterns have been observed in children on ART who were vaccinated with pneumococcal vaccines as well. The best responses were observed in children with a higher CD4 percentage and maximally suppressed HIV virus.88,89 A study on varicella vaccine in children on ART showed a response rate of around 60% after a two-dose regimen, which is significantly decreased as compared to healthy, HIV-negative children, who demonstrated up to 100% conversion rates after a single dose of the VZV vaccine.90,91 Whether the antibody levels will persist in these children remains to be seen. Moreover, antibodies did not rise significantly in VZV-positive HIV-positive children on ART who experienced a wild-type VZV reinfection.90

Recovery of Specific Cellular Immunity

HIV-Specific Cellular Immunity

Several studies have evaluated specific CD4 and CD8 cellular immunity against HIV in children on ART. It was observed that cytokine-secreting patterns of HIV-specific CD4 T cells of chronically infected children with a continued and maximal suppressed viral load differed from those of children who experienced viral blips or had viremia despite ART.91 CD4 HIV-specific T cells of children with optimal suppression secreting mainly interleukine-2 (IL-2) in response to stimulation with the HIV gag protein, whereas HIV-specific CD4 T cells of the other children secreted predominantly IFN-γ or a mixture of IL-2 plus IFN-γ. Overall, the frequency of HIV-specific CD4 T cells in children was significantly higher compared with that of chronically infected adults. This observation, in addition to the high proportion of IL-2-secreting HIV-specific CD4 T cells in successfully treated children, indicated a greater capacity of children to restore functionally active CD4 helper T cells than adults.93

When HIV-positive children were vaccinated with hepatitis A vaccine, around half the children had low antibody levels after the regular two-dose vaccination regimen. The best responses were observed in the group of children with CD4 T cells greater than 20%. Improved antibody levels could be generated with a third vaccination.92 Altogether, these studies show that even after CD4 recovery on ART, the quality of the immune response may still be compromised. The immune system may therefore need a more powerful boost to mount an adequate response to antigens and, in the case of vaccine-preventable diseases, follow-up may be indicated to monitor whether antibody levels remain adequate.
the age of one year as compared to children who had started after two years. However, total CD8 T-cell responses in the younger age group were comparable to those of age-matched controls that were not treated with ART. This indicated that the lower responses were due to younger age. A broad diversity of CD8 T-cell responses targeted at various HIV antigens was observed in a group of children between 6 and 17 years of age on ART. The magnitude and breadth of these responses were comparable to those found in adults.

Specific Cellular Response to Other Antigens
Specific cell-mediated immunity to pathogens other than HIV may not recover completely after the initiation of ART, or only after reexposure to the antigen. For example, the cellular immune responses to VZV did not improve during the course of more than three years of monitoring in children on ART, despite effectively reduced viral load and restoration of CD4 T cells. Among the children who had responded well to ART, adequate in vitro cellular responses against VZV were documented only after they had developed herpes zoster. In contrast, the children who had not responded well to ART did not show a good immune response, even after developing herpes zoster. From these findings it was concluded that reconstitution of cellular immunity to VZV requires not only adequate control of HIV replication, but also antigenic reexposure. A recent vaccination study showed that the serological response after VZV vaccination was significantly less in clinically stable HIV-positive children on ART as compared to their HIV-negative siblings. Moreover, a relatively high number of VZV reinfecions occurred in these children and VZV antibody titers did not rise significantly after the natural infection.

When evaluating the cellular immune responses to CMV it was expected that endogenous boosting by frequent CMV reactivation would promote the recovery of CMV-specific cellular responses. However, this was not observed in the study group of 35 CMV seropositive HIV-positive children on ART during three years of observation. Another study reported that CD4 and CD8 T cells were more activated in CMV seropositive HIV-positive children than in CMV-negative children. This difference in activation state disappeared once the children began ART. However, when compared to nonsecretors, children with prolonged CMV secretion in urine showed higher levels of CMV-specific IgG and more activated CMV-specific effector T cells, while CMV-specific IFN-γ-producing CD8 T-cell numbers were reduced. This may indicate an impairment in the ability to differentiate into functionally active effector cells and may explain the inability to completely suppress CMV.

Evaluation of antimycobacterial immune responses in children who had been previously vaccinated with BCG, and who had begun ART while having advanced disease, showed that initiation of ART was followed by a rapid and sustained recovery of specific responses against mycobacteria.

Studies on the reconstitution of NK and dendritic cells during ART in children demonstrated that while most NK subsets recovered on viral suppression, the level of the major subset of mature NK cells remained depressed. Plasmacytoid dendritic cell percentages in children recovered fully, in contrast to those in adults. However, other studies indicated that plasmacytoid cell numbers did not fully recover in children, despite full viral suppression. The functional capacity of plasmacytoid dendritic cells, as measured by their ability to produce interferon alpha, remained impaired in HIV-positive children on ART, irrespective of viral suppression. This may be one of the mechanisms explaining why a diminished response to antigens still occurs after immune reconstitution during ART.
SUMMARY

HIV infection affects essential components of the immune system and results in severe immunosuppression. In the majority of infants and young children, the ability to control HIV infection to some extent is clearly reduced when compared to adults and, as a result, HIV runs a rapid and devastating course in a significant proportion of untreated HIV-positive children. Similar to the process in adults, chronic activation of CD4 T cells appears to be a main factor contributing to the exhaustion and depletion of the CD4 T-cell pool.

The mechanisms behind the failure of the immune system to limit the HIV infection are only beginning to emerge. Immunologic responses have either been weaker or different from those observed in adults. On one hand, this may be explained by the immaturity of the immune system; on the other hand, recent findings indicate that HIV variants that already escaped cytotoxic actions of the genetically identical maternal immune system may be responsible for this phenomenon.

With progression of HIV infection, children develop deficiencies of both the humoral and cellular pillars of the immune system. Due to a continuous polyclonal activation of B cells, hypergammaglobulinemia develops, but specific antibody production deteriorates, as is reflected by a decreased capacity to respond to vaccination antigens and by a loss of protective antibody levels.

When interpreting CD4 values, physicians caring for HIV-positive children should keep in mind that basic CD4 T-cell numbers are physiologically higher in infants and change during childhood. Moreover, environmental factors such as a higher burden of parasitic infections appear to influence baseline levels of immunologic markers. This area requires further evaluation since the need for ART is determined on the basis of clinical symptoms and CD4 T-cell level.

Fortunately, the majority of children show a rapid clinical recovery and reconstitution of the CD4 T-cell pool in response to ART. However, it appears that even in children with a favorable clinical and virological response to ART and normalized CD4 levels, a functional impairment of the immune system is still present. Finally, because of the differences found between the immunologic responses in infants and adults, the exact mechanisms of the interaction between HIV and the infant’s immune system need to be unraveled to determine the value of novel immunotherapeutic strategies for improved control of HIV infection in children.
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HE USE OF ANTIRETROVIRAL THERAPY (ART) in developed countries has successfully reduced AIDS-related mortality by 90% and has significantly reduced opportunistic infections and other consequences of HIV disease. In developing countries, combination ART has transformed the AIDS epidemic, with significant decreases in mortality, hospitalizations, and incidence of opportunistic infections. Yet in sub-Saharan Africa, which accounts for more than 70% of the global burden of HIV/AIDS, only about 25% of the six million people who require ART have access to treatment. This is despite continued calls to get more people on treatment, including initiatives such as the “3 by 5” campaign of the World Health Organization (WHO) and Joint United Nations Program on HIV/AIDS (UNAIDS), and the Group of Eight (G8) pledge to provide “universal access to ART.”

In order to ensure universal access to ART and ART-related services, particularly in resource-limited settings, WHO and UNAIDS have advocated and promoted a public-health approach to combating HIV/AIDS. The public-health approach operates at both the national and community level, and includes the simplification and standardization of protocols and decentralization of comprehensive HIV services, while taking into account the realities of weak health-care systems and the experiences of pioneering ART programs. The key components of this approach include (1) standardization and simplification of regimens to ensure efficient and durable suppression of HIV, (2) ensuring equitable and standardized treatment that is accessible to all in need of ART, and (3) use of cost-effective combinations of antiretrovirals (ARVs) in the form of generics. This shift from an individual to a population-based approach is facilitating rapid access to ART and related services for millions of people. Other benefits of the public-health approach include the streamlining of education, training, and administration related to the provision of ART. Simplification and standardization of ARV drug combinations means that with adequate training, nurses and clinical officers (COs) can deliver ART in countries where there is a shortage of doctors. In addition, prospects for drug tolerability and adherence to ART are enhanced, as health-care workers need only be familiar with a few types of drugs.
BASIS PRINCIPLES AND OBJECTIVES OF ART

The treatment and care of people living with HIV requires the comprehensive integration of patient-centered medical and social services. These services include provision of clinical care, nursing care, nutritional care and support, psychological support, health information and counseling, legal protection, and economic assistance. Comprehensive clinical care for people living with HIV, one vital component of this group of services, includes early diagnosis, access to care, ART, palliative care, prophylaxis against opportunistic infections, treatment of opportunistic infections and malignancies, and end-of-life care. The provision of this wide spectrum of services requires multisectoral and multidisciplinary teams that are cross-linked in a continuum-of-care model, so that patients, their families, health-care providers, governmental and nongovernmental organizations, and the community are closely involved with and knowledgeable about all aspects of care.

Prevention of new infections should be integrated into HIV/AIDS treatment and care programs as well, as HIV remains an incurable infection despite advances in ARV treatment. Toward this end, “social immunization” (for example, through community mobilization, widespread education, counseling and testing, sexual abstinence until marriage, being faithful, use of condoms, and female empowerment) must be strengthened, as we await the development of effective vaginal microbicides, HIV vaccines, and other prevention strategies currently under investigation. On one hand, even if HIV transmission in resource-limited countries were to totally cease, the existing burden of HIV/AIDS would continue to task all stakeholders into the foreseeable future. On the other hand, a lack of adequate preventive measures would mean longer queues of people waiting to access ART, which would compound the present challenges in achieving universal access.

The main goals of ART remain to (1) clinically prevent disease progression, (2) improve the restoration of the body’s immunity, (3) control viral replication through durable suppression, and (4) possibly reduce individual infectivity. However, this must be done in the context of an optimal quality of life by ensuring that drugs are available, tolerable, and easy to administer; have little long-term toxicity; and involve no food or refrigeration restrictions. Despite their immense benefit to people living with HIV, ARVs are not without risks, including drug toxicity and viral resistance. Experience with combination ART in the last decade has taught providers the central role of informed patient participation, the need for meticulous medication adherence, the complexity of drug interactions, and the importance of regular monitoring.6

ASSESSING PATIENT READINESS

Guidelines for ART determine when patients are eligible to begin treatment. In order for treatment to be successful, patients must also be ready to take medications every day for the rest of their lives. In most cases, this requires adequate preparation and a significant amount of patient support before ART is initiated. There is no substitute for patient participation in the ART decision-making process, and patient education and adherence programs should be part of any HIV/AIDS care initiative. Patients need to be asked whether they are ready to start a lifetime of therapy and should only commence taking drugs when they are fully committed to this responsibility. Some patients may not be ready right away. In such cases, individuals can be scheduled for follow-up visits with adequate pretreatment counseling until they are ready to begin treatment.
MINIMIZING VIRAL RESISTANCE

Providers in resource-limited settings have important roles to play in delaying the occurrence of HIV resistance. This can be achieved through good patient adherence and responsible, well-informed prescribing practices. Recommended strategies to achieve these goals include the following:

- Never commence patients on ART in the absence of adequate adherence counseling and support. The use of family and community members (spouses, buddies, etc.) has been found to be invaluable as a form of treatment support. Similarly, ensuring that disclosure to family members has been observed will enhance adherence and positive living.
- Work with patients to minimize barriers to medication adherence.
- Use fixed-dose combinations or co-blister packs.
- Pay special attention to other medications and treatments and their potential interactions with ARVs (particularly anti-TB drugs) and other drugs taken for concomitant illnesses, including traditional medicines.
- Never prescribe monotherapy or dual therapy for treatment of chronic HIV infection.
- Never add or change a single drug in a failing regimen, as this would result in functional monotherapy or dual therapy.
- If there is a reason to stop treatment, such as serious side effects or lack of adherence, it is recommended that the non-nucleoside reverse transcriptase inhibitors (NNRTIs) be stopped first (because of their long plasma half-life) and the nucleoside reverse transcriptase inhibitors (NRTIs) only after several days, to minimize NNRTI resistance.

STEPS TO INITIATE ART

The following steps should be taken in initiating ART:

1. HIV pretest counseling
2. HIV testing using the WHO-recommended algorithm (with Enzyme-Linked Immuno-Sorbent Assay [ELISA] or rapid tests) or national guidelines (where available) and post-test counseling
3. Medical consultation:
   - Medical history, which should include previous history of ART exposure, any concomitant treatment for other conditions, and substance/drug abuse
   - Clinical examination, including clinical WHO staging and weight measurement
   - Screening for TB (pulmonary and extrapulmonary)
   - Biochemical and hematology tests, including complete blood counts, urea and creatinine, electrolytes, liver function tests, and serum lipids including triglycerides
   - Tests for other opportunistic infections/diseases, including hepatitis B virus (HBV), hepatitis C virus (HCV), sexually transmitted infections (STIs), and malaria
   - CD4 lymphocyte count and viral load (where available)
   - Pap smear (for women)
   - Pregnancy test (for women of childbearing age)
4. Patient follow-up:
   - Review of test results
   - Staging of disease and determination of eligibility for ART, including psychosocial considerations of active alcohol/substance abuse, depression, and disclosure
• Counseling and review of treatment options—treatment literacy counseling should be routine for all HIV-positive patients, and those requiring ART should receive treatment literacy and drug adherence counseling
• Cotrimoxazole prophylaxis for patients with CD4 counts less than 350 cells/mm³, as this protects them from diarrhea, respiratory infections, and malaria
• A socioeconomic assessment of the patient to determine adequacy of food supply and other potential barriers to adherence

5. Patient monitoring:
• Choosing the optimal ARV drug regimen and explaining it in detail to the patient
• Providing ART and organizing drug counseling for maximum adherence
• Providing ongoing counseling, including advice on safer sex and family planning
• Monitoring ART in the following areas:
  – Clinically—watching for weight changes, frequency/severity of opportunistic infections
  – Biologically—CD4 cell count, viral load, and resistance
  – Adherence
  – Adverse events

A physician or CO should be responsible for conducting the initial clinical history and physical examination in a secondary or tertiary health facility. This step is important, as this initial evaluation also assesses the patient for opportunistic infections, such as TB, and comorbidities that have been observed to lead to significant mortality at the onset of treatment or that can cause toxicities to ARV drugs. The physician or CO should assess the WHO staging of each patient and design a care and treatment plan for the patient during this initial assessment. It is the responsibility of the physician or CO to request any required lab tests and prescribe necessary medications for patients. In addition, the physician or CO will monitor the patient on an ongoing basis using clinical criteria and CD4 counts in addition to viral loads, where available. For patients already receiving ARVs, any side effects will be monitored and patients will be assessed for treatment failure based on clinical signs, CD4 counts, and viral loads.

The initial evaluation should also educate the patient about the need for a treatment partner or “buddy” to enhance adherence to ART. This is best done by an adherence nurse or adherence counselor, who will counsel patients on adherence for routine care and ARV treatment, and encourage personal risk reduction. Many ART clinics in resource-limited settings employ people living with HIV as adherence nurses/counselors, which can be a more effective way of getting patients to adhere to their drugs. Oftentimes it is easier for patients to trust the advice of those who are in a similar situation to their own, rather than the advice of a clinician. Support group members can be trained as peer educators/counselors for adherence counseling of their peers in the clinic and within the community. In addition, the adherence nurse/counselor will assess the need for nutritional support in those clinics where a qualified nutritionist is unavailable.

Most ART scale-up models in resource-limited settings have adopted a network model, which consists of clusters of primary health clinics (PHCs) feeding secondary health centers. In this model, secondary centers in a region or zone of the country develop referral linkages to a tertiary or referral center. This allows for vertical and horizontal referral of patients, with monitoring and mentoring cascading down from the referral center and district centers to the PHCs. In countries with reasonable human resources, ART is delivered at the tertiary and secondary (district) health facilities, with PHCs delivering ART-related services such as
Voluntary counseling and testing (VCT), prevention of mother-to-child transmission (PMTCT), STI treatment and prevention, and directly observed therapy short course (DOTS) for TB. In addition, PHCs can deliver food supplements, cotrimoxazole prophylaxis, and basic care kits (e.g., clean water, water guard, and bed nets).

Because of the chronic shortages of health staff in sub-Saharan Africa and elsewhere, nurses in many countries are being called upon to deliver comprehensive ART, including the dispensing of ARVs at district and community health facilities. Offering ART at the community level reduces transportation time and costs, as well as patient loss to follow-up. In countries employing such a model, there has been a gradual transition from a doctor-driven to a nurse-driven ART program. This shift has enhanced treatment equity by making ART available to a wider population, including those in rural areas. However, in order for such a model to work, it is critical to develop guidelines and standard operating procedures (SOPs) for the various cadres of staff involved in the program, including clinicians, nurses, pharmacists, laboratory staff, and data managers. Also critical are tools for referrals of patients to and from PHCs and district, regional, and/or tertiary care facilities, in order to guide health-care providers in proper patient management at the various levels of care.

In a decentralized model, community-level facilities (PHCs) are responsible for identifying HIV-positive patients through HIV counseling and testing (HCT) at all entry points, including VCT, PMTCT, TB, STI, Integrated Management of Childhood Illnesses (IMCI), Expanded Program on Immunization (EPI), and family planning. Community-level facilities are also responsible for preparing ART-eligible patients for up referral to the secondary or tertiary centers for initiation of ART. This will rapidly expand the pool of HIV-positive individuals who can access ART. By the same token, PHCs can receive and manage stable down-referred patients already receiving ART. To guarantee quality care, such schemes require intense capacity building of various cadres of staff and the development of referral tools, protocols, and guidelines. Integration of ART services with other PHC-based services, such as malaria treatment, facilitates patient identification through HCT. This allows for eligible adults and pregnant women to be speedily referred to the ART initiation center (i.e., a center where HIV-positive individuals are initially assessed and commenced on ART). HIV-exposed children less than 18 months of age are polymerase chain reaction (PCR) tested and positive cases referred early for treatment, while older children can be diagnosed using rapid tests and ELISA. The offering of comprehensive services, such as HCT, PMTCT, and ART, promotes a family-centered approach. Expanding HCT at the PHC level also provides expanded access to counseling for HIV-negative clients, to ensure that they protect themselves from infection.

**WHEN TO START ART**

A patient should meet the following clinical and social criteria in order for ART to be initiated:

1a. Clinical criteria where CD4 testing is available:
   - WHO clinical stage IV disease irrespective of CD4 cell counts
   - WHO stage III disease + CD4 cell count < 350 cells/mm³
   - WHO stage I or II disease + CD4 cell count < 200 cells/mm³

1b. Clinical criteria where CD4 testing is not available:
   - WHO stage II if total lymphocyte count is ≤1,200 cells/mm³
   - WHO stage III irrespective of total lymphocyte count
   - WHO stage IV irrespective of total lymphocyte count
FROM THE GROUND UP: ESTABLISHING A FRAMEWORK FOR SUCCESS

1c. Clinical criteria for adults coinfected with TB and HIV:
- CD4 <200 cells/mm³—Start TB treatment. Commence ART in two to eight weeks.
- CD4 200–350 cells/mm³—Start TB treatment. Commence ART after initiation phase or earlier with severe immunodeficiency.
- CD4 >350 cells/mm³—Start TB treatment. Defer ART.
- Extrapulmonary TB—ART should be started as soon as anti-TB treatment is tolerated.

2. Social criteria:
- The patient should be willing to visit the health facility regularly and be contacted anytime at home or elsewhere.
- Although it is not mandatory, patients should be encouraged to disclose their HIV-positive status to a family member or a close friend who will accompany the patient for adherence counseling sessions and support the patient’s medication adherence after starting ART.
- Living in the same locality as the clinic or not too far away enhances adherence to clinic follow-up visits and tracing by caregivers in cases of default.

Before therapy is initiated, patient education and preparation is essential to ensure that the patient understands the way ART works, as well as to assess his or her willingness to make a lifelong commitment to therapy. In adults, the decision of when to start ART and with what regimen is complicated by other prevailing factors, such as pregnancy, the presence of comorbidities (e.g., TB, hepatitis B or C), uninfected partners, anemia, and the availability and cost of the drugs. A successful ART regimen must take these factors into consideration.

The optimal time to initiate ART in adults living with HIV has remained one of the most controversial and hotly debated topics in HIV medicine. Commencing ART prematurely may lead to unnecessary side effects or early development of drug resistance, whereas starting late may lead to reduced therapeutic benefits and high mortality. The lack of randomized trials demonstrating the optimal time to start therapy has forced such decisions to be based on expert recommendations and consensus guidelines. Most guidelines in resource-limited settings have previously recommended initiating therapy in patients with WHO stage III or IV disease and others with CD4 cell counts of less than 200 cells/mm³. However, many countries have reviewed their guidelines in light of recent evidence and WHO recommendations for resource-limited settings that suggest treatment be considered for individuals with CD4 cell counts between 200 and 350 cells/mm³. The move toward earlier treatment initiation is related to recent evidence showing that earlier initiation is associated with quicker normalization of CD4 cell counts, with a longer-term benefit to patients. Recent cohort studies have demonstrated benefits associated with starting therapy at CD4 cell counts between 250 and 350 cells/mm³, and new WHO guidelines favor moving the bar upward. In addition, newer drug formulations are more convenient and better tolerated, have fewer side effects, and demonstrate better durability.

WHAT TO START: CHOOSING THE BEST COMBINATION ART REGIMEN
The first component of the public-health approach to HIV medicine has been the simplification and standardization of first- and second-line drug combinations. There are currently five main classes of ARV agents available: the three classes used widely in resource-limited settings, NRTIs, NNRTIs, and protease inhibitors (PIs), and the two newer classes, entry inhibitors and integrase inhibitors. In adopting a public-health approach, a triple-drug regimen is constructed...
Most ART programs in resource-limited settings use NNRTI-based regimens because they have reliable pharmacokinetic properties, are effective at high viral loads / low CD4 counts (many patients present at this stage in such settings), and allow the sparing of PIs, which can be reserved for second-line and salvage therapy. The NNRTI efavirenz (EFV) remains the “standard of care” based on reports from several clinical trials.17,18 While some experts have observed that nevirapine (NVP) was comparable to EFV in the 2NN study, others have interpreted the 2NN data as showing nevirapine’s inferiority.19 Regardless, this class of drugs has a low genetic barrier to resistance and suffers from extensive cross-resistance.20 In addition, mutations archived from the use of single-dose nevirapine (sdNVP) for PMTCT have been observed to negatively impact the effectiveness of subsequent ART combinations containing nevirapine.21 However, a recent study from South Africa assessing the efficacy of NNRTI-based regimens in women who had previously received single-dose nevirapine for PMTCT, in comparison to the efficacy in women who had not received single-dose nevirapine, found that if combination ART was initiated after 18 months of single-dose nevirapine, there was no difference in early virologic response through 24 weeks.22

Nevirapine can cause serious hepatic toxicities and skin reactions in patients with high CD4 counts23 and others coinfected with HBV or HCV.24 The risk of potentially fatal nevirapine hepatotoxicity, which can occur in the first six weeks of therapy, appears greatest in women with a CD4 count greater than 250 cells/mm³ and in men with a CD4 count greater than 400 cells/mm³.25 For this reason, nevirapine is contraindicated in these individuals. EFV can lead to serious central nervous system (CNS) side effects in 5% to 10% of patients in the first few weeks of treatment and is contraindicated in women of childbearing age in developing countries.
countries because of teratogenicity (i.e., potential ability to cause birth defects).

Triple NRTI-based regimens are simple to use, have a low pill burden, are well tolerated, and allow the sparing of PIs and NNRTIs. However, these regimens are less potent than other currently used regimens. Zidovudine toxicity may also pose a problem in many resource-limited settings, as patients presenting for ART often have marginal hemoglobin levels. However, there have been promising preliminary results from the DAART trial for the triple combination of tenofovir, zidovudine, and lamivudine (3TC).27

New First-Line Antiretroviral Combinations

New ARV combinations include the following:

- TDF + FTC + NVP
- TDF + FTC + EFV

Tenofovir, a nucleotide reverse transcriptase inhibitor (NtRTI), has proven very useful, particularly since it is effective and safe and may not share similar resistance mutations with thymidine analogues. Tenofovir, plus either lamivudine or emtricitabine (FTC), has been shown to be well tolerated and as effective as stavudine plus lamivudine.28 To date, it appears that long-term toxicities such as lipoatrophy and hypertriglyceridemia are lessened with the use of tenofovir as compared with stavudine-based treatment. By the same token, tenofovir is an alternative option for patients, and, as shown by Gallant et al,29 tenofovir-based regimens are now considered better than zidovudine-based regimens.

The coformulation of tenofovir plus emtricitabine (brand name Truvada) allows this combination to be taken as a once-daily regimen with efavirenz, requiring only two pills per day. Recently another coformulation of three drugs (TDF + FTC + EFV) under the brand name Atripla has been introduced onto the market. This combination is available as one single pill taken daily. However, two tenofovir-based combinations have recently shown high rates of virological failure. These include abacavir + lamivudine + tenofovir30 and didanosine + lamivudine + tenofovir.31 Tenofovir is very active against HBV and therefore is highly recommended in patients with coinfection of HIV with HBV.32 However, tenofovir has been linked with acute and chronic renal insufficiency, particularly in individuals with occult renal disease,33 and bone demineralization.34

Second-Line Therapy

Recommendations for second-line therapy include the following:

- Failed first-line AZT combination: switch to TDF + 3TC or FTC + LPVr
- Failed first-line TDF combination: switch to AZT + 3TC + LPVr

Boosted PI regimens are the backbones for most second-line and salvage regimens in the majority of resource-limited settings. Ritonavir-boosted lopinavir (LPVr), in particular, has demonstrated potency in multiple clinical trials.35 Findings from several studies have noted a high genetic barrier to resistance and efficacy in patients with high viral load and low CD4 counts taking boosted lopinavir.36 Although lamivudine loses its direct virologic potency in the presence of the M184V mutation, it may be retained in the regimen (as a third NRTI) because it allows for the persistence of M184V mutants that replicate poorly due to reduced viral fitness.37 The use of lamivudine or emtricitabine also remains helpful, as it may lead to hypersusceptibility to certain other NRTIs, such as tenofovir.38 Similarly, even when there is evidence of thymidine-analog mutations (TAMs), the addition of zidovudine to a tenofovir-containing second-line drug combination may enhance the efficacy
of the regimen. A plausible explanation for this has come from a recent study that observed that K65R mutation inhibits the excision of nucleotides from the growing DNA chain, thereby increasing the efficacy of zidovudine.

Third-Line or Salvage Therapy
Patients who fail second-line therapy will eventually need salvage or third-line treatment, which is complicated and costly. With the availability of more effective drugs, the goal of all therapy is to reduce the viral load to less than 50 copies/mL. To achieve durable virologic suppression, it is recommended that a minimum of two new drugs be used, ideally each from a new class of drugs. The development of new agents is the best hope for patients with multi-class resistance. These include “second-generation” agents in existing classes with unique profiles such as tripranavir (TPV), darunavir (TMC-114), and etravirine (TMC-125). Other agents come from novel classes with novel mechanisms of action to which there is no cross-resistance, such as raltegravir (MK-0518), an integrase inhibitor, and maraviroc, an entry inhibitor. It is important to note that two boosted PIs act as one drug, or monotherapy, and their use for salvage therapy should be discouraged. If no new drugs are available, it is recommended that the patient continue on current treatment until new drugs become available.

MONITORING PATIENTS ON ART
Prior to initiating therapy, the clinician and patient must agree on a schedule for monitoring the progress and effects of therapy. Following patients on ART is a lifelong activity. At a minimum, patients who are stable should be evaluated at the clinic every three months by the clinician and have a laboratory assessment twice annually (see Table 1). Monitoring should be more frequent at treatment initiation, at the time of any treatment change, or in the case of concurrent illnesses. Prior to selecting the ARV treatment regimen, patients will need to undergo a comprehensive clinical and laboratory evaluation, as outlined above.

A major obstacle to the effective use of ART has been a lack of agreement about how to monitor patients receiving ART and how to detect treatment failure. Plasma HIV-1 RNA (viral load) measurement remains the gold standard for monitoring patients in developed countries, but this test is considered too expensive or logistically difficult in many settings. Colebunders et al recently developed an algorithm for monitoring patients receiving ART in resource-limited settings that uses clinical and immunological indicators, including adherence, to assess treatment failure. A limited report from South Africa observed that despite some improvement in sensitivity for detecting virological failure compared with existing WHO criteria, the low sensitivity and specificity of the algorithm rendered it unusable as a substitute for virological monitoring. However, as suggested by Colebunders et al, less stringent models like this can be used as a screening tool for patients at risk of treatment failure who would then be candidates for targeted viral load testing. Without access to viral load testing, diagnosis of virological failure will be delayed. Therefore, although the search for other surrogate markers for treatment failure should be encouraged, there is an urgent need for the development of simpler and more cost-effective viral load assays.

The standard of care in many African countries has relied on the clinical assessment and clinical monitoring of patients. In such settings, CD4 cell counts and viral loads are often not measured, resulting in patients with low CD4 counts (less than 200 cells/mm³) not being considered for treatment because they may not have symptoms. This can lead to viral resistance and subsequent severe immune dysfunction being identified at a later stage, thus compromising any potential benefits from second-line ART. Some experts argue that monitoring ART in any setting will require CD4
and prepare samples that can be up referred to the regional center for viral load assays and PCR infant diagnosis. Community-level facilities should have the capacity to perform rapid tests for HIV serology, blood counts to identify anemia, and simple microscopy to diagnose TB and opportunistic diseases. One key element of a tiered laboratory program is the setting of national training standards for technicians/supervisors, test performers, and community health-care workers. In addition, the program should have quality assurance with a national or state/district quality assurance package incorporating proficiency testing and observed performance. The various laboratory assays should be guided by SoPs.

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**Table 1. Laboratory Tests for Patients on ART**

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
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<tr>
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<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Where available**

cell enumeration and plasma viral load determination, as plasma viral load is correlated with disease progression and is a critical parameter for assessing virologic failure. In tertiary and referral centers that have the necessary infrastructure and trained personnel to perform this assay, viral load determinations will provide the clinician and patient with critical information on the patient’s virological status during ART and will indicate when virologic failure has occurred. At points of care outside the referral center, where this assay is not available (such as at the district level), CD4 cell enumeration and clinical monitoring can be substituted. Other important monitoring tests that can be performed at district facilities include a sputum smear for TB, blood chemistry, serology for syphilis, HBV, HCV, and the hemoglobin or packed cell volume.

Laboratory services must be tiered if they are to function optimally during the scale-up to universal ART access. Regional or tertiary centers should have the capacity to perform all routine tests and be equipped to perform more sophisticated tests, including CD4 cell counts, viral load assays, PCR infant diagnosis, and, in rare cases, resistance genotyping. District-level laboratories should have the capacity to perform CD4 cell counts, carry out blood chemistry tests and counts, and prepare samples that can be up referred to the regional center for viral load assays and PCR infant diagnosis. Community-level facilities should have the capacity to perform rapid tests for HIV serology, blood counts to identify anemia, and simple microscopy to diagnose TB and opportunistic diseases. One key element of a tiered laboratory program is the setting of national training standards for technicians/supervisors, test performers, and community health-care workers. In addition, the program should have quality assurance with a national or state/district quality assurance package incorporating proficiency testing and observed performance. The various laboratory assays should be guided by SoPs.

**DETERMINING WHEN TREATMENT HAS SUCCEEDED OR FAILED**

Successful ART implies that a patient has taken his or her drugs and responded to treatment. Treatment failure is defined as an inadequate response to treatment for any of a variety of reasons. Clinical failure indicates progression of clinical symptoms or the emergence of new opportunistic infections, conditions, or death while on ART. Virological failure indicates the loss of control of viral replication. A successful response is associated with a rapid
decline in plasma HIV RNA and a corresponding increase in the CD4 cell count. Within 12 weeks of starting therapy, approximately 80% of patients will have HIV RNA of less than 400 copies/mL and a CD4 count increased by approximately 50 cells/mm³. The maximum effect of treatment should be observed in the majority of patients by 24 weeks. Over 95% should have plasma HIV RNA below 400 or 500 copies/mL and a CD4 count increased by 50 to 100 cells/mm³.

There is greater variability in the change in CD4 count as compared to HIV RNA, especially early on in treatment. Of note, approximately 10% of patients have a disconnect between response in HIV RNA and CD4 cell counts, meaning that HIV RNA declines, but the CD4 count increase is blunted. Such patients should be allowed to continue with their ARV combination. Factors associated with such reduced CD4 cell response include older age, a lower baseline CD4 cell count, and a very low nadir CD4 cell count. TB, and to a lesser extent malaria infection, has been associated with decreased CD4 cell counts. These coinfected patients require continued prophylaxis with cotrimoxazole for opportunistic infections if their CD4 cell count is below 350 cells/mm³. If the plasma HIV RNA does not decrease steadily over the first three months of treatment, or it rebounds to within 0.5 log₁₀ copies/mL of pre-therapy values, then the ART regimen is failing. By 24 weeks, if the HIV RNA has not decreased to a level below detection (less than 400 copies/mL), the patient should be considered as having failed therapy (i.e., virologic failure). Similarly, if (a) the CD4 cell count remains below 100 cells/mm³ after six months of treatment, (b) there is a return to or a fall below the pretreatment CD4 baseline after six months of treatment, or (c) there is a 50% decline from the on-treatment peak CD4 value, the patient should be considered as having immunological failure. The development of a new or recurrent WHO stage III or IV condition after six months is considered evidence of disease progression and therefore indicates treatment failure on a clinical basis.

In addition to the laboratory changes in HIV markers described above, patients during the first few months of therapy should feel better clinically if they were symptomatic prior to therapy. Patients typically describe an improved sense of well-being, weight gain, and less fatigue. They may note a decrease in oral or vaginal candidiasis, fewer herpes simplex outbreaks, improvement in skin and/or hair texture, regression of condylomata, and regression of Kaposi’s sarcoma. Serum cholesterol levels may increase and triglyceride levels decrease, corresponding to a return to pre-HIV infection status. However, it should be noted that some patients, especially those with severe immunosuppression at baseline, may develop immune reconstitution inflammatory syndrome (IRIS), where some lesions, including herpes simplex virus, condylomata, and even Kaposi’s sarcoma may get worse with commencement of ART (see chapter entitled “Immune Reconstitution Inflammatory Syndrome” for more information).

CONCLUSION

Current evidence indicates that starting therapy at CD4 cell counts of 200 cells/mm³ or below is too late. We must increase this threshold in light of evidence that patients do better when started on ART at a higher threshold now that we have new, more effective, less toxic, and more convenient drugs at our disposal. Combination ART should be commenced based on the degree of immunosuppression, using symptoms and CD4 cell counts as recommended by the WHO guidelines for scaling up ART in resource-limited settings. Patients should commence ART only when they have received enough education to understand what HIV is, as well as how the treatment works and what various treatment options exist. The importance of
adherence should be stressed, and, as much as possible, the use of treatment support partners should be encouraged to facilitate adherence to ART. Patients should be motivated and deemed “ready to start” ART before they commence treatment. Additionally, ART must be provided as a comprehensive package, consisting not only of ARVs but of regular counseling, psychological support, prophylaxis for and treatment of opportunistic infections, and nutritional support.

Most of the currently recommended ART regimens are effective. However, triple NRTIs are less effective than some other regimens. Regimens are differentiated by related complications, pill burden, tolerability, toxicity, monitoring requirements, potency, drug interactions, refrigeration requirements, suitability for use during pregnancy, and possible effects on comorbid conditions. The choice of regimens should be based on considerations of potency, tolerability, convenience, long-term toxicity, and drug resistance. Because of the long-term complications of lipodystrophy and peripheral neuropathy, stavudine-based regimens should be discouraged. Zidovudine- and tenofovir-based regimens are the preferred options, while boosted PIs should be reserved for second-line therapy. However, it remains to be seen whether the survival outcomes associated with this strategy in resource-limited settings are comparable to those associated with a combination of PIs and NRTIs. The goal of treatment for both first- and second-line treatment is the achievement of an undetectable viral load, a progressive rise in the CD4 cell count, and a decline in the frequency and severity of opportunistic infections using a public-health approach. Therefore, any progress short of these milestones may be associated with decreased durability and portend the development of drug resistance.

Task shifting from physicians to nurses and COs allows nurses and COs to assume broader clinical duties and provide leadership for the HIV care team, thereby freeing up physicians to treat more patients. However, more evidence is needed on how ART programs managed by nurses and COs compare to physician-led care in terms of individual and community-based outcomes. Community involvement through education, preparedness, support activities, and mobilization can greatly enhance drug adherence and reduce stigma and discrimination, which are major obstacles to ART access.

Finally, the strategy that may prove most useful for the massive scaling up of ART programs in resource-limited settings is one that employs a community-based approach and that provides ART services at no cost to the patients through a tiered delivery model, while preserving the quality of care. This strategy allows for the delivery of ART at zonal/regional centers of excellence (i.e., tertiary centers), at state/district facilities (i.e., secondary centers) that meet minimum requirements for ART, and at community-based facilities (PHCs) that do not meet the minimum requirements for ART but can provide care and support services, including VCT and referrals.


31. Jemsek J, Hutcherson P, Harper E. Poor virologic responses and early emergence of resistance in treatment naive, HIV infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF. Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA.


Antiretroviral Treatment Failure, Drug Resistance, and Management of Therapy-Experienced Patients

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MOST FIRST-LINE ANTIRETROVIRAL therapy (ART) in resource-limited settings comprises a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleos(t)ide reverse transcriptase inhibitors (NRTIs), or a combination of three NRTIs. Several treatment programs in such settings have recorded good adherence rates as well as virologic, immunologic, and clinical success comparable to what exists in industrialized countries; however, overall treatment capacity (trained personnel, available drugs, and infrastructural support) falls far short of the need. Many patients receive care from ART-inexperienced practitioners and clinics, where they may be prescribed nonsuppressive ART or unproven herbal remedies, in addition to suboptimal or inadequate follow-up and support. Furthermore, the use of single- or dual-agent ART for the prevention of mother-to-child transmission (PMTCT) is widespread. Cultural barriers including stigmatization and discrimination are frequently cited as additional impediments to adherence and viral suppression and, hence, as indirect promoters of resistance. Despite these issues, assumptions that antiretroviral resistance will inevitably be worse in resource-limited settings than in industrialized countries are unsubstantiated. The fear of resistance, therefore, should not constitute a barrier to treatment.

Some degree of resistance will emerge in all settings where ART is delivered: for example, rates of resistance in industrialized countries have been estimated at 27% by six years in patients starting on three or more drugs. By the same token, some patients in resource-limited settings will fail first-line ART or do poorly after being exposed to nonsuppressive regimens. This failure is often a reflection of resistance mediated by incomplete viral suppression and suboptimal adherence. Also, transmitted resistance is an emerging problem, although the scale is not well defined. Overall, a cumulative increase is expected in the number of patients who need second-line therapy or deeper salvage, but this can be lessened if maximum adherence and complete viral suppression are entrenched as the cornerstones of ART at individual and programmatic levels.

RESISTANCE

Human immunodeficiency virus (HIV) replication is an imperfect and error-prone process with frequent alterations in viral amino acid sequence
mutations) from wild-type (drug-sensitive) virus. Approximately one mutation occurs with every replication cycle, which translates into several billion mutations per day. Given this rapid turnover, each untreated person harbors a swarm, or quasispecies, of genetically related but distinguishable HIV strains, including some with “incidental” resistance mutations. In the absence of ART, such incidental mutations are temporary and nondominant for a simple reason: in order to maximize its chances of survival, the virus, like other pathogenic organisms, evolves toward the strains that are fittest for that particular environment. Thus, in the absence of ART, highly replicative wild-type virus is dominant. Conversely, when a patient is receiving ART, viral evolution favors strains that are best able to replicate in that environment, which tend to be the strains that are resistant to current ART. In summary, HIV resistance results from a dynamic interplay of (1) HIV diversity; (2) HIV replication; and (3) selection pressure exerted by ART. The most likely scenario for these three factors to coexist is when there is high-level viremia and poor adherence to ART. In contrast, while cryptic replication may persist in some cellular compartments of adherent patients who are aviremic (no detectable plasma virus), resistance is unlikely to develop. Also, new durable resistance is unlikely to develop in the absence of ART.

**PRIMARY VERSUS SECONDARY RESISTANCE**

HIV resistance can be classified as primary (transmitted) or secondary. Primary resistance is acquired from the index patient at the time of initial infection or reinfection (superinfection). It is important to distinguish resistance mutations from naturally occurring polymorphisms on protease and reverse transcriptase that may influence the emergence of resistance. Primary resistance is now reported in approximately 10% of newly infected patients in industrialized countries where ART has been in use for more than 10 years. Definitive data are scarce from resource-limited settings with limited ART experience, although it is likely to be comparatively low for now. Primary resistance may persist for several years in plasma or semen, and early virologic failure in patients receiving combination ART is sometimes traceable to resistance to a single component of the regimen. As the impact of primary resistance on HIV epidemiology and management in resource-limited settings plays out over the next decade, the preliminary report of a panel of experts convened by the World Health Organization (WHO) in 2003 is a good reference point for countries contemplating the relevance and logistics of resistance surveillance in their population. Some of the key recommendations were that resistance surveillance should (1) be conducted when ART programs are well established and have sufficient coverage, or when drug resistance may be greater than 5%; (2) focus on treatment-naive persons, with a preference for those who are recently infected; (3) focus on testing and counseling centers such as antenatal clinics; and (4) sample approximately 500 patients per site, which is sufficient to capture a change in resistance from 5% to 10%.

Secondary resistance refers to resistance that develops while the patient is receiving ART. This is thought to be the more common form of resistance at this time in resource-limited settings, and it is closely linked to incomplete viral suppression while on ART. The experience from Thailand, where increased prevalence of resistance was seen with expanded ART, buttresses the need for resistance surveillance in national ART programs. Apart from the potential adverse effects on clinical course and response to ART, patients with secondary resistance serve as reservoirs of the strains that result in primary resistance if transmitted to new persons. Unlike primary resistance that often remains detectable in plasma for long periods in
the absence of ART, secondarily developed resistance is typically rapidly replaced by wild-type if ART is withdrawn. The time for such “reversion” to wild-type may be as short as a few weeks.15

Even when resistance mutations become undetectable in plasma, they may be archived in proviral DNA and can repopulate plasma if the drug (or a similar drug) to which resistance was developed is reintroduced.16 An illustrative scenario is seen among patients with secondary resistance to efavirenz or nevirapine. If the NNRTI is discontinued, circulating viruses will likely change from NNRTI mutants to wild-type. However, the NNRTI-resistant strains will likely reemerge if the patient is reexposed to efavirenz or nevirapine.

**HIV DIVERSITY AND RESISTANCE**

Circulating HIV strains around the globe are diverse and complex17 with the main (M) type being predominant. Subtype C viruses, the most common subtype in South and East Africa as well as India, are the most prevalent worldwide. Subtype A is commonly found in East Africa, subtype B in North America, Europe, and Australia, and subtype D in East Africa. There are several circulating recombinant forms (CRFs) including CRF02_AG, which is common in West Africa. Groups O and N are mainly found in Cameroon, while HIV-2 is largely confined to West Africa. It is common for multiple subtypes to coexist in the same population. Most available data on ART resistance were derived from the B subtype.

While it remains uncertain what intrinsic differences, if any, exist in preferred resistance pathways or durability of selected mutations among different HIV subtypes, several preliminary observations testify to this potential. For example, polymorphisms have been demonstrated in non-B subtype HIV at protease and reverse transcriptase sites known to be associated with resistance.18,19 Theoretically, some of these polymorphisms may alter the steps to clinically significant mutations, or lead to novel pathways of mutational escape under drug pressure. This is illustrated by D30N, which is a common mutational pathway to high-grade nelfinavir resistance in subtype B patients, but is uncommon with non-B subtypes, probably because of existing polymorphisms.20 Also, the K103N mutation in recipients of single-dose nevirapine (sdNVP) tends to persist longer among those infected with HIV subtype D versus subtype A.21 For now, clinical practice in resource-limited settings is driven by the evidence of overlap in mutational pathways,22 and responses to ART among B and most non-B HIV subtypes. Differences likely exist, however, such as the suggestion that subtype G may be less susceptible to protease inhibitors (PIs).23,24 Clearly, research focusing on the relationships between the non-B HIV subtypes and HIV resistance is needed.

**OVERVIEW OF SELECTED MUTATIONS**

**M184V and M184I**

The M184I mutation is often the first to emerge during lamivudine or emtricitabine exposure; however, it has lower replicative capacity than M184V, which becomes the dominant mutation.25 M184V potently blocks the incorporation of lamivudine and emtricitabine into viral DNA chain, inducing high-level (up to > 500-fold) resistance to those drugs, and lower (often clinically insignificant) resistance to didanosine, zalcitabine, and abacavir.26 On the other hand, it causes increased susceptibility to zidovudine, stavudine, and tenofovir because it counteracts their excision from viral DNA.27,28 Strains with M184V have significantly reduced replicative capacity that may be beneficial clinically.29 Despite the low genetic barrier to resistance, lamivudine and emtricitabine are cornerstones of ART worldwide.
Thymidine-Associated Mutations

The thymidine-associated mutations, or TAMs (M41L, D67N, K70R, L210W, T215Y/F, and K219E/Q), are selected by zidovudine or stavudine, two commonly prescribed NRTIs in resource-limited settings. They tend to accumulate in patients who are left on a failing regimen with ongoing viral replication, typically in one of two clusters: M41L, L210W, and T215Y, leading to more-extensive cross-resistance to NRTIs, or D67N, K70R, T215F, and K219E/Q, leading to less-extensive cross-resistance. TAMs reduce viral susceptibility to many NRTIs, especially zidovudine and stavudine. However, single TAMs generally cause only relatively low-level resistance, which may not significantly compromise antiretroviral activity, although some patients have failed zidovudine-containing regimens when only 41L or 215Y/F mutation was present. Tenofovir usually retains significant antiretroviral activity in the presence of multiple TAMs, if M184V is present. Unlike M184V and K65R, isolated TAMs cause only a small reduction in viral replicative capacity, but a combination of several TAMs can significantly reduce viral replication.

K65R

This relatively uncommon mutation is antagonistic to TAMs, and is the preferred mutational pathway for tenofovir. In addition, it can emerge following exposure to didanosine or abacavir. Stavudine has been rarely associated with K65R, which may explain some of the reported cases in resource-limited settings among patients without prior exposure to tenofovir, didanosine, or abacavir. Subtype C viruses appear to select K65R more rapidly than other HIV-1 subtypes and HIV-2. K65R is associated with cross-resistance to many NRTIs including abacavir, tenofovir, lamivudine, and didanosine, which provides a rational explanation for the observation that patients who have failed tenofovir-containing ART because of resistance may also fail abacavir or didanosine, and vice-versa.

The likelihood of developing K65R is influenced by the ART regimen: (1) risk is increased in treatment-naive patients who receive tenofovir plus abacavir, didanosine plus abacavir, or tenofovir plus didanosine; and (2) the presence of TAMs or zidovudine in a regimen diverts resistance pathways away from K65R. K65R appears to increase viral susceptibility to zidovudine. Viruses with K65R mutation, like M184V, have replicative capacity that is approximately 50% of wild-type, thus the combination of K65R and M184V results in a virus with very significant reduction in replicative capacity.

Other NRTI-Associated Mutations

NRTI cross-resistance has also been associated with Q151M and T69 insertions. L74V occurred frequently with didanosine monotherapy, but it is infrequently encountered now that didanosine is usually combined with other ARV drugs. Also, L74V is one of the mutational pathways selected by abacavir. The presence of L74V and M184V leads to abacavir and didanosine resistance plus some resistance to tenofovir. Patients who fail abacavir or didanosine due to L74V may harbor small populations of K65R, which translates to increased risk of tenofovir failure, if exposed to the drug.

NNRTI Mutations

The most common mutations seen in persons on NNRTI (nevirapine or efavirenz) therapy are K103N and Y181C, which cause high-level NNRTI cross-resistance. Other notable mutations include V106A, Y188C/L/H, and P225H. Because of the ease of developing resistance against NNRTIs, these drugs are said to have a low genetic barrier against resistance, like lamivudine and emtricitabine. Among poorly adherent patients who fail initial NNRTI-based ART (the combination most
commonly used in first-line ART in resource-limited settings), the most common mutations are NNRTI associated, followed by M184V.

NNRTIs have prolonged steady-state half-lives (25–32 hours and 40–55 hours for nevirapine and efavirenz, respectively), compared with other antiretroviral drugs. As a result, they remain in circulation at therapeutic concentrations for several days, and at subtherapeutic concentrations for up to several weeks after discontinuation. Thus, simultaneous discontinuation of all the drugs in an NNRTI-based regimen may lead to a period of unintentional NNRTI monotherapy since other drugs clear faster from the blood. This predisposes to NNRTI resistance, especially among patients with high viremia. Although the best strategy to discontinue NNRTI-based regimens is debated, most authorities recommend stopping the NNRTI followed by the NRTI(s). More controversial is the optimal length of time between stopping the NNRTI and stopping the “NRTI tail.” Recommendations have ranged from four to five days to as long as four weeks, while most agree that a one-to-two-week NRTI tail is reasonable.

PI Mutations
In general, single mutations in the protease gene cause relatively low-level resistance that does not significantly compromise clinical efficacy, but exceptions include D30N and I50L, which cause high-level resistance to nelfinavir and atazanavir, respectively. The likelihood of developing resistance can be reduced by adding low-dose ritonavir to “boost” the pharmacokinetics of the PI (except nelfinavir). This is because ritonavir inhibits gastrointestinal and hepatic cytochrome P450 (CYP450) enzyme systems, which are necessary to metabolize PIs. As a result, ritonavir improves the pharmacokinetic parameters of the co-administered PI, including the trough concentration (C_{min}) and overall drug exposure as measured by the area under the plasma concentration versus time curve (AUC). These changes allow the use of lower PI doses. Also, the inhibitory quotient (ratio of C_{min}/concentration needed to inhibit viral replication by 50% [IC_{50}]), which influences the likelihood of developing resistance mutations, is improved with boosted PIs. In summary, ritonavir-boosted PIs generally have improved potency and much reduced risk of resistance compared with unboosted PIs.

SINGLE-DOSE NEVIRAPINE, OTHER NONSUPPRESSIVE ART REGIMENS, RESISTANCE, AND TREATMENT FAILURE
One of the most common uses of nonsuppressive ART in resource-limited settings is sdNVP for PMTCT. Although recommended by WHO and unavoidable in certain situations (for example, women who present in labor), the main criticism of this intervention is that it predisposes to the development of K103N and Y181C mutations, which cause cross-resistance to nevirapine and efavirenz. The incidence of these mutations can be reduced by co-administering a short course of AZT/3TC to mother and baby. These mutations tend to fade over time, but may remain detectable for several years in some patients, and can be transmitted to the infants of affected women. Factors associated with delayed fading include high pre-sdNVP viral load and perhaps viral subtype.

The major clinical concerns related to the resistant mutations that can follow sdNVP are subsequent reduction in the effectiveness of ART that contains nevirapine or efavirenz, and reduced success of sdNVP in future pregnancies. Recent preliminary studies, however, have shed some light on the magnitude of these risks and provided justification for continued use of sdNVP when the woman is ineligible for combination ART for her own disease and better options do not exist. The first finding was the absence of a significant
difference in the efficacy of sdNVP between first versus second use.48,49 Equally notable were the studies that showed similar responses to NNRTI-containing combination ART among women with prior sdNVP exposure versus those without previous exposure, provided the combination ART was started at least six months after the sdNVP. Patients who initiated NNRTI-based ART within six months of sdNVP had poorer outcomes.30,31

Taken together, these findings suggest that despite the propensity of sdNVP to induce resistance mutations, it can be reused in subsequent pregnancies, and NNRTI-containing combination ART can be used in sdNVP recipients, but it is best to delay its use until at least six months after the exposure to sdNVP. Researchers are trying to reconcile the relative effectiveness of NNRTI-containing ART in patients who had evidence of NNRTI mutations after sdNVP only versus its lack of effectiveness in patients who failed previous NNRTI-containing ART. One yet to be proven hypothesis is that the quantity of resistant virions and archived mutations is much smaller after sdNVP alone; hence, it may be easier for it to be permanently overwhelmed by wild-type.

Another common, but certainly more harmful, scenario of nonsuppressive ART in resource-limited settings occurs through its provision by health providers with no experience in ART. This poses both short-term and long-term danger to individual patients and public health because it provides an ideal environment for iatrogenic resistance. To reduce this, adequate training should be provided to those who prescribe ART, and treatment outlets expanded by integrating them into existing healthcare infrastructure. Further, minimum monitoring capabilities should be made available, and strong systems put in place to fend off the threat of drug adulteration. Public enlightenment on the hazards of combining herbal preparations with ART should be undertaken. Unchecked inappropriate use of anti-HIV drugs can engender large-scale iatrogenic resistance and seriously limit the morbidity and mortality benefits that are derivable from ART.

**PRACTICAL APPROACH TO TREATMENT FAILURE**

Treatment failure occurs in approximately 30% of patients undergoing initial therapy,32 although it can be as low as 5% or may exceed 50% depending on the particular clinical setting and patient population.33-37 The most common cause of treatment failure is poor adherence as demonstrated by two observations: first, virologic failure rates can be as low as 5% when adherence is enforced such as through directly observed therapy (DOT) in correctional facilities;57 and second, patients failing initial therapy most commonly have drug-sensitive virus.58

**Optimizing Adherence to Prevent Resistance**

The management of treatment failure starts with its prevention, and the most effective tool from both cost and clinical perspectives is optimization of adherence in all patients. In general, timely and appropriate ingestion of at least 95% of prescribed ART is essential.59 The foundation for excellent adherence should be laid before the first dose of ART is prescribed, and systems for continual reevaluation and reinforcement should be in place. To improve adherence, selected ART should be simple, well tolerated, and have the fewest number of pills and a single daily dose if possible. Treatment literacy should be encouraged by educating patients about their regimen, including how to address adverse effects and contact their providers if needed; otherwise, they are likely to stop taking prescribed medications once they associate it with untoward effects. Further, support structures should be developed around each patient. The support models that have been used successfully in resource-limited settings...
differ in their specific methodologies, but most link patients to other people for motivation and assistance with disclosure and other psychosocial issues. In addition, the treatment supporters provide practical support with adherence and management of adverse effects. One model in Haiti used community-based health workers (accompagnateurs) to provide DOT, while other models used treatment partners (a relative or close friend) to promote adherence. In the clinic, all cadres of staff should be involved in adherence promotion, and specially trained counselors should be utilized whenever feasible. Tools such as pillboxes, drug identification charts, diaries, and educational materials are useful, especially if they are culturally competent. Finally, adherence should be addressed at every medical encounter, and a detailed record of drug pickup patterns should be kept. As ART programs expand, further research will be needed to identify best practices for treatment adherence support.

**Diagnosis of Treatment Failure**
The criteria used to define treatment failure are influenced by local resources and guidelines. In general, clinical, immunologic, and virologic factors are considered (Table 1).

### Table 1. Recognition of Treatment Failure: Adapted from the WHO 2006 Guidelines for Resource-Limited Settings

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Development of new or recurrence of a WHO stage 4 diagnosis</td>
</tr>
<tr>
<td>Immunological</td>
<td>Decline in CD4 count to levels at or below pretherapy level; or 50% decline from the peak level achieved during treatment; or failure of CD4 count to rise above 100 cells/mm³*</td>
</tr>
<tr>
<td>Virological</td>
<td>Persistent viral load &gt; 1,000 copies/ml</td>
</tr>
</tbody>
</table>

*Viral load is the earliest and best indicator of treatment failure.

**Managing First-Line Treatment Failure**

**Patients with Poor Adherence**

When confronted with a patient who is failing initial ART, the first step should be to determine the patient’s adherence. This can be done by appraising the pattern of ART pickup from the pharmacy, direct patient questioning, and a review of adherence tools such as drug diaries and pillboxes. In doing this, the clinician must recognize that the usefulness of these exercises in general, and direct patient questioning in particular, is directly linked to the skill with which the inquiry is undertaken and the quality of collected data. For example, the question “You have not been skipping your medications, right?” probably has a greater likelihood of eliciting an erroneous response than “How many doses have you missed in the last three days?” or “Tell me how you have been doing with the medications.” Further, the clinician should bear in mind that admissions of poor adherence are almost always accurate; claims of excellent adherence may be exaggerated; and health-care providers are often inaccurate in their subjective estimation of a patient’s level of adherence. Given the complexities of assessing adherence, clinicians should be prepared to apply both the art and the science of medical practice and expect surprises.

If a history of poor adherence is elicited, the clinician and patient should identify reversible
causes, and craft practical interventions to correct them. The underlying cause may be as simple as the inability to reach the ART site because of transportation problems or it may be something more complex such as deliberate avoidance of the clinic because of concerns about future discrimination and stigmatization, domestic abuse, or substance abuse. Also, requiring co-payment (no matter how little) from patients before they are given ART has been identified as a barrier to adherence. In appropriate settings, good results may be derived from referring patients to structured adherence programs where they can interact with other HIV-seropositive patients or adherence counselors.

Patients failing due to poor adherence should continue the initial regimen after corrective measures have been undertaken as it stands a good chance of being effective. Plans should be made to reevaluate in the near future. On the other hand, patients who fail despite proven adherence over several months likely harbor resistant virus and may need ART change.

2. Treatment Failure Despite Good Adherence
It is not uncommon for a patient to fail while all objective and subjective assessments indicate greater than 95% adherence to prescribed ART. In this situation, the clinician has to consider many possibilities, including the following:

Drug-drug interactions. This is particularly applicable to some resource-limited settings since patients often combine herbal medications with prescribed ART. It is also common for patients to self-prescribe “immune-boosters.” Some of these compounds have yet uncharacterized interactions with ARTs and should be avoided. Also, the integrity of the ART that the patient is taking should be confirmed. Drug adulteration—the addition of an impure, cheap, or unnecessary ingredient to cheapen or falsify a preparation—though not reported yet, is a potential hazard that merits continual vigilance. Patients who fail due to drug-drug interactions can have a retrial of initial ART after discontinuing the unnecessary adjuvant.

Current inappropriate ART. It is insufficient to document that a patient is on “ART.” The clinician must ascertain the specific components being used because the patient may be receiving an inappropriate combination.

Presence of resistant virus before initiating treatment. For patients failing initial NNRTI-based ART, a history of sdNVP during previous pregnancy should be excluded since this may explain treatment failure, which is more likely if combination ART was initiated within six months of the sdNVP exposure. Also, patients who have received inappropriate ART combinations in the past may harbor resistant strains. Primary resistance, or infection with HIV-2 or HIV-1 group O, which are constitutively resistant to NNRTIs, should be considered as well.

Inadequate dosing. Resistance may develop during treatment due to inadequate dosing. One scenario for this is failure to adjust the drug dose following weight gain, particularly in pediatric patients as well as adults with low baseline weight.

Resistance Testing
Resistance testing provides useful information, although its availability in resource-limited settings is currently limited to just a few tertiary institutions and internationally supported programs. There are two types of resistance tests: genotypic and phenotypic resistance assays. These tests are better at forecasting the drug(s) that a patient is not likely to respond to. Resistance mutations that account for less than 20% of the total viral pool in the tested sample are easily missed. Resistance tests are more accurate if performed while the patient is on ART or as close to the time of discontinuation as possible. Tests performed off ART are prone to errors since wild-type virus is likely to be dominant, while
resistant mutants, if present, may exist in subpopulations that are below the limits of detection.

Genotypic testing utilizes techniques such as nucleic acid sequencing or hybridization to detect point mutations in the viral genome. It can be completed in one to two weeks, whereas phenotypic testing requires a much longer time. Also, genotyping is less technically cumbersome, cheaper, and somewhat better at detecting resistant mutants that are present in low concentrations. Standard phenotypic resistance testing involves direct measurement of viral susceptibility to various drugs, expressed as the drug concentration required to inhibit viral growth by 50% (IC\textsubscript{50}). Resistance to a drug is presented as the fold-change (ratio of the IC\textsubscript{50} of sample virus to the IC\textsubscript{50} of wild-type virus), which has to be evaluated for clinical relevance. In general, interpretation of genotype requires more expertise compared with phenotype, especially in heavily treatment-experienced patients, who may harbor multiple, complex, and poorly characterized mutations. Clinical outcome information is not yet available for some mutations, especially those associated with non-B HIV subtype.

While resistance testing in all failing patients is clearly not feasible, a public health approach that includes centrally coordinated monitoring and evaluation can reduce resistance and inform clinical management in resource-limited settings. The specific activities should include pharmacovigilance to ensure early detection and accurate characterization of the incidence and clinical features of adverse effects caused by antiretroviral drugs, since adverse effects are a leading cause of poor adherence, and indirectly resistance. The findings from monitoring and evaluation activities, including pharmacovigilance, should be incorporated into ART guidelines. For example, the recent change in the recommended dose of stavudine, a commonly used NRTI in resource-limited settings, from 40 milligrams twice daily to 30 milligrams twice daily is aimed at reducing peripheral neuropathy and suboptimal adherence associated with the higher dose. Monitoring and evaluation should be used also to determine locally sustainable best practices for uninterrupted procurement of antiretroviral drugs, drug storage, clinician training, and patient follow-up. Trends in transmitted and secondary resistance should be followed and applied to the care of HIV-infected patients and the prevention of new infections.

**Selecting a Second-Line Regimen**

Once it is determined that a patient is failing initial ART despite addressing adherence and related issues, a prompt treatment change is imperative. One of the major barriers to achieving this goal in resource-limited settings is the dearth of facilities for HIV RNA quantitation (viral load). Of the three potential parameters for determining failure (Table 1), an increase in viral load is the sentinel event, and typically precedes a decline in CD4 count by approximately six months, which itself precedes clinical manifestation(s) by several months or even years. Thus, a reliance on parameters other than viral load for identifying clinical failure implies there is likely to be a delay of six months or longer before treatment failure is recognized. This delay has potentially serious implications since patients who are inadvertently left on a failing regimen run the risk of developing (acquiring) more mutations, which can compromise future ART. In one study, 77% of patients left on a virologically failing regimen (viral load > 400 copies/mL) acquired one or more mutations over an average follow-up period of six months. Given the importance of viral load determinations in assessing treatment success and failure, accelerated research initiatives to develop locally adaptable and sustainable techniques are a priority for resource-limited settings.

Second-line combination ART should contain at least two new drugs (Table 2). Although WHO
FROM THE GROUND UP: ESTABLISHING A FRAMEWORK FOR SUCCESS

...can be a boosted PI plus two new NRTIs or other options shown in Table 2.

...two NRTIs in the new regimen should be selected based on the initial combination. Tenofovir is a particularly valuable component of second-line regimens because it often retains activity when other NRTIs are no longer effective; however, it is often unavailable. Disturbingly, high rates of resistance to tenofovir in patients without prior exposure to the drug have been reported recently in Malawi and other parts of sub-Saharan Africa, so this drug is not always the best option, and its use is best guided by knowledge of local mutational patterns. The combination of tenofovir and zidovudine has reduced propensity for development of the K65R mutation and overall bidirectional synergy, making it a desirable combination in many situations. Didanosine plus tenofovir has been associated with low CD4 counts, although it is virologically effective. The dose of didanosine should be adjusted downward if they are co-administered. Regardless of the two new NRTIs selected, it is reasonable to consider leaving lamivudine or emtricitabine as an additional agent. This is to preserve M184V mutation, which reduces viral replicative capacity, induces hypersusceptibility to some other NRTIs, and increases viral fidelity.70 It is also important to remember that discontinuation of hepatitis B virus active drug (lamivudine, emtricitabine, or tenofovir) in a patient with active hepatitis B can result in a life-threatening hepatitis flare.

Treatment after Second Failure

The management of patients who have failed second-line ART is complicated by the absence of genotype and phenotype resistance testing in most resource-limited settings. Virtually all salvage combinations are more complex than those used in earlier regimens, and adherence may be more difficult...
because of this. In general, it is reasonable to include lamivudine or emtricitabine in the regimen for the same reasons it is valuable in second-line regimens.\(^7\) Boosted PIs, tenofovir, and other NRTIs may also be beneficial, and local experts should be consulted whenever possible. Although newer drugs such as novel PIs and enfuvirtide, a fusion inhibitor, are frequently used in industrialized countries, these are not available in most resource-limited settings at this time. An example is tipranavir, a ritonavir-boosted PI that may be effective in some multi-drug-resistant, heavily pretreated cases when combined with an optimized background of other agents.\(^7\) Also, darunavir, another novel PI, has shown at least comparable efficacy and probably better tolerability and safety in similar patients.\(^7\) Etravirine is a second-generation NNRTI with activity against nevirapine- and efavirenz-resistant viruses,\(^7\) while maraviroc\(^7\) and raltegravir\(^7\) are a valuable CCR5 receptor antagonist and integrase inhibitor, respectively. Novel compounds like these have significantly expanded options for salvaging advanced patients, and it is inevitable that they will be needed in resource-limited settings (Table 3).

Even when the ART options available to a highly resistant salvage patient fail to fully suppress plasma virus, continuation of such a regimen may stabilize the patient’s CD4 cell count and clinical status\(^7\) until better options become available. Another strategy that has preliminarily demonstrated some benefit, compared with no therapy at all, is the use of lamivudine (and likely emtricitabine) monotherapy in patients who already harbor M184V. Expected benefits include slower rates of CD4 cell decline, viral rebound, and recovery of HIV-1 replication capacity.\(^8\)
<table>
<thead>
<tr>
<th>Initial Regimen</th>
<th>Possible Second-Line Regimen</th>
<th>Example of Second-Line Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI plus two NRTIs (NVP or EFV) + 3TC + (AZT or d4T)</td>
<td>Two NRTIs likely or proven to be active + PI (with or without low-dose ritonavir)</td>
<td>TDF + AZT + LPV/r</td>
</tr>
<tr>
<td>PI (with or without low-dose ritonavir) + two NRTIs NFV + 3TC + (AZT or d4T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two NRTIs likely or proven to be active + NNRTI</td>
<td>TDF + AZT + (NVP or EFV)</td>
</tr>
<tr>
<td></td>
<td>Two NRTIs likely or proven to be active + another PI (with low-dose ritonavir) likely or proven to be active</td>
<td>TDF + AZT + LPV/r</td>
</tr>
<tr>
<td></td>
<td>NRTI(s) likely or proven to be active + another PI (with low-dose ritonavir) likely or proven to be effective + NNRTI</td>
<td>TDF ± AZT + LPV/r (higher dose needed due to interaction with the NNRTIs) + (NVP or EFV)</td>
</tr>
<tr>
<td>Triple NRTI AZT + 3TC + TDF</td>
<td>Two NRTIs likely or proven to be active + NNRTI or PI (with or without low-dose ritonavir). Resistance testing is highly recommended for this approach; otherwise use other options.</td>
<td>TDF ± AZT + (NVP or EFV) or LPV/r. Resistance testing is highly recommended for this approach.</td>
</tr>
<tr>
<td></td>
<td>NRTI(s) likely or proven to be active + NNRTI + PI (with low-dose ritonavir)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NNRTI + PI (with low-dose ritonavir)</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- PI with low-dose ritonavir (for example, LPV/r, SQV/r, IDV/r, ATZ/r, FPV/r) is preferred to PI without low-dose ritonavir.
- Resistance testing should guide the selection of new drugs whenever feasible.
- Always consider continuing lamivudine or emtricitabine. These NRTIs are interchangeable but should not be used together.
- Zidovudine (AZT), lamivudine (3TC), stavudine (d4T), tenofovir (TDF), nelfinavir (NFV), lopinavir (LPV), low-dose ritonavir (r), saquinavir (SQV), indinavir (IDV), atazanavir (ATZ), fosamprenavir (FPV), nevirapine (NVP), efavirenz (EFV).
Table 3. Deep Salvage

<table>
<thead>
<tr>
<th>Baseline Patient Characteristics</th>
<th>Possible Salvage Regimen after Resistance Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous exposure to NRTIs, NNRTIs, and PIs with evidence of resistance to drugs in all the classes</td>
<td>Significant benefit can be derived from using a regimen that includes at least two new agents that have full activity along with an optimized combination of NRTIs. Drugs that are likely to have full activity in this context include darunavir/r, raltegravir, enfuvirtide, and maraviroc. Etravirine potentially has a role as well but it should be combined with a potent boosted-PI such as darunavir/r and other active drugs in patients with prior exposure to nevirapine or efavirenz.</td>
</tr>
</tbody>
</table>

Notes:

- The utility of the CCR5 co-receptor antagonist, maraviroc, is limited to persons with exclusively CCR5-tropic virus. The assay for CD4 co-receptor tropism is not available in resource-limited settings at this time.
- Tipranavir cannot be co-administered with etravirine. It requires a higher dose of ritonavir, and has been associated with fatal and nonfatal hepatitis and intracranial hemorrhage.
- Darunavir/r has a similar side-effect profile to other boosted PIs and has been associated with rashes, including Stevens-Johnson syndrome.


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Drug-Drug Interactions in HIV Disease Management

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PHARMACOTHERAPY IS AN ESSENTIAL component of HIV disease management. Treatment with multiple agents is often necessary to cure or control HIV/AIDS-related illnesses, to treat or prevent non-HIV-related acute or chronic conditions (e.g., arterial hypertension, hyperlipidemia, seizure disorders), and eventually to suppress HIV viremia. As interactions between different drugs might jeopardize the desired treatment outcome, health-care workers who prescribe, dispense, and/or monitor treatment effects need to be aware of potential drug interactions, as do the patients themselves.

Drug interactions can be defined as a change in the pharmacology of one drug in the presence of another drug. The combined effect of two or more drugs can be synergistic when the overall effect is greater than the sum effects of the individual drugs; it is antagonistic when one drug reduces or nullifies the effect of another drug. In some instances, expected drug-drug interactions can be beneficial, such as the pharmacologic enhancing effect of boosted protease inhibitors (PIs), which will be discussed later.

Regularly updated Web-based interactive drug interaction charts are available to help health-care providers cope with ever-increasing information on drug-drug interactions in clinical practice.\textsuperscript{1,2} Fortunately, only a minority of reported drug-drug interactions require absolute dose modification or drug substitution, but monitoring of toxicity or efficacy in light of these interactions is critical. Challenges specific to resource-limited settings include limited accessibility to existing, easy-to-use Web-based references; a limited range of available alternative drugs; and a lack of lab-based monitoring tools necessary to measure drug levels, toxicities, and treatment efficacy.

This chapter aims to summarize the most clinically significant drug interactions encountered in HIV disease management, to explain the underlying pharmacologic principles, and to recommend appropriate clinical management strategies.

KEY MECHANISMS OF DRUG INTERACTIONS

Successful pharmacotherapy depends on the administration of a drug dose sufficient to achieve the desired clinical effect with minimal toxicity. The relationship between drug dose and effect can be divided into pharmacokinetic (the body’s impact on the drug and the resulting drug concentration)
and pharmacodynamic (the drug’s effect on the body at a given concentration) components. The drug concentration at the site of action provides the link between the pharmacokinetic and pharmacodynamic properties of a drug and is an important parameter in the approach to establish rational drug dosing. The area under the plasma concentration time curve (referred to as “area under the curve,” or AUC) is a commonly used pharmacokinetic parameter to describe the bioavailability and clearance of a particular drug and to measure the effect of drug-drug interactions.

Here we describe mechanisms of drug interactions as they relate to commonly used drugs to treat HIV-related illnesses.3

Pharmacokinetic Drug Interactions
Pharmacokinetic drug interactions can occur at any step from the initial administration of the drug to its final clearance from the body, in particular during the process of drug absorption, biotransformation (activation or inactivation), and elimination.

A major site of drug metabolism is the liver. Biotransformation of drugs is broadly divided into two categories, namely drug oxidation (e.g., by the cytochrome P450 [CYP] enzyme system, which is a phase I reaction) and drug conjugation (e.g., glucuronidation or acetylation, which are phase II reactions).

CYP Metabolism
Many drug interactions occur among drugs that are metabolized by the CYP enzyme system, either when two co-administered drugs are metabolized by the same CYP enzyme or when one drug inhibits or induces (slows down or speeds up, respectively) the activity of a CYP enzyme impacting the biotransformation of the other drug.

The list of drugs that are substrates for CYP enzyme metabolism is long and includes the non-nucleoside reverse transcriptase inhibitors (NNRTIs), the PIs, and drugs used to treat opportunistic infections, such asazole antifungal agents, anti-TB drugs, macrolide antibiotics, lipid-lowering medications (the statins), certain antidepressants (serotonin uptake inhibitors such as fluoxetine), anticonvulsants (carbamazepine, phenobarbital, and phenytoin), anxiolytic drugs (benzodiazepines), oral contraceptives, drugs used to treat erectile dysfunction, and certain recreational drugs such as methylenedioxymethamphetamine (ecstasy) or methadone. In addition to being metabolized by the CYP enzyme system, many of these drugs also induce or inhibit the CYP enzyme activity.

CYP enzyme inhibitors: Most PIs are CYP inhibitors, leading to increased concentrations of simultaneously administered drugs that are metabolized via CYP enzymes. Ritonavir is the most potent inhibitor and, even in low dosages (50–100 mg per day), is able to increase the serum levels of other co-administered PIs (see also under PI boosting). Among PIs, saquinavir has the mildest inhibitory effects. Other important inhibitors are theazole antifungal drugs (itraconazole, fluconazole, and ketoconazole), the macrolide antibiotics (erythromycin and clarithromycin), and the H2 blockers (cimetidine and ranitidine).

CYP enzyme inducers: Inducers enhance the action of CYP enzymes, leading to decreased concentrations of concomitantly administered drugs metabolized by CYP enzymes. The strongest inducer is the anti-TB medication rifampicin. Other important inducers include nevirapine (NVP) as well as certain anticonvulsant drugs, namely phenytoin, carbamazepine, and phenobarbital. Some protease inhibitors have the potential to also induce CYP enzymes, so careful review of drug interaction potential based on the specific ARV combination being used is warranted.

CYP enzyme mixed inhibitors and inducers: Inducing or inhibiting effects are not limited to
individual drugs. For example, some drugs, such as efavirenz (EFV), exert both inhibitory and inducing effects. In clinical situations, EFV has been demonstrated to act primarily as an inducer (such as when combined with PIs); however, laboratory studies have shown that EFV is also an inhibitor of CYP, making it difficult to anticipate the exact interaction without drug-interaction study data. Similarly, ritonavir, a strong inhibitor of the CYP3A enzymes, can also induce the metabolism of oral estrogens, theophylline, atovaquone, and warfarin via other CYP enzymes.

Renal Elimination
All nucleoside reverse transcriptase inhibitors (NRTIs) undergo primarily renal excretion, with the exception of zidovudine (ZDV), which is metabolized by hepatic glucuronidation and subsequently excreted via bile and urine, and abacavir, which is metabolized via alcohol dehydrogenase. Drugs that are inhibitors of renal tubular secretion, such as trimethoprim, probenecide, and cimetidine, may inhibit NRTI elimination. However, the clinical importance of these interactions is unknown.

Transporter Proteins
Transporter proteins are cell membrane carriers that are specialized to expel foreign molecules and may be a key determinant of the underlying pharmacokinetic considerations for an individual drug. One of the best-characterized drug transporter proteins is P-glycoprotein. P-glycoprotein is implicated in various drug-drug interactions involving treatment with PIs, rifampicin, immunosuppressants, antibiotics, antifungal medications, and digoxin. Tipranavir is a potent P-glycoprotein inducer and should be used with caution or not at all in conjunction with other PIs that are substrates of P-glycoprotein.

Pharmacodynamic Drug Interactions
Pharmacodynamic drug interactions can occur when drugs with a similar biological effect also overlap in their toxicity profile or when two concurrently administered drugs compete for activity at a site of action, such as ZDV and stavudine (d4T). Overlapping toxicities are discussed later in this chapter.

Other Factors Influencing Drug Response
The drug response may be influenced by various physiological factors, which include age, gender, and underlying hepatic and renal function, and also by interaction with concomitant medications. In recent years, drug responses have shown to also be under the influence of host genetic factors, a fact that has sparked off the rapidly evolving field of pharmacogenetics. Variation in genes involved in pharmacokinetic or pharmacodynamic pathways may result in altered metabolism or increased susceptibility to adverse drug effects. For example, the major histocompatibility complex HLA B*5701 allele has been associated with abacavir hypersensitivity. A single nucleotide polymorphism (SNP) in the CYP2B6 enzyme has been linked to heightened plasma exposure to EFV and may increase the risk for central nervous system toxicity. A variant in the gene that codes for the drug transporter protein P-glycoprotein has been suggested to influence plasma drug concentrations achieved by P-glycoprotein substrates and may also impact the CD4 cell response.

Predicting Drug Interactions
Drug interactions can influence the efficacy and/or the tolerability of a drug regimen. Anticipating the resultant interaction between drugs can often be complex, but information pertaining to drug-drug interactions is constantly expanding. This chapter discusses basic principles and underlying mechanisms of drug interactions to assist all health-care
workers involved in HIV care in identifying potential drug interactions.

As discussed above, interactions impacting drug efficacy can be due to the inducing or inhibiting effect of drugs on the activity of the CYP enzyme system, or by impaired drug absorption, caused either by drug-food interaction or by drugs that change the gastric environment.

Drug tolerability can be affected when a concomitant medication or condition increases the drug concentration to toxic levels (dose-related toxicity) or when concomitant drugs exert similar adverse effects (overlapping toxicity).

Drug interactions with major clinical implications will be discussed in the following sections.

**PI Boosting**

Interactions between ritonavir and other PIs are used advantageously in a process called PI boosting. Ritonavir is the most potent inhibitor of the CYP3A4 enzyme among the available PIs. A small, virologically ineffective dose of ritonavir will significantly increase the blood concentration of the co-administered active PI. Ritonavir also inhibits the activity of P-glycoprotein, impacting the absorption and distribution of other drugs that are substrates of P-glycoprotein, including the other PIs. Ritonavir dramatically increases the absorption and overall pharmacokinetic exposure of most other PIs.

PI boosting thus reduces pill burden, allows for a more favorable dosing interval, and may remove food co-administration restrictions. Commonly boosted PIs include lopinavir, saquinavir, indinavir, and atazanavir. In order to achieve virologically effective concentrations, newer PIs such as lopinavir, darunavir, and tipranavir cannot be administered without the co-administration of ritonavir. A commonly used formulation that combines ritonavir and lopinavir into a single pill is Kaletra or Aluvia (lopinavir/ritonavir, LPV/r). The only PI that does not benefit from ritonavir boosting is nelfinavir, which is metabolized via several isoenzymes in addition to CYP3A4.

**Drug-Food Interactions**

Generally, it is convenient to take oral medications along with food or at mealtimes. A few drugs used for treatment of HIV-related illnesses, however, require a specific gastrointestinal tract environment for optimal absorption. The original formulation of didanosine (ddl, Videx) contains a buffering agent to protect ddl from degradation by gastric acid and needs to be taken on an empty stomach (30 minutes to one hour before or two hours after a meal) for optimal absorption. The newer, enteric-coated ddl (Videx EC) does not contain the buffer, but this formulation still requires administration on an empty stomach. PIs (except unboosted indinavir) should generally be given with food, to enhance absorption and decrease side effects. EFV should be given on an empty stomach, or with a low-fat snack, as taking it with food, especially a high-fat meal, leads to higher EFV concentrations in the blood and may increase side effects. Tenofovir is recommended to be given with food in European guidelines, while U.S. guidelines suggest it may be given with or without food. Unboosted indinavir should be taken on an empty stomach, or with a low-calorie snack, to ensure adequate absorption. Other antiretrovirals (ARVs) not mentioned here can generally be given without regard to food.

Other drugs commonly used in HIV comorbidity management also have some gastric environment restrictions. Depending on the type of erythromycin base given and the type of tetracycline, administration on an empty stomach may be preferable. It is recommended that griseofulvin and itraconazole capsules be taken with food. Fluoroquinolones and tetracyclines are prone to bind with other compounds (i.e., aluminum, iron,
calcium, and magnesium) so co-administration with products containing these elements will affect their bioavailability. Doses of the antibiotic and cation element should be separated by two hours when a patient requires both products.

Some drugs require a specific gastric acidity to be properly dissolved and absorbed, such as ddI, discussed above. When patients receive concomitant medications that change the gastric acidity, such as antacids, H2 receptor blockers, or proton pump inhibitors, caution should be used with some HIV therapies. See Table 1 for some common HIV therapies that require caution when administered with gastric-acid-reducing agents. Consult a drug interaction reference for specific recommendations based on the acid-reducing agent and co-administered drug, as this interaction may or may not be overcome by separation of the doses.

### Interactions between NNRTIs/PIs and Other Drugs

The whole spectrum of confirmed and theoretical drug interactions is beyond the scope of this overview. However, a few classes of medications deserve special mention, as they are routinely prescribed in HIV clinical practice and their drug-drug interactions may be clinically significant. This information is generalized and not intended as specific medical advice. See Table 2 for an overview.

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**Table 1. Common HIV-Related Drugs with Specific Gastric Environment Requirements**

<table>
<thead>
<tr>
<th>Administer with Food</th>
<th>Administer on Empty Stomach</th>
<th>Caution with Co-administered Antacids</th>
<th>Caution with Co-administered Divalent or Trivalent Cations&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone</td>
<td>Didanosine (buffered tablets and enteric-coated capsules)</td>
<td>Atazanavir</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Erythromycin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dapsone</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Efavirenz&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Fosamprenavir</td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Indinavir (unboosted&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Indinavir (unboosted&lt;sup&gt;d&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>(except unboosted&lt;sup&gt;a&lt;/sup&gt; indinavir)</td>
<td>Tetracycline</td>
<td>Itraconazole capsules</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nelfinavir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tipranavir</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Unboosted refers to indinavir given without concurrent ritonavir.

<sup>b</sup>Depending on erythromycin base administered, this restriction may not exist. Specifically, erythromycin ethylsuccinate, erythromycin estolate, or enteric-coated preparations may be taken with food.

<sup>c</sup>May be given with a low-calorie snack.

<sup>d</sup>Includes multivitamin or antacid preparations that contain aluminum, calcium, magnesium, or iron.
Table 2. Common Drug Interactions between Non-nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors and Other Drugs

<table>
<thead>
<tr>
<th>Drug Affected</th>
<th>Ritonavir-Boosted Protease Inhibitors&lt;sup&gt;a,c&lt;/sup&gt;</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>↓ warfarin&lt;br&gt;Monitor efficacy</td>
<td>↓ or ↑ warfarin&lt;br&gt;Monitor efficacy</td>
<td>↓ warfarin&lt;br&gt;Monitor efficacy</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↓ protease inhibitor&lt;br&gt;↑ carbamazepine&lt;br&gt;Monitor efficacy and toxicity</td>
<td>↓ efavirenz&lt;br&gt;↓ carbamazepine&lt;br&gt;Monitor efficacy</td>
<td>↓ nevirapine&lt;br&gt;↓ carbamazepine&lt;br&gt;Monitor efficacy</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↓ protease inhibitor&lt;br&gt;Monitor efficacy</td>
<td>↓ efavirenz&lt;br&gt;↓ phenobarbital&lt;br&gt;Monitor efficacy</td>
<td>↓ nevirapine&lt;br&gt;↓ phenobarbital&lt;br&gt;Monitor efficacy</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↓ protease inhibitor concentrations&lt;br&gt;↓ phenytoin&lt;br&gt;Monitor efficacy</td>
<td>↓ efavirenz&lt;br&gt;↓ phenytoin&lt;br&gt;Monitor efficacy</td>
<td>↓ nevirapine&lt;br&gt;↓ phenytoin&lt;br&gt;Monitor efficacy</td>
</tr>
<tr>
<td>Valproate</td>
<td>↓ valproate&lt;br&gt;Monitor efficacy</td>
<td>No clinically significant interaction</td>
<td>No data&lt;br&gt;May ↓ valproate</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>No clinically significant interaction</td>
<td>No clinically significant interaction</td>
<td>↑ nevirapine&lt;br&gt;Monitor toxicity</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>↑ itraconazole&lt;br&gt;Avoid doses &gt;200 mg per day if possible</td>
<td>↓ itraconazole&lt;br&gt;Consider alternative therapy or monitor efficacy</td>
<td>↓ itraconazole&lt;br&gt;Consider alternative therapy or monitor efficacy</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>↑ ketoconazole&lt;br&gt;Avoid doses &gt;200 mg per day if possible</td>
<td>No data&lt;br&gt;May ↑ efavirenz&lt;br&gt;May ↓ ketoconazole</td>
<td>↑ nevirapine&lt;br&gt;↓ ketoconazole&lt;br&gt;Avoid if possible</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>↓ voriconazole&lt;br&gt;Consider avoiding unless no alternatives exist</td>
<td>↑ efavirenz&lt;br&gt;↓ voriconazole&lt;br&gt;Dose modification of both agents required</td>
<td>No data&lt;br&gt;May ↓ nevirapine&lt;br&gt;May ↓ voriconazole</td>
</tr>
</tbody>
</table>

*Note: ↑ / ↓ = blood level of drug increased/decreased.*
Table 2. Common Drug Interactions between Non-nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors and Other Drugs (cont.)

<table>
<thead>
<tr>
<th>Drug Affected</th>
<th>Ritonavir-boosted Protease Inhibitors&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astemizole</td>
<td>↑ astemizole Contraindicated</td>
<td>↑ astemizole CONTRAINDICATED</td>
<td>No data Use cautiously</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>↑ terfenadine CONTRAINDICATED</td>
<td>↑ terfenadine CONTRAINDICATED</td>
<td>No data Use cautiously</td>
</tr>
<tr>
<td><strong>Antimalarials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amodiaquine</td>
<td>No data Use cautiously</td>
<td>↑ amodiaquine AVOID combination due to toxicity</td>
<td>No data</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>↑ halofantrine CONTRAINDICATED</td>
<td>No data Use cautiously</td>
<td>No data Use cautiously</td>
</tr>
<tr>
<td>Lumefantrine</td>
<td>↑ lumefantrine Monitor for toxicity</td>
<td>No data Use cautiously</td>
<td>No data Use cautiously</td>
</tr>
<tr>
<td>Quinine</td>
<td>No data ↑ quinine Monitor for toxicity</td>
<td>No data ↓ quinine Monitor efficacy</td>
<td>No data ↓ quinine Monitor efficacy</td>
</tr>
<tr>
<td><strong>Antimigraine Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergotamines</td>
<td>Increased ergotamines, contraindicated</td>
<td>↑ ergotamines CONTRAINDICATED</td>
<td>No data ↓ ergotamines</td>
</tr>
<tr>
<td><strong>Anti-TB Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>↑ rifabutin Use lower dose of rifabutin</td>
<td>↓ rifabutin Use higher dose of rifabutin</td>
<td>↓ nevirapine Use with caution</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>↓ protease inhibitor levels CONTRAINDICATED at standard doses</td>
<td>↓ efavirenz Consider increasing EFV to 800 mg in patients &gt;60 kg</td>
<td>↓ nevirapine CONTRAINDICATED</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>↑ midazolam CONTRAINDICATED</td>
<td>↑ midazolam CONTRAINDICATED</td>
<td>No data May ↓ midazolam</td>
</tr>
<tr>
<td>Triazolam</td>
<td>↑ triazolam CONTRAINDICATED</td>
<td>↑ triazolam CONTRAINDICATED</td>
<td>No data May ↓ triazolam</td>
</tr>
</tbody>
</table>

*Note: ↑ / ↓ = blood level of drug increased/decreased.*
Table 2. Common Drug Interactions between Non-nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors and Other Drugs (cont.)

<table>
<thead>
<tr>
<th>Drug Affected</th>
<th>Ritonavir-Boosted Protease Inhibitors&lt;sup&gt;a,c&lt;/sup&gt;</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bepridil</td>
<td>↑ bepridil Avoid combination</td>
<td>↑ bepridil Avoid combination</td>
<td>No data May ↓ bepridil</td>
</tr>
<tr>
<td>Calcium channel blockers (CCB)</td>
<td>↑ CCB Use lowest starting dose and monitor</td>
<td>↓ CCB Monitor efficacy</td>
<td>↓ CCB Monitor efficacy</td>
</tr>
<tr>
<td><strong>Erectile Dysfunction Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>↑ sildenafil Use lowest dose and monitor</td>
<td>No data May ↓ sildenafil</td>
<td>No data May ↓ sildenafil</td>
</tr>
<tr>
<td>Tadafal</td>
<td>↑ tadafal Use lowest dose and monitor</td>
<td>No data May ↓ tadafal</td>
<td>No data May ↓ tadafal</td>
</tr>
<tr>
<td><strong>Gastrointestinal Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td>↑ cisapride Contraindicated</td>
<td>↑ cisapride Contraindicated</td>
<td>No data May ↓ cisapride</td>
</tr>
<tr>
<td>Loperamide</td>
<td>↑ loperamide Titrate dose per response</td>
<td>No data</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td><strong>Lipid-Lowering Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↑ atorvastatin Use lowest starting dose and adjust per response</td>
<td>↓ atorvastatin Adjust dose per response</td>
<td>No data May ↓ atorvastatin</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↑ lovastatin Contraindicated</td>
<td>No data to guide co-administration</td>
<td>No data May ↓ lovastatin</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>↑ or ↓ pravastatin Safe to co-administer</td>
<td>↓ pravastatin Adjust dose per response</td>
<td>No data Considered safe to co-administer</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑ simvastatin Contraindicated</td>
<td>↓ simvastatin Adjust dose per response</td>
<td>No data May ↓ simvastatin</td>
</tr>
</tbody>
</table>

*Note: ↑ / ↓ = blood level of drug increased/decreased.*
Drugs Not to Be Used with PIs and/or EFV
Certain drugs should not be co-administered with PIs and/or EFV, as co-administration may increase their drug concentration, causing potentially life-threatening side effects. Examples include (a) the lipid-lowering medications simvastatin and lovastatin; (b) the antihistamines astemizole and terfenadine; (c) the anxiolytic drugs midazolam

Table 2. Common Drug Interactions between Non-nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors and Other Drugs

<table>
<thead>
<tr>
<th>Drug Affected</th>
<th>Ritonavir-Boosted Protease Inhibitors&lt;sup&gt;‡&lt;/sup&gt;</th>
<th>Efavirenz</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolide Antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>↑ clarithromycin Consider decreased dose in patients with renal insufficiency</td>
<td>↓ clarithromycin Monitor or use alternative</td>
<td>↑ nevirapine ↓ clarithromycin Monitor or use alternative</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>May ↑ erythromycin Monitor toxicity</td>
<td>No data</td>
<td>↑ nevirapine Use cautiously</td>
</tr>
<tr>
<td><strong>Psychotropic Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>May ↑ haloperidol Monitor toxicity</td>
<td>No clinically significant interaction</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>↑ fluoxetine Start with lowest dose and monitor</td>
<td>No clinically significant interaction</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td>Pimozide</td>
<td>↑ pimozide Contraindicated</td>
<td>↑ pimozide Contraindicated</td>
<td>No data</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>↑ prednisolone Monitor toxicity</td>
<td>↓ prednisolone Monitor for efficacy</td>
<td>No data May ↓ prednisolone</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>No data May ↑ dexamethasone</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Hormonal Contraceptives</td>
<td>↓ estradiol ↓ progestin Use alternate form of contraception</td>
<td>↑ estradiol Consider alternate form of contraception</td>
<td>↓ estradiol Consider alternate form of contraception</td>
</tr>
</tbody>
</table>

Notes:
- ↑ / ↓ = blood level of drug increased/decreased.
- ‡When no specific pharmacokinetic data are available, the anticipated interaction based on the pharmacology of each agent is listed.
- *Consult a pharmacology reference for more information and specific dosing for given interactions.
- †These are generalized recommendations. Consult a drug interaction reference for specific information on the individual protease inhibitor being used.
- Panel on Antiretroviral Guidelines for Adults and Adolescents and Liverpool HIV Pharmacology Group.
and triazolam; (d) all ergot alkaloid derivatives used for the treatment of migraine headaches; and (e) other medications, including cisapride, pimozide, and bepridil.

**Simvastatin and Lovastatin**
The two lipid-lowering medications simvastatin and lovastatin are contraindicated with PIs. The inhibitory effect of PIs on the CYP system raises the levels of these statin drugs to toxic levels, leading to life-threatening side effects such as rhabdomyolysis and renal failure. The lipid-lowering drugs pravastatin and fluvastatin are safe alternatives.

**Astemizole and Terfenadine**
Similarly, co-administration of PIs, EFV, and/or other CYP inhibitors with the antihistamines astemizole and terfenadine is contraindicated, as case reports of serious adverse events, including death and cardiac arrhythmias, have been recorded when levels of these drugs exceed the upper therapeutic threshold. As a result, these antihistamine medications have been removed from the American market. Chlorpheniramine (Allergex) is a safe antihistamine alternative for the treatment of mild to moderate allergic symptoms, including pruritus, rash, and other signs and symptoms related to allergic reactions.

**Midazolam and Triazolam**
The benzodiazepines midazolam and triazolam are contraindicated for patients on PIs and EFV. Their concentrations can reach dangerously high levels in the presence of CYP inhibitors, potentially causing fatal respiratory arrest. Safer alternatives include lorazepam, oxazepam, and temazepam.

**Ergot Alkaloid Derivates**
Ergot alkaloid derivates should be avoided in conjunction with PIs, EFV, and other CYP inhibitors. This may lead to potentially life-threatening ergot alkaloid toxicity, characterized by peripheral vasospasm, ischemia, thrombosis, tachycardia, and hypertension. Safe alternative treatment of migraine includes nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, metoclopramide, and prochlorperazine.

**Cisapride**
Toxic levels of cisapride can be reached when this drug is co-administered with CYP inhibitors (azole antifungals, macrolides, PIs, EFV, and cimetidine). These interactions may lead to prolongation of the QT interval, cardiac arrest, or sudden death. Cisapride has been withdrawn from the American market. Safe alternatives with most ARVs are antacids (Maalox, milk of magnesia, and metoclopramide).

**Pimozide**
Recent reports also caution against the use of the antipsychotic drug pimozide in combination with PIs or EFV. Inhibition of the metabolism of pimozide by PIs or EFV may lead to the development of life-threatening cardiac arrhythmias.

**Bepridil**
The calcium channel blocker bepridil is contraindicated for concomitant use with PIs or EFV. Bepridil has been removed from the American market.

**Drugs Requiring Dose Modification or Cautious Use**
The following drug classes may contain drugs that interact with ARV drugs: azole antifungals, statins, anticonvulsants, anti-TB medications, antimalarials, macrolide antibiotics, hormones (oral contraceptives), erectile dysfunction medications, anticoagulants, calcium channel blockers, antipsychotics, and antidepressants.

**Azole Antifungals**
Due to the potential for considerable bidirectional interaction between the azole antifungals and the
ARV classes of PIs and NNRTIs, caution may be required when such agents are concomitantly administered. In general, fluconazole can safely be used with NNRTIs and PIs. However, the concentration of NVP is increased when given with 200 mg of fluconazole. Therefore, patients receiving this combination should be monitored closely for NVP-related side effects.

Ketoconazole anditraconazole levels are increased when co-administered with ritonavir-boosted PIs, so in some cases the drug dosages of itraconazole and ketoconazole should not exceed 200 mg daily. Nelfinavir co-administration with ketoconazole or itraconazole appears to have less potential for this interaction. Ketoconazole and itraconazole levels are reduced by EFV and NVP, and alternate antifungal agents such as fluconazole should be strongly considered. Dose adjustment of the newazole antifungal agent voriconazole is required with ritonavir-boosted PIs and EFV because voriconazole’s clearance is decreased by these agents. Caution is also advised when co-administering voriconazole with NVP, as voriconazole levels may be decreased and NVP levels may be increased.

Statins
The clearance of the lipid-lowering drug atorvastatin is decreased by PIs. Therefore, when co-administering atorvastatin with a PI, the health-care worker should start with the lowest available atorvastatin dose (typically 10 mg) and monitor for toxicity before increasing the dose. The lipid-lowering drugs pravastatin and fluvastatin are safe alternatives.

Anticonvulsants
Bidirectional interactions can be expected when the anticonvulsants phenobarbital, phenytoin, and carbamazepine are co-administered with NNRTI- and PI-containing regimens. In general, anticonvulsant levels and overall virologic response (plasma viral load levels) should be monitored regularly.

Valproate (valproic acid), gabapentin (Neurontin), and lamotrigine (Lamictal) may be alternatives with lower potential for interactions. Valproate levels, however, may be decreased by concomitant ritonavir administration due to induction of CYP2C9 and glucuronidation.

Anti-TB Drugs
The anti-TB drug rifampicin (rifampin) induces the activity of a number of drug-metabolizing enzymes and has the greatest effect on the expression of CYP3A4 compared to other rifamycins (followed by rifapentine, while rifabutin is the least potent CYP inducer). In addition, rifampicin induces the activity of certain drug transporter proteins, such as intestinal and hepatic P-glycoprotein. As a result, the cellular and plasma concentrations of PIs are significantly reduced by rifampicin. Rifampicin also compromises the treatment effect of oral contraceptives, azole antifungals, corticosteroids, oral midazolam, triazolam, simvastatin, verapamil, and most dihydropyridine calcium channel antagonists. The use of rifampicin with PIs and NNRTIs needs special attention and will be discussed below.

Antimalarial Agents
Pharmacokinetic data regarding the combination of ARVs and antimalarials are just becoming available. Generally, halofantrine, lumefantrine, quinine, and amodiaquine may be impacted by NNRTIs and PIs. Because this is a common comorbidity in resource-limited settings, special attention will be given to this topic below.

Macrolide Antibiotics
Macrolide antibiotics are substrates and inhibitors of the CYP enzyme system. Clarithromycin has the potential to increase the level of NVP, and close monitoring for hepatic abnormalities is recommended. In the presence of EFV, clarithromycin levels may be reduced, and alternatives for clarithromycin should
be considered. A moderate increase in the concentration of clarithromycin is expected in the presence of LPV/r. Dose modification is not necessary if kidney function is normal. However, clarithromycin dose reduction should be considered in patients with renal impairment. The macrolide erythromycin should be avoided in the presence of ritonavir-containing PIs, as fatal cardiac arrhythmia has been associated with increased erythromycin levels in other clinical situations. Azithromycin is a safe alternative in the presence of PIs and NNRTIs. Most other antibiotics can be safely co-administered with ARVs.

**Hormones (Oral Contraceptives)**
The oral contraceptive ethinyl estradiol may interact with PIs and NNRTIs in complex ways. The clinical significance of these interactions has not been evaluated thoroughly, but co-administration may cause contraceptive failure (NVP, ritonavir, LPV/r, nelfinavir) or oral contraceptive side effects (EFV, atazanavir).

**Erectile Dysfunction Medication**
The levels of the phosphodiesterase inhibitors sildenafil, tadalafil, and vardenafil commonly used to treat erectile dysfunction are significantly increased in the presence of PIs and may be reduced in the presence of NNRTIs. Dose reduction is needed when co-administered with PIs.

**Anticoagulants**
The concentration of the anticoagulant drug warfarin, a drug with a narrow therapeutic index, may be altered when co-administered with PIs, especially ritonavir, or NNRTIs. Close monitoring of the anticoagulant effect is required when these drugs are co-administered.

**Calcium Channel Blockers**
The levels of calcium channel blockers nifedipine, verapamil, and diltiazem and the antiarrhythmic drug quinidine may increase in the presence of PIs or be reduced in the presence of NVP or EFV. These combinations should be used with caution, and calcium channel blocker dose adjustment should be guided by clinical response.

**Antipsychotics**
Many antipsychotic agents are metabolized via the CYP enzyme system, and drug interactions with ARVs are often very complex. Most antipsychotic agents can be affected by co-administration with PIs or NNRTIs; therefore, close monitoring of clinical response and toxicity is recommended.

**Antidepressants**
Tricyclic and selective serotonin reuptake inhibitor antidepressants can generally be combined with PIs and EFV. However, some changes in antidepressant concentrations have been shown. Therefore, close monitoring for efficacy and toxicity is recommended. St John’s wort, an herbal remedy, should be avoided as it has been demonstrated to decrease blood levels of PIs and NNRTIs.

**COMBINING PIs AND NNRTIs**

**PI/NNRTI Interactions**
Co-administration of PIs and an NNRTI is reserved for the management of specific cases, such as in salvage therapy involving multiclass drug resistance or as an NRTI-sparing regimen (e.g., to avoid the risk of lactic acidosis). Some data exist regarding drug interactions between these two classes to guide therapy.

The dual PI combination saquinavir/ritonavir 400/400 mg twice daily in combination with an NNRTI does not require dose modification. Clinicians should consider increasing LPV/r to 533/133 mg (or 600/150 mg of the new tablet version of Aluvia) twice daily in the presence of NNRTIs. Atazanavir must be boosted with
ritonavir in the presence of NNRTIs. Potential interactions between nelfinavir and NNRTIs exist, but alteration of drug doses may not be required. It is generally advisable to monitor liver enzymes when NNRTIs are used in combination with PIs, as both classes may cause hepatotoxicity.

**Dual PI Interactions**

Dual boosted PIs, also only used in specific cases, consist of two PI agents in addition to low-dose ritonavir.

The long-term safety and efficacy of LPV/r in combinations with other PIs has not been formally established. However, pharmacokinetic and clinical data on LPV/r combined with saquinavir (1,000 mg BD [twice a day]) suggest that this combination is a potential option for patients with prior treatment failure or toxicities. The combination of atazanavir (300 mg OD [daily]) and LPV/r resulted in appropriate drug concentrations of each agent in healthy volunteers. Dose adjustment and drug monitoring are recommended when LPV/r is co-administered with either nelfinavir or amprenavir.

The newer PIs tipranavir and darunavir are not recommended in combination with other PIs, as they have not been studied in dual PI combination or have shown existing interactions.

**INTERACTIONS INVOLVING NRTIs**

There are few known pharmacokinetic interactions that occur when NRTIs are co-administered with other drugs, in part because NRTIs are not metabolized by the CYP enzyme system. Emtricitabine, lamivudine, ddI, d4T, and tenofovir are primarily cleared by renal excretion, while ZDV is metabolized by hepatic glucuronidation and abacavir is catalyzed by alcohol dehydrogenase. A large alcohol dose might compete with abacavir clearance through competition with the alcohol dehydrogenase; however, this is currently a theoretical interaction.

Importantly, co-administration of the two thymidine analogues, ZDV and d4T, is contraindicated due to intracellular pharmacologic antagonism, which will compromise the antiviral effect of these drugs.

A few drug interactions have been reported that might affect the safety or efficacy of ZDV. Valproic acid and fluconazole, when co-administered with ZDV, have been shown to increase ZDV levels. Patients should be monitored closely for potential toxicity of ZDV. Limited data suggest that rifampicin decreases the concentration of ZDV, which may result in a partial or total loss of efficacy of ZDV. Advice on concurrent usage is conflicting and ranges from “should be avoided” (European summary of product characteristics) to “dose modification not warranted” (U.S. prescribing information). Similarly, tipranavir/ritonavir reduces plasma ZDV levels; the clinical relevance of these reductions has not been established but may decrease the efficacy of these ARV agents.

Tenofovir and ddI co-administration should be avoided because (a) this combination carries a high risk for developing drug resistance and (b) tenofovir increases plasma levels of ddI (both buffered and enteric-coated formula). If co-administration is needed, ddI should be dose reduced, and efficacy and ddI-associated toxicity should be closely monitored. Drug interactions have been reported between tenofovir and PIs; however, they are not known to be clinically relevant. One exception to this is the drug interaction between tenofovir and atazanavir. Due to still-unclear mechanisms, tenofovir reduces atazanavir concentrations; therefore, unboosted atazanavir should not be administered with tenofovir. Boosting atazanavir with ritonavir results in more consistent atazanavir concentrations that are similar to atazanavir concentrations without the presence of tenofovir. Conversely, tenofovir levels are increased when used with LPV/r or darunavir/ritonavir,
and the potential renal adverse effects should be monitored.12

NEW DRUG CLASSES
The development of new ARV drugs is rapidly advancing. Some of these drugs have different sites of action, such as fusion inhibitors, CCR5 antagonists, or integrase inhibitors. Information on the interactions of these drugs with other medications is still evolving. The fusion inhibitor enfuvirtide, in use for several years in developed countries, is a peptide drug (administered subcutaneously) and has a low potential for drug interactions. The integrase inhibitor raltegravir (Isentress, MK-0518) has recently been approved in the United States for the treatment of HIV-1 infection in treatment-experienced adults. Raltegravir is metabolized by hepatic glucuronidation and does not seem to influence drugs metabolized by CYP enzymes; however, drugs that affect glucuronidation (such as atazanavir or rifampicin) will result in a pharmacokinetic interaction. A second integrase inhibitor (elvitegravir) is in advanced clinical trials. The CCR5 antagonist maraviroc (Selzentry) was also recently approved for use in antiretroviral-experienced patients. Maraviroc is primarily metabolized by CYP3A enzymes and has complex dosing depending on the co-administered PIs or NNRTIs. Current information on the potential interactions of these drugs should be obtained from Web-based drug interaction charts or the manufacturers’ summaries of product characteristics.

OVERLAPPING TOXICITIES
A number of drugs used in the management of HIV disease have similar adverse-effect profiles. Table 3 categorizes frequently used drugs by their effect on specific tissues, such as the bone marrow, pancreas, kidney, liver, peripheral nerves, and skin. Hematological parameters should be monitored when combining ZDV with myelosuppressive drugs (e.g., anticancer treatment; antifungal treatment with amphotericin or flucytosine; or treatment or prophylaxis with cotrimoxazole, dapsone, or pyrimethamine). Didanosine and 4T combinations are contraindicated due to increased liver, pancreas, and neurotoxicity as well as the risk of lactic acidosis. The risk of liver toxicity is increased by several drugs, including anti-TB medication, alcohol, azole antifungals, NNRTIs, and PIs. Severe cutaneous adverse effects can be induced by NVP, abacavir, cotrimoxazole, and dapsone.

SPECIAL CONSIDERATIONS

Anti-TB Treatment plus Combination Antiretroviral Therapy
HIV/TB coinfection is a very common clinical condition in many developing countries. Treatment involves multidrug regimens with significant risk of drug interactions. Rifampicin, an indispensable component of standard first-line TB regimens, is also one of the strongest inducers of the CYP enzyme system and will interfere with dosing of NNRTIs, PIs, ZDV, and other drugs co-administered to manage TB disease. For example, the prednisolone dose should be increased when used together with rifampicin.33

Because rifampicin produces a significant lowering of NVP concentrations,34,35 the concomitant use of rifampicin and NVP is not recommended. A small pilot study showed that an increase of NVP (300 mg twice daily) can effectively increase NVP levels.36 However, this approach needs to be confirmed by a formal clinical trial to ensure safety and efficacy. The effect of rifampicin is less pronounced when combined with EFV37,38 (AUC 26% decrease). To compensate for this decrease, some experts recommend that the dose of EFV be increased to 800 mg per day in patients weighing more than 60 kg. However, some argue that this dose increase may not be necessary, irrespective of weight, and
Table 3. HIV-Related Drugs with Overlapping Toxicities

<table>
<thead>
<tr>
<th>Bone Marrow Suppression</th>
<th>Peripheral Neuropathy</th>
<th>Nephrotoxicity</th>
<th>Hepatotoxicity</th>
<th>Rash</th>
<th>Diarrhea</th>
<th>Other Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Didanosine</td>
<td>Aцикловир (IV, high dose)</td>
<td>Azithromycin</td>
<td>Abacavir</td>
<td>Atovaquone</td>
<td>Atovaquone Clindamycin</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Didanosine</td>
<td>Adefovir</td>
<td>Clarithromycin</td>
<td>Alpha-2-Macroglobulin</td>
<td>Clindamycin</td>
<td>Darunavir</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Lamivudine (children)</td>
<td>Aminoglycosides</td>
<td>Delavirdine</td>
<td>Atazanavir</td>
<td>Atovaquone</td>
<td>Darunavir</td>
</tr>
<tr>
<td>Cytotoxic Chemotherapy</td>
<td>Pentamidine</td>
<td>Aцикловир (IV, high dose)</td>
<td>Efavirenz</td>
<td>Dapsone</td>
<td>Darunavir</td>
<td>Darunavir</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Ritonavir</td>
<td>Aцикловир (IV, high dose)</td>
<td>Fluconazole</td>
<td>Delavirdine</td>
<td>Darunavir</td>
<td>Lopinavir/ritonavir</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Stravudine</td>
<td>Aцикловир (IV, high dose)</td>
<td>Isoniazid</td>
<td>Delavirdine</td>
<td>Darunavir</td>
<td>Lopinavir/ritonavir</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Foscarinet</td>
<td>Aцикловир (IV, high dose)</td>
<td>Ltrimatol</td>
<td>Fosamprenavir</td>
<td>Darunavir</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Indinavir</td>
<td>Ritonavir</td>
<td>Maraviroc</td>
<td>Maraviroc</td>
<td>Maraviroc</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Pentamidine</td>
<td>Nevirapine</td>
<td>Nevirapine</td>
<td>Nevirapine</td>
<td>Nevirapine</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Tenofovir</td>
<td>NRTIs</td>
<td>Tenofovir</td>
<td>Sulfadiazine</td>
<td>Sulfadiazine</td>
<td>Voriconazole</td>
</tr>
<tr>
<td>Peginterferon-α</td>
<td></td>
<td>PIs (esp.</td>
<td>Voriconazole</td>
<td>Tiranavir</td>
<td>Tiranavir</td>
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<tr>
<td>Primaquine</td>
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<td>Tipranavir</td>
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<tr>
<td>Pyrimethamine</td>
<td></td>
<td>Ritonavir</td>
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<tr>
<td>Ribavirin</td>
<td></td>
<td>Nevirapine</td>
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<tr>
<td>Rifabutin</td>
<td></td>
<td>Ritonavir</td>
<td></td>
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<tr>
<td>Sulfadiazine</td>
<td></td>
<td>Ritonavir</td>
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<tr>
<td>Trimetrexate</td>
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<td>Ritonavir</td>
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<tr>
<td>Valganciclovir</td>
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<td>Ritonavir</td>
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<tr>
<td>Zidovudine</td>
<td></td>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Source: U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (Table 19, p. 84).16

Further research into the appropriate dose of EFV when combined with rifampicin is ongoing. Alternatively, physicians may consider switching to a triple NRTI combination for a variable period of time, depending on the TB treatment regimen. This is also a possible strategy for HIV-positive pregnant women on first-line combination antiretroviral therapy (ART) who develop TB.

While guidelines are conflicting regarding co-administration of rifampicin and ZDV, as rifampicin is reported to reduce the plasma ZDV concentration, this combination is widely used in resource-limited settings. The clinical impact of this reduction in plasma concentrations has not been established.

The co-administration of rifampicin and PIs will often require expert advice from TB and HIV specialists. Co-administration of rifampicin with PIs will reduce the PI plasma concentration by about 90%, greatly jeopardizing the success of the ART. The combination of saquinavir/ritonavir plus rifampicin had previously been recommended.
as an effective HIV/TB coinfection therapy.\textsuperscript{39} However, potentially life-threatening side effects, such as the risk of severe hepatocellular toxicity, have been reported from this co-administration.\textsuperscript{40,41} Therefore, rifampicin is contraindicated in patients taking ritonavir-boosted saquinavir as part of an ART regimen.

Co-administration of rifampicin and standard doses of LPV/r results in subtherapeutic concentrations of lopinavir and is not recommended.\textsuperscript{42} One study reported that either adding 300 mg ritonavir to the coformulated LPV/r for a total dose of LPV/r 400/400 mg BD, or increasing LPV/r to 800/200 mg BD, resulted in a favorable AUC for all drugs\textsuperscript{43}; however, more evidence regarding the safety and efficacy of this combination is needed before this can be routinely recommended.

Where available, rifabutin, also a rifamycin derivate, can be used with most PIs, provided that the rifabutin dose is reduced, as rifabutin is metabolized by the CYP enzymes inhibited by most PIs. Conversely, EFV acts as a CYP inducer to reduce rifabutin concentrations, necessitating an increase in the dose of rifabutin.

It is particularly important to remember that after rifampicin is discontinued, the concentrations of many other drugs used by the patient will increase as the induction starts to wear off. Patients should be encouraged to notify their health-care providers if they stop or change any medications so the proper dosage adjustments can be made.

**PI Dosing in Pregnancy**

Current pharmacokinetic studies in pregnancy do not suggest dose modifications for NRTIs and NVP. Lower than optimal levels of LPV/r and nelfinavir are seen in the third trimester of pregnancy.\textsuperscript{44} Current recommendations suggest that an increase of LPV/r to 533/133 mg BD (or 600/150 mg of the new tablet version, Aluvia) be considered and that nelfinavir should always be dosed as 1,250 mg BD during pregnancy (versus 750 mg TD [three times a day]).\textsuperscript{45,46} EFV is contraindicated in the first trimester due to teratogenicity. The combination of ddI and d4T should not be given in pregnancy due to increased risk of adverse events. Initiation of NVP in pregnancy at CD4 levels above 250 cells/mm\textsuperscript{3} poses a high risk for hepatotoxicity and should be administered only when the benefit clearly outweighs the risk, and under strict monitoring.

**Malaria**

Malaria is one of the leading infectious diseases worldwide. Coinfection of HIV and malaria is common in many areas of sub-Saharan Africa, Southeast Asia, and South America. ARV drugs seem to be safe in the presence of prophylactic anti-malaria regimens such as proguanil (Paludrine), chloroquine, mefloquine, pyrimethamine/dapsone (Maloprim), or atovaquone/proguanil (Malarone). Treatment of malaria with atovaquone/proguanil, dapsone/proguanil, sulfadoxine/pyrimethamine (Fansidar), or mefloquine seems to be safe in persons on ARV drugs. The antibiotics doxycycline, tetracycline, and clindamycin neither affect nor are affected by ARV therapy.

Caution is advised when using quinine, as quinine concentrations in the blood are reduced in the presence of NNRTIs and increased in the presence of PIs. The effect of NNRTIs and PIs on the potency and safety of artemisinins is unclear, so close monitoring of efficacy is required (manufacturer’s summary of product characteristics). Halofantrine is contraindicated with PIs and should be used cautiously with NNRTIs because it is extensively metabolized by CYP3A4, and inhibition could prolong the QT interval, leading to potentially life-threatening cardiac arrhythmia.

Lumefantrine is structurally related to halofantrine; however, it has not been associated with cardiotoxicity. One pharmacokinetic study has evaluated lumefantrine concentrations in combination
with LPV/r. Though lumefantrine concentrations were increased (AUC increased 193%), no EKG changes were observed. Because of the safe profile of lumefantrine, and the association between higher lumefantrine concentrations and malaria clearance, this combination may be considered.67

In contrast to this apparently safe increase in lumefantrine concentrations, another study evaluating amodiaquine and EFV found a significant increase in the amodiaquine AUC (114%–302%) along with significant elevations in the liver function tests. Therefore, amodiaquine should be avoided with EFV and should be used cautiously with PIs until the mechanism of this interaction can be evaluated.48

**Alternative Therapies/Herbal and Traditional Medicine**

A few natural compounds, such as garlic and echinacea,49 have been implicated in ARV drug interactions and should be used with caution. Grapefruit juice has been shown to inhibit CYP activity in the intestine and was thought to be able to boost saquinavir levels50; however, the effect on treatment response is clinically insignificant. As mentioned above, the herbal therapy St. John’s wort is contraindicated with PIs and NNRTIs, as it has been shown to decrease ARV concentrations.

The use of traditional medicines and practices is widespread in many parts of the world. Often, belief in these practices is stronger than reliance on Western medications. As the content of traditional remedies is rarely known, it is extremely difficult to predict any interaction with modern medications. It is therefore very important to inform and educate patients on the unknown but potentially hazardous effects that traditional medicines might have on ART or on therapy for opportunistic infections. Clinicians should also consider a potential interaction between traditional or herbal medications and ARVs when unexpected treatment responses (either suboptimal viral suppression or toxicity) are observed.

**MANAGEMENT OF DRUG INTERACTIONS**

The list of interactions involving ARV drugs is extensive and constantly expanding. To minimize the risk of drug interaction, awareness and vigilance are essential. Prescribing health-care providers need to review the patient’s complete drug history at each visit, and potential drug interactions should be a prime consideration when changing or adding new drugs. Likewise, patients need to understand the importance of informing the healthcare worker about all medicinal products they are using, including traditional medicines and nonprescription drugs. Drug interactions should always be considered as a potential cause in the event of treatment failure or unusual or severe side effects.

For management of serious adverse events, refer to the chapter entitled “Recognition and Management of Antiretroviral Toxicities in Adults”.

Monitoring of ARV treatment efficacy should follow locally adapted guidelines. Determination of drug serum levels (e.g., antiepileptic or anticoagulant drugs) could play a role in specific clinical situations. It is hardly possible to know all possible interactions or to keep up with the increasing list of interactions, but basic knowledge of metabolism of the major drug classes, possible interactions, and available drug interaction references is essential. Detailed information for an individual case can be obtained from online databases such as those from the University of Liverpool1 or the University of California, San Francisco,2 or from paper-based drug interaction charts that are updated frequently.


19. Villani P, Regazzi MB, Castelli F, et al. Pharmacokinetics of efavirenz (EFV) alone and


25. Aptivus [product label]. Ingelheim, Germany: Boehringer Ingelheim GmbH.


37. Friedland G, Khoo S, Jack C, et al. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients...


BEGINNING IN 2002 AND ON A LARGER scale since 2004, antiretroviral therapy (ART) treatment programs have been rolled out in public-sector health facilities in sub-Saharan Africa, the region of the world most affected by the AIDS pandemic. In January 2002, ART became available in Botswana in public-sector health facilities through the national antiretroviral (ARV) treatment program, Masa. *Masa* means “new dawn” in Setswana. The first national public site was at the outpatient Infectious Disease Care Clinic (IDCC) at Princess Marina Hospital, the largest referral hospital in the capital city of Gaborone. The Masa program now provides public ART to more than 100,000 people at more than 32 designated national outpatient treatment sites. Similar programs have been implemented in other regions and countries supported by the World Health Organization (WHO) and the President’s Emergency Plan for AIDS Relief (PEPFAR).

The current international standard recommendation for first-line ART in adults consists of two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI).\(^1\,^3\) Protease inhibitors (PIs) are reserved for second-line treatment, as needed, due to issues of cost, dosing frequency, drug-drug interactions, potential for long-term side effects, and higher pill burden.

In resource-rich settings, the current gold-standard first-line ART regimen is tenofovir (TDF) plus emtricitabine (FTC)—co-formulated as Truvada—with the NNRTI efavirenz (EFV, or Sustiva), or, more recently, these three ARV medications combined into one tablet per day, namely Atripla. In multiple adult head-to-head clinical trials, ARV-treated individuals receiving the NNRTI EFV (previously with zidovudine [AZT/ZDV] plus lamivudine [3TC] co-formulated as Combivir, and more recently with Truvada) have experienced the most favorable immunologic and virological outcomes. In sub-Saharan Africa, the vast majority of ART-treated persons receive either stavudine (d4T) and 3TC or AZT and 3TC with either nevirapine (NVP) or EFV. Persons failing these first-line regimens are then typically offered the PI lopinavir/ritonavir (Kaletra/Aluvia) with two different NRTIs. Table 1 lists the ARVs currently available for use in resource-limited settings.
### Table 1. Currently Approved and Available Antiretroviral Medications Licensed for Use in Resource-Limited Settings

<table>
<thead>
<tr>
<th>Antiretroviral (ARV) Medication</th>
<th>Routinely Available</th>
<th>Special Order Required</th>
<th>More Widespread Availability or Use Expected in Next 1–2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (AZT/ZDV) (with lamivudine [3TC] as Combivir or Lamzid)</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>3TC (with AZT as Combivir or Lamzid)</td>
<td>YES</td>
<td>NO</td>
<td>N/A</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>NO</td>
<td>YES (majority of countries)</td>
<td>YES (cost is still a major issue)</td>
</tr>
<tr>
<td>Tenofovir (TDF) (with emtricitabine [FTC] as Truvada)</td>
<td>NO</td>
<td>YES (majority of countries)</td>
<td>YES</td>
</tr>
<tr>
<td>FTC (with TDF as Truvada)</td>
<td>NO</td>
<td>YES (majority of countries)</td>
<td>YES</td>
</tr>
<tr>
<td>AZT, 3TC, plus ABC (coformulated as Trizivir)</td>
<td>NO</td>
<td>NO (not widely used)</td>
<td>NO (unless new indication for use identified, e.g., treating pregnant women with higher CD4 cell counts [&gt; 250] based on ongoing clinical trials or for treatment of HIV/TB coinfected patients on second-line ART in whom ritonavir-boosted PIs are not an option.)</td>
</tr>
<tr>
<td><strong>Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>YES</td>
<td>NO</td>
<td>N/A</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>YES</td>
<td>NO</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Protease Inhibitors (PIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LOP/r) (Kaletra/Aluvia)</td>
<td>YES</td>
<td>NO (most widely used PI for second-line ART)</td>
<td>YES</td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>YES</td>
<td>NO (very limited use)</td>
<td>NO</td>
</tr>
<tr>
<td>Ritonavir (RTV) / Saquinavir (SQV)</td>
<td>YES</td>
<td>NO (for special cases, e.g., patients with TB requiring antitubercular therapy and PI-based ART)</td>
<td>NO</td>
</tr>
</tbody>
</table>
Table 1. Currently Approved and Available Antiretroviral Medications Licensed for Use in Resource-Limited Settings (cont.)

<table>
<thead>
<tr>
<th>Antiretroviral (ARV) Medication</th>
<th>Routinely Available</th>
<th>Special Order Required</th>
<th>More Widespread Availability or Use Expected in Next 1–2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newer ARV Medications/Classes Not Yet Officially Licensed/Registered for Use in Developing-World Settings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/ritonavir (ATV/r)</td>
<td>YES (limited availability)</td>
<td>YES (very limited use/supplies)</td>
<td>YES</td>
</tr>
<tr>
<td>Tipranavir/ritonavir (TPV/r)</td>
<td>NO</td>
<td>YES (very limited use/supplies)</td>
<td>NO (for deep salvage, private-sector experienced patients)</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir (FPV/r)</td>
<td>NO</td>
<td>Not available</td>
<td>NO (for deep salvage, private-sector experienced and failing patients)</td>
</tr>
<tr>
<td>Darunavir/ritonavir (DRV/r)</td>
<td>NO</td>
<td>Not available</td>
<td>YES (for deep salvage, private-sector experienced and failing patients)</td>
</tr>
<tr>
<td>Fusion Inhibitors</td>
<td></td>
<td>? YES (for treatment of experienced patients)</td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide (T-20)</td>
<td>NO</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>CCR5 Receptor Antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc (MVC)</td>
<td>NO</td>
<td>Not available</td>
<td>NO (for deep salvage, private-sector experienced and failing patients)</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td></td>
<td>? YES (for treatment of experienced patients)</td>
<td></td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>NO</td>
<td>Not yet available/limited availability expected very soon</td>
<td>YES (for treatment of experienced patients)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td>? YES (for treatment of experienced patients)</td>
<td></td>
</tr>
<tr>
<td>Etravirine (TMC-125) (ETV)</td>
<td>NO</td>
<td>Not available</td>
<td></td>
</tr>
</tbody>
</table>

The major ARV-associated toxicities seen among ART-treated adults in resource-limited settings are very similar to those reported in the United States and Western Europe among HIV-1 subtype B-infected adults. For discussion purposes, ARV-associated toxicities will be broken down into categories, and the definitions will be based on two factors: (a) usual time of onset (“short-term” or “long-term”) and (b) severity (“mild/moderate” and “severe”). For severity grading, we will use the most current
Short-term toxicities: Short-term toxicities will be defined as those ARV-associated toxicities that occur within the first three to six months following ART initiation.

Long-term toxicities: Long-term toxicities will be those ARV-associated toxicities that occur more than six months after ART initiation.

In summary, we will use the following guiding principles when estimating the grade of severity of signs and symptoms:

- **Mild**: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- **Moderate**: Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- **Severe**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
- **Life-threatening**: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Note: For all laboratory-related toxicities, we will use the Adult DAIDS grading scale (December 2004).4

For each category, we will also describe how best to recognize and manage these toxicities, some of which may be life-threatening.

**Key Definitions and Concepts**

- **Side effect**: Side effects are usually self-limited and not life-threatening, and usually resolve over a short period of time and with symptomatic support. Side effects typically occur early after ARV initiation.

- **Toxicity**: The term toxicity carries with it a more “severe” meaning, as toxicities can be life-threatening and may occur anytime following ART initiation.4

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4To maintain consistency and uniformity in this text, we have decided to use the term toxicity when referring to any and all ARV-associated events.
of 23.8% (95% CI, 15.5%-31.2%); and 47 of the 153 (30.7%) having treatment-modifying toxicities, with a Kaplan-Meier estimate of developing a treatment-modifying toxicity by year one of 32.2% (95% CI, 23.0%-40.4%). The study also found that 29% of these treatment-modifying toxicities were for severe peripheral neuropathy, 6% for hepatotoxicity, and 4% for ddI-related pancreatitis and NVP-related cutaneous hypersensitivity.

Additional preliminary regional data from Botswana evaluating 306 ART-naive adults treated with PI-sparing public ART as per existing national ARV treatment guidelines (Combivir/NVP [48%] and Combivir/EFV [52%]) showed that 8.0% developed severe (grade 3-4) anemia (mean time to development = 11.6 weeks), 2.7% developed Stevens-Johnson syndrome (mean time to development = 28.0 days on ART), and 3.4% developed grade 3-4 liver function test (serum SGOT/AST and/or SGPT/ALT) abnormalities (mean time to development = 12.6 weeks). This initial group of ART-treated patients was quite ill at the time of ART initiation, with a median CD4 cell count of 81 cells/mm³, with a median plasma HIV-1 RNA level of 442,000 copies/mL, and with 89.2% having WHO clinical stage 3 or 4 disease at the time of ART initiation.

Longer-term ART outcomes data from Khayelitsha, South Africa, have shown similar toxicity rates from 287 adults with advanced baseline HIV-1 disease (median CD4 cell count of 43 cells/mm³; mean log₁₀ HIV RNA of 5.18 copies/mL) treated with Combivir-based ART with either EFV (60%) or NVP (38%). In this cohort, the cumulative probability of changing a single ARV medication by 24 months was 15.1% due to toxicity or contraindications, and 8.4% due to toxicity alone. Most changes occurred soon after ART initiation (median time 42 days; interquartile range 28-56 days). Additional data from this same cohort showed that by 24 months on therapy, similar proportions of patients had switched from d4T, AZT, and NVP due to toxicity (8.5%, 8.7%, and 8.9%, respectively). In contrast, only 1.7% had switched from 3TC. Most drug regimen changes (36 of 44, or approximately 82%) were attributable to anemia among AZT-treated patients.

Data from Uganda (n = 137) among adults receiving d4T- and 3TC-based ART with primarily NVP (77%) or EFV (14%) showed that 55% of patients experienced some level of discomfort, while reporting pain, numbness, tingling of the hands or feet, or skin rash with dryness or pruritus (51%). Rash was reported in 49% of the 125 patients treated with an NNRTI-containing regimen.

Data from 1,000 patients in Haiti treated primarily with AZT and 3TC with either EFV (47%) or NVP (42%) showed that 25% of ART-treated patients required a change in their first-line regimen, with 11% changing for reasons of toxicity. Anemia (5%), central nervous system (CNS) side effects (6%), and rash (3%) were the most common, with two patients developing Stevens-Johnson syndrome, one of whom died. Overall, less than 1% of NVP-treated patients developed hepatitis.

Longer-term data from a large cohort of ART-treated adults in Botswana receiving primarily the dual NRTI combination of ZDV/ddI, ZDV/3TC, or d4T/3TC with either NVP or EFV (n = 650 total) showed that 17.7% of patients experienced a treatment-modifying toxicity, with the most common toxicities being anemia (3% of all patients in the cohort), lipodystrophy (3%), grade 3 hypersensitivity cutaneous reactions or Stevens-Johnson syndrome (3%), neutropenia (2%), lactic acidosis (1.0%), moderate to severe symptomatic hyperlactatemia (1%), hepatotoxicity (1%), neuropsychiatric symptoms (1%), and pancreatitis (1%).

Preliminary data from southern Africa have shown differences in the patterns and rates of toxicities among HIV-1 subtype C-infected adults when compared to HIV-1 subtype B-infected, ART-treated counterparts in resource-rich settings.
Preliminary regional data have reported higher than expected rates of lactic acidosis (1.0%-1.1%) among ART-treated adults, with expected rates from Western literature in the range of 0.1%-0.4% among ART-treated cohorts. The development of lactic acidosis in sub-Saharan Africa appears to be related to female gender, body habitus (being overweight, body mass index > 25 or body weight > 75 kilograms), and use of one or more “D” drugs (d4T and/or ddi). Reasons for this remain to be fully elucidated but most likely involve host genetic differences. More in-depth studies are under way and additional ones are planned. Early on (2002-2004) in public-ART-treated cohorts, there were significant rates of AZT-associated anemia, as high as 8%. Anemia can pose a significant problem, especially in more remote areas where patients have to travel long distances to reach a district or referral hospital and where blood supplies are scarce. Preliminary data have also shown that ART-treated adults appear to have higher than expected rates (as high as 2.7%) of NVP-associated cutaneous hypersensitivity reactions (Stevens-Johnson syndrome) and lipodystrophy.8,13,15

Rates of lipid abnormalities, defined as cholesterol and triglyceride elevations, are not yet known, as few patients have received PI-based ART for prolonged periods of time, although patients can certainly have lipid elevations from d4T or EFV. ART-treated adults, the majority of whom are female in sub-Saharan Africa, are experiencing significant rates of body habitus changes—namely lipoatrophy involving the buttocks, thighs, and face—especially those who have been on ART for more than two years. These body habitus changes have been attributed to d4T use and, along with the higher than expected rates of lactic acidosis, have prompted many policymakers to reconsider first-line ART options for their public ART programs. Public ART programs have already begun to move away from d4T- and AZT-based ART regimens and are switching to TDF (Truvada)-based first-line ART regimens with more favorable tolerability profiles. Certainly, longer-term data on the risk for renal insufficiency and bone porosity changes related to TDF are needed to better inform policymakers. Cost still remains a significant issue, but progress has been made with pharmaceutical corporations and involved foundations (e.g., the Clinton Foundation) working diligently to negotiate more favorable drug access prices.

**MAIN MILD/MODERATE SHORT-TERM TOXICITIES**

**AZT**

The main short-term mild/moderate toxicities experienced among AZT-treated patients are gastrointestinal (GI) problems (nausea, with or without emesis) and headaches. In the majority of cases, these side effects occur within the first few weeks to one month on treatment and resolve on their own without the need for treatment holds and/or substitutions. A small percentage of patients, especially those taking AZT-based ART for postexposure prophylaxis, may need to discontinue their AZT and change to d4T, ddi, or TDF. Neutropenia is a short- to medium-term toxicity associated with AZT due to its effect on myeloid precursors. As persons of African descent have lower total lymphocyte counts (1,500 compared to 2,500 elsewhere), the development of neutropenia is not as clinically significant in sub-Saharan Africa, and there are no studies to determine what absolute neutrophil count (ANC) best correlates with heightened risk for infections. AZT-treated patients who develop neutropenia will typically do so within the first two to six months following ART initiation, and in the vast majority of cases these patients are completely asymptomatic. Mild/moderate decreases in the ANC are of minimal significance and should result in ARV medication switches (to d4T or TDF) only if the ANC is less than 500 cells.
x 10^3 microliters. Persons with moderate decreases in their ANC (ANC values 500 to 750) may have their AZT doses reduced from 300 mg twice daily to 200 mg twice daily and have their ANCs monitored over time. Patients must receive education and counseling on the risk of infections and be told to call or go to the clinic if they develop persistent fevers or any other signs or symptoms of suspected significant bacterial infection.

One additional short- to medium-term potential side effect of AZT therapy is hyperpigmentation. Hyperpigmentation can be caused by other processes or medications but has been seen among AZT-treated patients. It occurs mostly in the nail beds of fingers and toes but may also involve darkening of the mucosal surfaces (oropharyngeal mucosa). No medical therapy or intervention is required.

**d4T and ddI**

The most common short- to medium-term toxicity associated with the “D” drugs (d4T more than ddI) is the development of peripheral neuropathy (PN), namely paresthesias and burning in a stocking-glove distribution, typically involving the feet only. Persons experiencing this ARV-associated toxicity must be monitored very closely, and if PN progresses, drug regimen changes are often indicated. Patients with moderate PN can be managed by treatment with a tricyclic antidepressant (amitriptyline, initial dose 25-50 mg at bedtime but can be increased to 100-150 mg) or ideally neurontin (gabapentin) at an initial dose of 400 mg twice a day and increasing up to 1,600-2,000 mg total per day, as needed. In addition, patients can be given nonsteroidal anti-inflammatory agents (ibuprofen/Motrin [Brufen]) and vitamin supplements (multivitamins and folic acid), but there are no randomized clinical trial outcomes to provide evidence-based benefits of such adjunctive measures in the treatment of PN. One other possible management strategy for patients experiencing moderate PN is to dose-reduce their d4T, but results are inconsistent for the majority of cases. Patients with progressive PN symptoms do best when their d4T and/or ddI is switched to an alternative NRTI such as TDF or ABC.

(Note: AZT can also cause PN, but to a lesser degree than the “D” drugs. Also, PN can be caused by the HIV virus itself, so it is imperative to ask and to document the presence [or absence] of mild/moderate PN prior to ART initiation. TB preventative therapy with isoniazid can also cause PN, even in patients receiving concomitant therapy with vitamin B6 [pyridoxine] given in an attempt to reduce the likelihood of isoniazid-related PN.)

**EFV**

EFV can cause mild/moderate CNS toxicities, with the majority of these toxicities occurring within the first two to four weeks following EFV-based ART initiation. The vast majority (more than 90%-95%) of these mild/moderate CNS side effects are self-limiting and completely resolve within one month on treatment. Rarely do these CNS side effects persist beyond one month of treatment or intensify, necessitating an ARV substitution to NVP. If contraindicated, a PI such as lopinavir/ritonavir (Kaletra/Aluvia) may be substituted instead. The major mild/moderate CNS side effects seen are the following: sleep disturbances, including vivid dreams, nightmares, and insomnia; dizziness, lethargy, or fatigue due to insomnia or reduced sleeping; decreased or increased libido; and euphoria.

**MAIN SEVERE SHORT-TERM TOXICITIES**

**AZT**

The most serious and potentially life-threatening short-term complication related to AZT treatment is anemia. AZT can affect bone marrow progenitor cells and, as a result of its myelosuppressive effects, it can affect all marrow cell lines and can cause
neutropenia, anemia, and thrombocytopenia. In rare cases, idiosyncratic reactions resulting in pancytopenia have been reported. AZT-associated anemia typically develops within the first one to four months following ART initiation. Clinical presentation is varied, but the vast majority of patients complain of increased fatigue, weakness, and dyspnea, depending on the percentage loss of red blood cell mass or volume and the extent to which oxygen-carrying capacity is affected. Patients often have scleral pallor and may have a holosystolic cardiac “flow” murmur (I-III/VI) heard best over their left lower sternal border. For screening purposes, all adults treated with AZT-based ART should have a baseline full blood count performed and should not be initiated on AZT if their baseline hemoglobin (Hgb) is less than 8.0 grams/dL (or less than 7.0-7.5 grams/dL in some settings, depending on existing national ARV treatment guidelines). In addition, patients should receive extensive counseling and education on signs and symptoms that may be suggestive of underlying anemia and should be advised to go to the clinic or contact their treating care provider if any suggestive signs or symptoms of anemia develop. AZT-treated patients should also at a minimum have a full blood count performed at months one and three following ART initiation. If any suspicion of anemia exists at any time during the first four months on ART, then an urgent full blood count should be performed. Some care providers also opt to perform a routine full blood count at two months following ART initiation, which may be advisable, especially in regions, such as sub-Saharan Africa, where at least initially large percentages of patients have advanced immunosuppression (CD4 cell counts less than 50-100 cells/mm³) at the time of ART initiation. AZT-treated patients found to have severe anemia, hemoglobin values less than 6.0 grams/dL, and/or a significant percentage drop from baseline (25%-50% or more) need to be urgently hospitalized, transfused the necessary amount of packed red blood cells, and have their AZT switched to d4T, TDF, or ABC. All patients with severe anemia need to have other possible causes of their anemia ruled out: infectious causes such as malaria or acute parvovirus B19 infection (causing pure red blood cell aplasia); GI bleeding (peptic ulcer disease / severe gastritis, variceal bleeding from end-stage liver disease / cirrhosis from underlying hepatitis B or C, alcoholic liver disease, etc.); obstetric/gynecologic causes (ectopic pregnancy, etc.); and/or malignancies (colon carcinoma, etc.). There appears to be no established role for erythropoietin in the acute setting, but some care providers have administered such therapy with favorable outcomes.

**ddI- or d4T-Related Pancreatitis**

Patients treated with ddI as well as d4T (rare) and even 3TC (extremely rare) may develop chemical or clinical pancreatitis. Based on the definitions used by the Adult Clinical Trials Group (ACTG) as per the DAIDS grading scales, chemical pancreatitis is defined as the presence of a grade 3 lipase elevation on at least two determinations obtained within a two-week period. Clinical pancreatitis is graded based on the highest severity level achieved in the description of associated symptoms, which include abdominal pain (typically peri-umbilical), nausea, and/or vomiting. Patients diagnosed as having clinical pancreatitis (grade 3-4) should have their ART held and should be evaluated for other possible etiologies, such as alcohol use/abuse, traditional medication use, concomitant medications that can also cause pancreatitis (pentamidine, cotrimoxazole [rarely], etc.), gallbladder disease, and so on.

**d4T- or ddI-Related PN**

One possible short- to medium-term toxicity associated with the “D” drugs (d4T more than ddI) is the development of PN, namely paresthesia and burning in a stocking-glove distribution, typically involving the feet only. Patients developing severe PN will
normal, ART should be held and patients should be comprehensively evaluated for other possible contributing causes, such as alcohol, traditional or herbal medications, anti-tuberculosis therapy (ATT), and so on. An abdominal ultrasound may also need to be performed to aid in the diagnosis, looking for fatty hepatic infiltration or changes. Once the patient has improved clinically and the liver function tests have returned to normal (or near normal levels—at least less than five times the upper limits of normal), then ART can be reinitiated on a case-by-case basis. Patients should not be reinitiated with the dual NRTI combination of d4T plus ddI, but instead the following dual NRTI combinations should be considered (if they are not contraindicated): ZDV/3TC, TDF/FTC, TDF/3TC, or ABC/3TC.

Abacavir-Related Hypersensitivity Reactions

The most potential severe short-term toxicity associated with abacavir (ABC) use is the ABC hypersensitivity reaction (ABC HSR), which has been reported in up to 5% of ABC-treated patients. ABC HSR can be fatal and is characterized by fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and/or nonspecific respiratory symptoms such as sore throat, cough, and dyspnea. These symptoms can be easily confused with influenza-like symptoms, especially during colder periods of the year. The case fatalities have primarily occurred among patients who did not recognize this potential toxicity and therefore did not contact their physicians before they rechallenged themselves with ABC. This potentially life-threatening toxicity may be difficult to distinguish from other intercurrent illnesses such as influenza and viral illnesses and other HSRs such as cotrimoxazole- or NVP-associated cutaneous and systemic reactions. Patients with ABC HSR typically present with acute-onset fever, tachycardia, flushing...
(diffuse erythema—which may be difficult to fully appreciate among persons with darker skin), and hypotension and mimic persons presenting in early septic shock. Patients with NVP- or cotrimoxazole-associated systemic reactions, in contrast, tend to present with fevers and diffuse, clearly visible cutaneous rash and inflammation, which in severe cases typically involve the mucous membranes as well as the trunk and extremities. This potentially life-threatening toxicity typically occurs within the first two to four months following ABC initiation. Studies have shown a significant genetic predisposition to the risk for ABC HSR\textsuperscript{16,17}, namely, persons with the HLA B*5701 allele (and also HLA DR7 and HLA DQ3) are at significantly higher risk for toxicity. Genetic studies have also shown that this allele is more common in Caucasian populations (present in up to approximately 5% of studied Caucasian adults of European descent)\textsuperscript{18,19} and is rare among African American and African populations. The management of ABC HSR is mainly supportive, with the most important component being the discontinuation of ABC. Dispensing staff must collect all dispensed ABC to ensure that persons do not rechallenge themselves with ABC, as rechallenge—that is, failure to recognize the toxicity—has been implicated in all the ABC-associated fatalities reported in the literature.

**NVP-Related Hepatotoxicity**

Hepatotoxicity can be caused by a number of medications and/or substances, including alcohol, anti-TB medications, acetaminophen intoxication, and the majority of PIs, both NNRTIs and NRTIs. NVP has been associated with the development of potentially life-threatening hepatotoxicity, especially during the first 4 to 18 weeks on treatment. Women initiating NVP-containing ART for the first time with baseline CD4 cell counts greater than 250 cells/mm\(^3\) (and men with CD4 cell counts greater than 400 cells/mm\(^3\)) are at significantly heightened risk (up to 10- to 12-fold higher) for the development of serious hepatotoxicity than are those initiating NVP-based ART for the first time with CD4 cell counts less than 250 cells/mm\(^3\). Treatment is largely supportive, with ART being held until liver function tests have normalized or nearly normalized.

**NVP-Related Cutaneous Toxicity**

The most severe forms of NVP-related rashes are known as Stevens-Johnson syndrome, characterized by mucous membrane involvement. If more than 30% of the body surface is involved, it is referred to as toxic epidermal necrolysis (TEN). This rash typically occurs within the first 4 to 16 weeks following NVP-based ART initiation. Females and those of African, Asian, and Hispanic descent appear to be at heightened risk for this potentially life-threatening toxicity. Systemic symptoms include fever, arthralgias, and malaise or fatigue. The rash begins typically as truncal skin eruptions, which can progress to involve mucous membrane surfaces (eyes, genitals, and oropharynx) and may even progress to epidermal detachment and/or skin necrosis that mimics severe body burns. Cotrimoxazole and phenytoin can also cause similarly severe cutaneous reactions. Treatment consists of stopping all ARVs (while considering the administration of a three to five day dual NRTI tail to preserve future EFV use in individuals with moderate [not severe] symptomatology), as well as aggressive wound care, intravenous hydration, antihistamines, parenteral nutrition (if necessary), and antipyretics. The brief use of high-dose corticosteroids for three to five days among individuals with severe Stevens-Johnson syndrome is very controversial, but has been done without appreciable detriment in select Batswana adults.

**EFV-Related CNS Toxicity**

Due to its ability to readily cross the blood-brain barrier, EFV has been associated with numerous CNS toxicities, which typically develop within the
first two to four weeks following initiation. These CNS toxicities include sleep disturbances (insomnia, vivid dreams or nightmares, hallucinations, excessive somnolence), mood disorders (euphoria, mania, decreased or increased libido, and very rarely homicidal or suicidal ideation), and other CNS toxicities such as seizures and dizziness. In the vast majority of cases, these potentially debilitating toxicities are self-limited and resolve with continued treatment by the first month following ART initiation. In select cases, especially those involving persons operating heavy machinery, drivers of commercial transport vehicles (buses, trains, etc.), and airline pilots, a furlough for approximately two weeks following EFV initiation would minimize risk in case these patients develop CNS side effects.

MAIN MILD/MODERATE LONG-TERM TOXICITIES (INCLUDING THOSE TOXICITIES WITH POTENTIAL LONG-TERM COMPLICATIONS)

Fat Maldistribution Syndromes (PIs, EFV, d4T)
Peripheral fat loss (lipoatrophy), manifested as facial, buttocks, and/or thigh thinning, can be very cosmetically unappealing and stigmatizing among involved individuals. This is typically a longer-term complication (i.e., months following ART initiation). Treatment consists of switching to an individual NRTI medication (i.e., TDF or ABC, co-administered with either FTC or 3TC) minimally associated with lipoatrophy. Injectable agents for the treatment of lipoatrophy (poly-L-lactic acid, etc.) are not currently available in the developing world due to high cost.

Increased fat accumulation (lipohypertrophy) involving the abdomen, breasts, and neck (dorsocervical fat pad) have been reported following treatment with EFV and/or the entire class of PIs. Treatment consists of switching to other ARV medications (i.e., PIs less commonly associated with body habitus changes). Response is often slow and may not occur until three to four months following the ARV medication switch.

Nelfinavir-Related Diarrhea
Diarrhea has been reported among nelfinavir (NFV)-treated patients, especially early on in their treatment course. In the majority of cases, this is self-limited and can be managed successfully while continuing NFV by increasing fiber intake and/or by taking calcium supplements.

Indinavir-Related Nephrolithiasis
Anytime following indinavir (IDV)-based ART initiation, persons may develop nephrolithiasis, which manifests as dysuria, hematuria, and rarely as a rise in serum creatinine or acute renal failure. The risk is highest during times of reduced fluid intake. This often debilitating complication has been reported in up to 34% of IDV-treated patients (range: 4.7%-34.4%). Those at risk include patients with a previous history of nephrolithiasis, those with high peak IDV concentrations, and those unable to maintain adequate hydration. Treatment consists of aggressive IV hydration, pain control, and switching the ARV medication to another PI. Stent placement may be required for severe cases.

Insulin Resistance or Diabetes Mellitus (PIs)
Weeks to months following PI-containing ART regimens, patients can develop diabetes mellitus, which clinically manifests as expected—namely, patients present with the following: polyuria, polydipsia, polyphagia, unexplained weight loss, and fatigue or weakness. Case reports of diabetes mellitus have been reported in up to 5% of patients receiving PI-based ART regimens. Baseline fasting blood-glucose levels should be tested for patients about to initiate PIs, and this should be repeated
Symptomatic osteonecrosis has been reported in up to 1.3% of PI-treated individuals. The initial management is conservative and consists of decreased weight bearing on the involved joint or joints and analgesic control, with surgical intervention (core decompression and total joint replacement) reserved for severe refractory cases.

**Hyperlipidemia (PIs)**

All PIs have been associated with the development of hyperlipidemia. Atazanavir/ritonavir (ATV/r), and more so unboosted atazanavir (ATV), have been reported to cause less adverse effects on lipids than the other PIs. Other ARV medications, including d4T and EFV, have also been associated with the development of hyperlipidemia. Typical onset is months following ART initiation. Risk factors include preexisting hyperlipidemia. Patients about to initiate PIs should therefore have a baseline lipid profile (cholesterol, LDL and HDL cholesterol, and triglycerides) performed, and this should be repeated 1 to 3 months following PI initiation and then every 12 months thereafter. Hyperlipidemia increases the risk of large-vessel atherosclerosis, including myocardial ischemia or infarction and cerebrovascular accidents (CVAs). Management includes lifestyle modifications (i.e., diet, exercise, and/or smoking cessation), switching to agents less likely to cause lipid changes, and pharmacologic intervention that may include treatment with lipid-lowering agents such as pravastatin or atorvastatin. Hypertriglyceridemia requiring pharmacologic intervention should be treated with benzafibrate (or fenofibrate), gemfibrozil, or niacin.

**Osteonecrosis (PIs)**

Although occurrences are rare, all PIs have been associated with the development of osteonecrosis. The clinical presentation is nearly identical to that in HIV-negative individuals, in that persons typically present with periarticular discomfort, often brought on while weight bearing or ambulating.
by nonspecific symptoms such as nausea, emesis, weight loss, abdominal pain, and fatigue or weakness. Subsequent symptoms may be more rapid in onset and may include dyspnea, tachycardia, jaundice, muscular weakness, worsening PN, mental status changes, and/or respiratory distress. Some patients may present with multisystem organ failure, such as fulminant hepatic failure, acute pancreatitis, encephalopathy, or respiratory failure. Laboratory findings include decreased serum bicarbonate (< 20 mmol/L), low arterial pH (< 7.30), increased serum lactate (> 5.0 mmol/L), increased LDH, mild to moderate elevations in AST/SGOT and/or ALT/SGPT, elevated amylase and/or serum lipase, and increased anion gap (> 12-14). Management includes the discontinuation of all ART, and supportive care, including mechanical ventilation if needed.

**Rapidly Ascending Neuromuscular Weakness (d4T)**

Rapidly ascending neuromuscular weakness has been reported among persons receiving NRTI-based ART, particularly those receiving d4T and/or ddI. Patients complain of acute onset weakness that mimics Guillain-Barré syndrome and may progress to respiratory paralysis and death. This rare syndrome typically occurs months after ART initiation and may be associated with markedly elevated creatine phosphokinase (CPK) levels, elevated serum lactate levels, and an anion gap acidosis. Treatment involves supportive therapy and discontinuation of ARVs. Mechanical ventilation can be instituted, if needed. Other treatments to consider, which have had variable success rates and outcomes, include plasmapheresis, high-dose corticosteroids, intravenous immunoglobulin (IVIG), and L-carnitine.

**ddl-Related Pancreatitis (Also Possible from d4T and/or 3TC)**

Pancreatitis may develop in one of two forms: chemical or clinical pancreatitis. Chemical pancreatitis is defined as the presence of a grade 3 lipase elevation on at least two determinations obtained within a two-week period. Clinical pancreatitis is graded based on the highest severity level achieved in the description of associated clinical symptoms. The diagnosis is based on the presence of clinical symptoms (using the DAIDS/ACTG toxicity grading scale): nausea, vomiting, and/or abdominal pain (typically periumbilical) plus a confirmed grade 3 lipase elevation plus (for persistent symptoms and/or persistent lipase elevations to grade 1-2 levels) radiographic evidence of pancreatic inflammation or edema on an abdominal ultrasound and/or abdominal computed tomography (CT) scan. Clinical pancreatitis may be life-threatening and has been associated with d4T and/or ddI use in adults and 3TC use in children (very rarely adults). Clinical pancreatitis may develop two or more months following ART initiation, and persons on d4T and/or ddI need to be monitored closely for the development of GI symptoms (i.e., abdominal pains, nausea, and/or emesis). Other risk factors for pancreatitis include alcohol use/abuse, hypertriglyceridemia, a previous history of pancreatitis, and the use of TDF plus ddI without the ddI dose reduction to 250 mg. Diagnosis is made by checking a serum lipase and by abdominal imaging study (abdominal ultrasound and/or abdominal CT scan). Patients with confirmed clinical pancreatitis should have their ART held, and, once they are stabilized, their NRTIs should be switched from d4T and/or ddI to TDF/FTC, TDF/3TC, or ZDV/3TC.

**d4T- or ddI-Related PN**

One possible severe toxicity associated with the “D” drugs (d4T more than ddI) is the development of PN, namely paresthesia and burning in a stocking-glove distribution, typically involving the feet only. Patients developing severe PN will also by definition have difficulty ambulating and/or sleeping, due to the severity of their paresthesia, and discomfort will significantly impair their ability to perform the
activities of daily living. The vast majority of ART-treated patients developing grade 3-4 PN should have their treatment modified. Patients with severe PN need to have their d4T and/or ddI switched to an alternative NRTI such as TDF or ABC. (Note: Such patients should be told that it may take several [two to four] months following their ARV medication switch before they experience any significant improvement in these often debilitating symptoms.)

**Bleeding Episodes (Increase in Hemophiliac Patients)**

Although occurrences are rare, PI-treated hemophiliac patients, within the first few weeks following ART initiation, can develop spontaneous bleeding as manifested acutely by bleeding into joints, soft tissues, and muscles. Treatment consists of switching to an NNRTI, and acutely affected patients may require factor VIII products.

**Nephrotoxicity (IDV, Possibly TDF)**

In the literature, there are case reports of IDV- and TDF-associated nephrotoxicity leading to renal insufficiency or failure. Patients are often asymptomatic, so patients at heightened risk for renal insufficiency (history of renal insufficiency, underlying renal disease, etc.) should be given IDV or TDF only if the benefit clearly outweighs the risk of treatment.

All patients should have their creatinine clearance calculated using the Cockcroft-Gault method prior to TDF initiation, and patients should be monitored for worsening renal function, especially during the first six months on treatment. Patients often present completely asymptptomatically, and cases of TDF-induced Fanconi syndrome have been reported. Their diagnosis requires urine microscopy plus phase or Millipore analysis. Patients having a creatinine clearance of less than 60 cc/minute should not initiate TDF, and all TDF-treated patients should ideally have their creatinine clearance measured at least every six months and more frequently if they appear to be at heightened risk for nephrotoxicity (i.e., older than age 60, having preexisting renal insufficiency/disease, being on or having recently received other potentially nephrotoxic medications [e.g., amphotericin B], and/or having diabetes mellitus or poorly controlled hypertension).

IDV-treated patients may develop renal insufficiency or failure caused by partial or complete urinary obstruction due to the development of IDV-induced nephrolithiasis. Diagnosis can be made by urine microscopy and renal ultrasound (hydrenephrosis); treatment consists of IDV discontinuation and supportive care, including IV hydration and pain management.

**Risk for Myocardial Infarction (Possibly ABC More Than ddI)**

Attention has focused primarily on the role of PIs and the risk of myocardial infarction (MI). However, recent data presented at the Fifteenth Conference on Retroviruses and Opportunistic Infections (CROI) from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) collaborative cohort study unexpectedly showed that recent use of ABC and ddI was associated with an increased risk of MI, by 90% and 49%, respectively. The excess risk of MI associated with ABC and ddI use was most significant—in absolute terms—among patients with high underlying cardiovascular risk. Preferential use of ABC and ddI in patients with an a priori increased cardiovascular risk appears not to explain these unexpected findings. Certainly, more intensive longer-term follow-up is needed, but in HIV-1 infected adults with multiple risk factors for coronary disease (high cardiovascular risk), physicians may opt to prescribe alternative NRTI combinations, avoiding ABC and/or ddI in such patients until additional long-term, and ideally randomized clinical trial data, become available.
CONCLUSION

In summary, ARV medications are very well tolerated with minimal toxicities in the vast majority of ART-treated adults. However, potentially life-threatening short- and long-term toxicities can occur and require that all involved healthcare personnel carefully and consistently educate their patients to improve the recognition and significantly reduce the likelihood of adverse outcomes. Toxicity profiles preliminarily appear to differ in the developing world when compared to Western European and North American cohorts. Additional in-depth research is clearly warranted.
<table>
<thead>
<tr>
<th><strong>Toxicity</strong></th>
<th><strong>Most Likely Causative Antiretrovirus (ARV) Medication</strong></th>
<th><strong>Other Possible Etiologies or Contributing Causes</strong></th>
<th><strong>Duration on ART</strong></th>
<th><strong>Clinical Presentation</strong></th>
<th><strong>Diagnosis</strong></th>
<th><strong>Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>AZT/ZDV (zidovudine)</td>
<td>Gastrointestinal bleeding, hemolysis, cytotoxic chemotherapy, ganciclovir, cotrimoxazole</td>
<td>2–12 weeks</td>
<td>Fatigue, dyspnea, pallor, weakness</td>
<td>Full blood count, hematology</td>
<td>Rule out other possible etiologies and discontinue AZT; transfuse when clinically indicated; and then switch AZT to d4T (stavudine) or TDF (tenofovir)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>AZT &gt; d4T (stavudine)</td>
<td>Cytotoxic chemotherapy</td>
<td>1–9 months</td>
<td>Asymptomatic (vast majority), recurrent bacterial infections (severe)</td>
<td>Full blood count/ hematology</td>
<td>Once confirmed, if grade 3, consider dose-reduced AZT (200 mg twice a day) and monitor; if grade 4, switch AZT to d4T or TDF</td>
</tr>
<tr>
<td>Hepatotoxicity (elevated SGOT/AST and SGPT/ALT)</td>
<td>NVP (nevirapine)</td>
<td>Traditional medications, alcohol, isoniazid, rifampicin, hepatitis (A, B, or C)</td>
<td>2–18 weeks (most serious cases)</td>
<td>Right upper-quadrant pain, nausea/emesis, jaundice, darkened urine/stools, fevers</td>
<td>Chemistry (AST/SGOT, ALT/SGPT)</td>
<td>Hold all ART when AST/SGOT and/or ALT/SGPT greater than five times the upper limit of normal; consult HIV specialist especially for patients requiring both ART and anti-TB therapy, as patients with persistent liver function test elevations need very close monitoring and may need their anti-TB therapy to be re-initiated one drug at a time</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>TDF</td>
<td>Amphotericin B, aminoglycosides</td>
<td>2+ months</td>
<td>Asymptomatic, decreased urine output (severe)</td>
<td>Chemistry (urea/creatinine); creatinine clearance (Cockcroft-Gault equation)</td>
<td>Rule out other possible etiologies, perform renal ultrasound when indicated (to rule out obstruction), and hold/discontinue TDF when creatinine clearance less than 50–60 mLs/minute.</td>
</tr>
</tbody>
</table>

**Table 2. Antiretrovirus-Associated Toxicities: Recognition and Management Strategies**
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Most Likely Causative Antiretrovirus (ARV) Medication</th>
<th>Other Possible Etiologies or Contributing Causes</th>
<th>Duration on ART</th>
<th>Clinical Presentation</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe skin rash; Stevens-Johnson syndrome / toxic epidermal necrolysis</td>
<td>NVP</td>
<td>Cotrimoxazole, phenytoin</td>
<td>2–16 weeks</td>
<td>Diffuse, moist</td>
<td>Clinical evaluation / exam</td>
<td>Discontinue NVP; treat with antihistamines (chlorpheniramine or equivalent) and non-steroidal anti-inflammatory agents (ibuprofen); the role of IV/PO steroids is very controversial but one may consider a very short course (3-5 days total) of high-dose prednisone (60 mgs per day or the IV equivalent) in severe cases.</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>d4T &gt; ddI (didanosine) &gt; AZT &gt; 3TC (lamivudine)/FTC (emtricitabine) &gt; ABC (abacavir) &gt; TDF</td>
<td>Sepsis, pancreatitis</td>
<td>&gt; 6 months</td>
<td>Nausea/emesis, unexplained weight loss, fatigue, dyspnea (late), motor weakness, worsening peripheral neuropathy</td>
<td>Serum lactate measurement (gray top tube on ice versus newer validated portable device)</td>
<td>Hold all ART in patients with symptoms and lactate levels &gt; 5.0 mmol/L unexplained by other possible etiologies (i.e., sepsis); if lactic acidosis, would consider avoiding all NRTIs when ART resumed versus only using the NRTIs much less likely to cause mitochondrial toxicity, such as TDF/FTC, TDF/3TC, or ABC/3TC</td>
</tr>
<tr>
<td>Lipoatrophy (face, thighs, buttocks)</td>
<td>d4T &gt; ddI &gt; AZT</td>
<td>&gt; 6 months</td>
<td>Significant muscle mass loss in involved area</td>
<td>Atrophy of involved area of the body noticed by treating physician/nurse, patient, and/or his or her spouse, partner, or family member</td>
<td>Switch to TDF/FTC, TDF/3TC, or ABC/3TC</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Antiretrovirus-Associated Toxicities: Recognition and Management Strategies (cont.)
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Most Likely Causative Antiretrovirus (ARV) Medication</th>
<th>Other Possible Etiologies or Contributing Causes</th>
<th>Duration on ART</th>
<th>Clinical Presentation</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipohypertrophy (abdomen, breast tissue, posterior neck)</td>
<td>Protease inhibitors (PIs), EFV (efavirenz) (gynecomastia)</td>
<td>Significant fat accumulation in involved areas</td>
<td>&gt; 6 months</td>
<td>Lipohypertrophy of involved area of the body noticed by treating physician/nurse, patient, and/or his or her spouse, partner, or family member</td>
<td>Switch from EFV to NVP or from PIs to NVP or a PI (ATV [atazanavir], LOP/r [lopinavir/ritonavir]) less likely to cause fat maldistribution problems</td>
<td></td>
</tr>
<tr>
<td>Central nervous system abnormalities</td>
<td>EFV</td>
<td>Within first month, rarely beyond 1–2 months on ART</td>
<td>Sleep, mood, or general behavior abnormalities/disturbances</td>
<td>Diagnosed clinically</td>
<td>Switch from EFV to NVP or PI</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>ddl &gt; d4T</td>
<td>Pentamidine, 3TC (rare)</td>
<td>&gt; 3–6 months</td>
<td>Abdominal pain (typically periumbilical), nausea, and/or emesis</td>
<td>The presence of clinical symptoms with or without radiographic evidence (edema/swelling of pancreas on ultrasound and/or abdominal CT scan)</td>
<td>Hold all ART; and if confirmed grade 3 or 4 clinical pancreatitis, switch d4T and/or ddl to TDF/FTC, TDF/3TC, ABC/3TC, or ZDV/3TC, with either a NNRTI or PI</td>
</tr>
<tr>
<td>Lipid abnormalities</td>
<td></td>
<td></td>
<td>&gt; 6 months</td>
<td>Asymptomatic</td>
<td>Routine screening blood tests (total, HDL, and LDL cholesterol, and serum triglycerides)</td>
<td>Dietary and lifestyle modifications plus lipid-lowering agents</td>
</tr>
</tbody>
</table>
REFERENCE LIST


4. National Institute of Allergy and Infectious Diseases, Division of AIDS (DAIDS). Table for grading the severity of adult adverse events; November 2004.


33. Sabin C, et al. Do thymidine analogues abacavir, didanosine, and lamuvidine contribute to the risk of myocardial infarction? Presented at: 15th Conference on Retroviruses and Opportunistic Infections (CROI); February 3-6, 2008; Boston, MA. Abstract 957c.
Immune Reconstitution Inflammatory Syndrome

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Between 10% and 40% of individuals initiating combination antiretroviral therapy (ART) for HIV-1 infection experience an immune reconstitution inflammatory syndrome (IRIS), also known as immune reconstitution disease. 1-7 IRIS is caused by immunological responses resulting from the immune system’s renewed activity against latent pathogens or other antigens. Although extensively described in the literature, IRIS lacks a universally recognized case definition because of its diverse clinical spectrum and the difficulty in clearly differentiating the syndrome from other conditions, such as drug toxicity or new opportunistic infections (OIs).

Epidemiology and Clinical Spectrum

A wide range of infectious and noninfectious forms of IRIS has been reported, as summarized in Table 1.

“Paradoxical” and “Unmasking” IRIS

IRIS may present as two distinct clinical scenarios (see Box 1) with different clinical features and differential diagnoses. “Paradoxical” IRIS occurs when a patient with a previously diagnosed OI or malignancy experiences a deterioration in clinical status after the initiation of ART, usually despite effective treatment of the underlying OI. Similar reactions have been described in HIV-negative patients receiving antituberculous therapy (ATT) 8 and may be indistinguishable from ART-induced IRIS. However, higher rates of paradoxical reactions are reported in patients receiving both ART and ATT (incidence of 28% to 36%) than in those treated for TB alone (2% to 10%). 9 Worldwide, the most common and clinically significant paradoxical forms of IRIS are those associated with TB and cryptococcal disease. In seven cohort studies of

Box 1. Common Pathologic Scenarios of HIV Immune Reconstitution Syndrome

<table>
<thead>
<tr>
<th>Unmasking IRIS</th>
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<tbody>
<tr>
<td>■ Occult, subclinical opportunistic infection</td>
</tr>
<tr>
<td>■ Unmasked by ART, typically within first 12 weeks</td>
</tr>
<tr>
<td>■ Infectious pathogens present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paradoxical IRIS</th>
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<tbody>
<tr>
<td>■ Clinical recrudescence of a successfully treated infection</td>
</tr>
<tr>
<td>■ Symptomatic relapse despite microbiological treatment success</td>
</tr>
<tr>
<td>■ Antigen-driven immune activation</td>
</tr>
<tr>
<td>■ Sterile cultures</td>
</tr>
</tbody>
</table>
patients with known TB initiating ART, the incidence of paradoxical TB IRIS ranged from 7.6% to 43%.9,48-53 The incidence of cryptococcal paradoxical IRIS in three studies of patients on treatment for cryptococcal disease who subsequently initiated ART was 8.3% to 33.9%.20,49,54

“Unmasking” IRIS occurs when an OI develops in a patient who before starting ART did not manifest the condition. In this situation, subclinical or undiagnosed OIs are “unmasked” by the emergence of pathogen-specific immune responses. Unmasking IRIS has been much less well described than paradoxical IRIS, and its incidence varies according to the underlying distribution of various pathogens in the population, and by the level of screening for OIs before the initiation of ART. For example, the use of routine chest X-rays and sputum smear examination for acid-fast bacilli (AFB) in both symptomatic and asymptomatic patients increases the ascertainment and treatment of TB prior to ART initiation.

Table 1. Reported Infectious and Noninfectious Syndromes Associated with IRIS

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Class of pathogen</th>
<th>Specific pathogen or disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Mycobacteria and bacteria</td>
<td>Mycobacterium tuberculosis9,12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mycobacterium avium complex9,13</td>
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<td></td>
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<td>Mycobacterium leprae14,15</td>
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<td></td>
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<td>Bartonella henselae1</td>
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<td></td>
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<td>Chlamydia trachomatis (as Reiter's syndrome)16</td>
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<td>Fungi</td>
<td></td>
<td>Cryptococcus neoformans17-20</td>
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<tr>
<td></td>
<td></td>
<td>Pneumocystis jirovecii20</td>
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<td>Histoplasma21</td>
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<td></td>
<td></td>
<td>Tinea (dermatophytes)22</td>
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<tr>
<td>Viruses</td>
<td></td>
<td>Cytomegalovirus21,26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Herpes simplex virus type 1 and 225</td>
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<tr>
<td></td>
<td></td>
<td>Hepatitis B and C22,26,27</td>
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<tr>
<td></td>
<td></td>
<td>Varicella zoster virus28,29</td>
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<td></td>
<td></td>
<td>Human papillomavirus30</td>
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<td></td>
<td></td>
<td>JC virus (as progressive multifocal leukoencephalopathy)30</td>
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<td></td>
<td></td>
<td>Parvovirus B19 (as encephalitis)30</td>
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<td>Protozoa</td>
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<td>Leishmania spp.33,36</td>
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<td></td>
<td></td>
<td>Toxoplasma37</td>
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<td>Helminths</td>
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<td>Schistosoma38</td>
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<td></td>
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<td>Strongyloides36</td>
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<td>Virally driven malignancy</td>
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<td>Eppstein-Barr virus (as non-Hodgkin’s lymphoma)37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human herpesvirus 8 (as Kaposi’s sarcoma)38-40</td>
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<tr>
<td>Presumed noninfectious</td>
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<td>Systemic lupus erythematosus41</td>
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<td></td>
<td></td>
<td>Sarcoidosis42</td>
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<tr>
<td></td>
<td></td>
<td>Grave’s disease43</td>
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<tr>
<td>Possibly infectious</td>
<td></td>
<td>Guillain-Barré syndrome44</td>
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<tr>
<td></td>
<td></td>
<td>Appendicitis45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eosinophilic folliculitis46,47</td>
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<tr>
<td></td>
<td></td>
<td>Papular pruritic eruption47</td>
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</tbody>
</table>
Incidence of IRIS
Four retrospective cohort studies from South Africa, Europe, and Australia have reported on the incidence and clinical spectrum of IRIS in all patients starting ART (Table 2). Cumulative incidence ranged from 10.4% to 25%, and rates ranged from 5.8 to 51.5 per 100 person-years (PYs). The median time to the development of IRIS was 7 to 20 weeks, with more than half of events occurring within the first three months of ART. Of 201 IRIS cases reported in the four cohort studies, the most common pathogens associated with IRIS were varicella zoster virus (42 cases [21%]), herpes simplex virus (35 cases [17%]), Mycobacterium tuberculosis (31 cases [15%]), hepatitis C virus (16 cases [8%]), and human papillomavirus (13 cases [6%]). Their relative incidence in different studies partially reflects the characteristics of the study populations in terms of the underlying prevalence of infections in various geographic settings, the level of immunosuppression, the type of HIV risk exposure (e.g., a higher prevalence of hepatitis B and C coinfection among injecting drug users), and level of screening for underlying OIs in the clinic population.

Other cohort studies of the epidemiology of IRIS have included only patients receiving treatment for specific OIs and have estimated the incidence of IRIS related to those OIs. There are six published studies of patients with TB (from the United States, India, Spain, France, South Africa, and Thailand); two studies of patients with cryptococcosis (France and the United States); and one study of patients with either TB, cryptococcosis, or Mycobacterium avium complex (MAC) infection (the United States). The incidence of IRIS in the TB cohorts ranged from 7.6% to 36%, with rates from 13.6 to 31.6 per 100 PYs, and the incidence of cryptococcal IRIS ranged from 8.3% to 33.9%, with rates from 4.2 to 17.9 per 100 PYs. The single study of IRIS secondary to MAC infection found an incidence of 31.4% and a rate of 15.1 per 100 PYs. A higher incidence of IRIS was observed in patients with TB initiating ART in high-resource settings compared with resource-limited settings (35% to 43% versus 7.6% to 12.6%, respectively). Reasons for these differences include a shorter time between diagnosis of OI and ART initiation in high-resource settings, and varying intensity of clinical surveillance during follow-up.

Clinical Features
Almost any organ or system may be affected by IRIS, and the clinical features depend on the site affected, the pathogen involved, and the host-parasite interaction. The clinical spectrum of IRIS in a cohort in Durban is summarized in Figure 1, and presentations of the most common and important IRIS syndromes are described in the following sections.

Tuberculosis and MAC
IRIS in response to M. tuberculosis infection is probably the most common and clinically significant form of IRIS, as well as the most extensively described in case reports and cohort studies. TB IRIS may present as unmasking or paradoxical IRIS, and presents with various clinical manifestations dependent on the site of disease. It accounts for approximately one-half of the HIV-related IRIS events in resource-limited settings where HIV/TB coinfection is common. Studies performed in Europe and the United States reported an incidence of TB IRIS among patients with a prior diagnosis of infection (i.e., paradoxical IRIS) varying between 30% and 43%. Only one study provides an estimate of the incidence of unmasking TB IRIS, of around 5% in Johannesburg, South Africa. A detailed review of all species of mycobacterial IRIS summarizes 86 cases of TB IRIS from 27 papers. Among those cases, the most common manifestation was lymphadenopathy (71% of cases), with or without overt lymphadenitis. Pulmonary disease was
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Incidence of outcome</th>
<th>Time on antiretroviral therapy (ART) before event</th>
<th>Risk factors (number of studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any IRIS (unselected cohort)</td>
<td>2</td>
<td>10.4%–22.7%</td>
<td>Median 7–12 weeks</td>
<td>Lower baseline CD4:CD8 ratio (1)</td>
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<td></td>
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<td>Lower baseline CD4% (1)</td>
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<td></td>
<td></td>
<td>Lower baseline CD4 count (1)</td>
</tr>
<tr>
<td>Major opportunistic infection (OI) early in ART</td>
<td>4</td>
<td>5.9%–25%</td>
<td>Within 20 weeks in 50% and 8 weeks in 68% of cases</td>
<td>Lower baseline CD4 count (3)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Higher baseline viral load (1)</td>
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<td>Higher final CD4 count (1)</td>
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<td>CDC stage C (1)</td>
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<td></td>
<td>Younger age (1)</td>
</tr>
<tr>
<td>TB IRIS in patients with known TB (high-resource settings)</td>
<td>4</td>
<td>30%–43%</td>
<td>Median 2–7 weeks</td>
<td>Greater decrease in viral load (2)</td>
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<td></td>
<td></td>
<td>Shorter time between OI diagnosis and ART initiation (2)</td>
</tr>
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<td></td>
<td></td>
<td>Greater increase in CD4:CD8 ratio (1)</td>
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<td></td>
<td></td>
<td>Greater increase in CD4% (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ART naive (1)</td>
</tr>
<tr>
<td>TB IRIS in patients with known TB (resource-limited settings)</td>
<td>3</td>
<td>7.6%–12.6%</td>
<td>Median 2–6 weeks</td>
<td>Extrapulmonary TB (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Shorter time between OI diagnosis and ART (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower baseline CD4 (1)</td>
</tr>
<tr>
<td>Cryptococcal IRIS in patients previously treated for cryptococcal infection</td>
<td>3</td>
<td>8.3%–33.9%</td>
<td>Median 4–34 weeks</td>
<td>Shorter time between OI diagnosis and ART initiation (2)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Higher level of cerebrospinal fluid cryptococcal antigen (1)</td>
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<td></td>
<td></td>
<td></td>
<td>Fungemia (1)</td>
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<td></td>
<td></td>
<td></td>
<td>HIV infection revealed by cryptococcosis (1)</td>
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<td></td>
<td>ART naive (1)</td>
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<td></td>
<td></td>
<td></td>
<td>Higher baseline viral load (1)</td>
</tr>
<tr>
<td>Mycobacterium avium complex (MAC) IRIS in patients with known MAC</td>
<td>1</td>
<td>31.4%</td>
<td>Not specified</td>
<td>Greater decrease in viral load (1)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Shorter time between OI diagnosis and ART initiation (1)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>ART naive (1)</td>
</tr>
</tbody>
</table>
also common, occurring in 28% of reported cases. On radiological imaging, increased pulmonary infiltrates, pleural effusions, mediastinal lymphadenopathy, and tracheal compression have been reported. Other manifestations include ascites, focal abscesses, hypercalcemia, and central nervous system (CNS) lesions (including tuberculosis). A case definition of both paradoxical and unmasking TB IRIS has recently been developed (see Box 2), although this now requires validation in different practice settings.

Although MAC IRIS is well described, the significance of the infection is eclipsed by TB in resource-limited settings. Clinical presentations of MAC IRIS in patients with advanced disease tend to be atypical, with focal rather than disseminated infection. For example, lymphadenopathy was seen in 69% of reported cases (44 of 64), also with pneumonia, pyomyositis, and soft tissue infections.

Two cases of unmasking TB IRIS from the authors’ clinical practice are briefly presented here. The first is a patient with a baseline CD4 lymphocyte count of 79 cells/mm³ and a history of oral thrush but no other OIs. A chest X-ray just prior to ART initiation showed no signs of TB. After about eight weeks of ART associated with a CD4 count increase to 142 cells/mm³, she developed a mass in the left axilla, which subsequently started to discharge purulent material (Plate 1). Ziehl-Neelsen staining of the pus revealed AFB, typical of TB. The second case was a patient with
Cryptococcal disease is the most common fatal CNS infection in late-stage HIV patients in sub-Saharan Africa and, after TB, is the most common serious form of IRIS in resource-limited settings. Between 8% and 43% of patients with cryptococcal disease who are treated with ART exhibit a paradoxical deterioration due to IRIS, with the most common manifestations being aseptic meningitis. A CD4 count of 68 cells/mm³ who was diagnosed with a bacterial meningitis. Investigations for TB were negative (Plate 2a), and one month after recovery, the patient was started on ART. Two weeks later she developed night sweats, and after a further two weeks, cough and weight loss. A chest X-ray revealed right-upper-lobe consolidation (Plate 2b), and sputum was AFB smear positive.

### Box 2. Summary of Published Case Definitions for TB IRIS for Use in Resource-Limited Settings

<table>
<thead>
<tr>
<th><strong>Paradoxical TB IRIS definition</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) Antecedent requirements:</strong></td>
</tr>
<tr>
<td>• Diagnosis of TB was made before starting ART according to World Health Organization (WHO) criteria</td>
</tr>
<tr>
<td>• Initial response to TB treatment (does not apply to patients starting ART within 2 weeks of starting TB treatment)</td>
</tr>
<tr>
<td><strong>(B) Clinical criteria:</strong></td>
</tr>
<tr>
<td>• Onset of TB-associated IRIS should be within 3 months of ART initiation, reinitiation, or regimen change</td>
</tr>
<tr>
<td>• Of the following, at least one major or two minor criteria are required:</td>
</tr>
<tr>
<td>Major criteria:</td>
</tr>
<tr>
<td>• Lymph nodes, cold abscesses, or other focal tissue involvement</td>
</tr>
<tr>
<td>• Radiological features of TB</td>
</tr>
<tr>
<td>• CNS TB</td>
</tr>
<tr>
<td>• Serositis (pleural effusion, ascites, or pericardial effusion)</td>
</tr>
<tr>
<td>Minor criteria:</td>
</tr>
<tr>
<td>• Constitutional symptoms</td>
</tr>
<tr>
<td>• Respiratory symptoms</td>
</tr>
<tr>
<td>• Abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or adenopathy</td>
</tr>
<tr>
<td><strong>(C) Alternative explanations excluded:</strong></td>
</tr>
<tr>
<td>• Failure of TB treatment because of TB drug resistance</td>
</tr>
<tr>
<td>• Poor adherence to TB treatment</td>
</tr>
<tr>
<td>• Another OI or neoplasm</td>
</tr>
<tr>
<td>• Drug toxicity</td>
</tr>
</tbody>
</table>

*Note: In resource-limited settings, cases in which there is failure to exclude TB drug resistance and certain OIs and neoplasms should be regarded as “probable” IRIS, unless resolution of the episode occurs without a change in treatment.*

<table>
<thead>
<tr>
<th><strong>Unmasking TB IRIS definition</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ART-associated TB</strong> should be defined as follows:</td>
</tr>
<tr>
<td>• Patient is not receiving treatment for TB when ART is initiated</td>
</tr>
<tr>
<td>• Active TB is diagnosed after initiation of ART</td>
</tr>
<tr>
<td>• Diagnosis of TB fulfills WHO criteria</td>
</tr>
<tr>
<td><strong>Unmasking TB-associated IRIS (provisional)</strong> is suggested by:</td>
</tr>
<tr>
<td>• ART-associated TB within 3 months of ART initiation</td>
</tr>
<tr>
<td>• One of the following:</td>
</tr>
<tr>
<td>• Heightened intensity of clinical manifestations</td>
</tr>
<tr>
<td>• Once established on TB treatment, clinical course is complicated by a paradoxical reaction</td>
</tr>
</tbody>
</table>
meningitis, increased intracranial pressure (ICP), development of intracranial cryptococcomas, and lymphadenitis. In the majority of individuals, these symptoms develop despite apparent antifungal treatment success as evidenced by sterile fungal cultures. Although a detailed review of 25 reported cryptococcal IRIS cases found that more than half (56%) presented with lymphadenitis or sterile abscesses, most cryptococcal IRIS reported in the literature manifested as CNS disease. Pulmonary, ocular, breast, and soft tissue involvement have also been described (Plate 3). Since lymphadenitis and soft tissue swellings may be clinically indistinguishable from other OIs, such as mycobacterial infection, it is important to examine and culture material aspirated from the lesions.

We report an illustrative case from clinical practice. A 34-year-old Ugandan woman with a CD4 count of 9 cells/mm³ was diagnosed with HIV-1 infection and cryptococcal meningitis, and received three weeks of amphotericin therapy prior to ART initiation. Two weeks later, the patient presented with symptomatic raised ICP characterized by papilledema and a visual field defect. She experienced a good clinical response, with a reduction in her cerebrospinal fluid (CSF) cryptococcal antigen (CRAG) titer from 1:640 to 1:20, and conversion of her CSF fungal culture from positive to negative, while the CSF protein rose from 290 mg/L to 535 mg/L and the CSF white cell count remained unchanged at less than 5 cells/mm³. However, this case illustrates that although cryptococcal IRIS of the CNS is often described as associated with an increased CSF leukocyte count, protein, and opening pressure, these features are too inconsistent for use in confirmation of IRIS and exclusion of the alternative diagnosis of failure of antifungal therapy. In this case, strong evidence in support of a diagnosis of IRIS was the negative India ink stain and fungal cultures in the presence of persistently positive CSF CRAG, and clinical evidence of recurrent meningitis.

Kaposi’s Sarcoma
Published data on Kaposi’s sarcoma (KS) IRIS are limited largely to case reports, but recent conference abstracts have highlighted an increasingly important role for this phenomenon in sub-Saharan Africa. Around two-thirds of all patients with KS prior to ART initiation may develop subsequent paradoxical KS IRIS, although rates of unmasking KS IRIS have yet to be quantified. Risk factors specific to KS IRIS include higher levels of pre-ART quantitative human herpesvirus 8 (HHV-8) viral load (VL). The clinical spectrum is highly variable in both characteristics and severity, including swelling, tenderness, and inflammation of cutaneous and visceral lesions, expansion of pleural effusions, deterioration in parenchymal lung disease, and worsening lymphedema. Fatalities have been described. In the authors’ own practice, the rapid and massive enlargement of both palatal and pulmonary lesions in one patient led to acute fatal respiratory failure.

Inflammatory Dermatoses
In an observational cohort in Durban, South Africa, dermatological conditions were the most frequent manifestations of IRIS, occurring in about 11% of all patients initiating ART (unpublished data). Of dermatological IRIS, itchy folliculitis and papular pruritic eruptions accounted for around 60% of all IRIS events. The typical appearances of itchy facial folliculitis (Plates 4a to 4c) affect mainly the face, trunk, and proximal upper limbs. The histological entities of eosinophilic, neutrophilic, lymphocytic, and mixed folliculitis may be clinically indistinguishable, and may present either as paradoxical IRIS, with a rapid worsening in the setting of previously stable or mild disease, or as an unmasking event, presenting for the first time shortly after initiating ART. The condition is usually itchy, and
disfiguring hyperpigmentation may result. Other dermatological manifestations of IRIS include warts, molluscum contagiosum, papular pruritic eruption, and tinea.\textsuperscript{30,47,55}

**Herpes Simplex and Varicella Zoster Virus**
Herpes simplex virus (HSV) and varicella zoster virus (VZV) infection are common in patients living with HIV. Although sustained ART-related improvements in immune function should ultimately reduce the burden of both diseases, patients frequently present with these clinical events within the first three months of ART.\textsuperscript{25,28,29} Such cases may present as the first manifestation of shingles or genital herpes in a patient recently started on ART (unmasking), or as a more florid expression of disease in someone with previous symptomatic disease (paradoxical). In most resource-limited settings, there is ubiquitous exposure, with seroprevalence of VZV and HSV-1 in adults approaching 100%, making new acquisition of infection after ART initiation unlikely. Plate 5 shows an example of oral herpes due to HSV-1 infection presenting for the first time in a 39-year-old adult who had started ART four months previously. The CD4 count had risen from 81 cells/mm\(^3\) at baseline to 108 cells/mm\(^3\) when the lesions appeared.

**Chronic Viral Hepatitis**
Distinguishing IRIS from other causes, such as drug toxicity or reactivation of hepatitis B or C, can be very challenging. Elevation of transaminases following initiation of ART is common, affecting up to 18% of patients.\textsuperscript{69,70} In addition, associated symptoms, such as fatigue, abdominal pain, vomiting, and jaundice, are nonspecific.\textsuperscript{26,27} Features that are more suggestive of IRIS are a lack of a rise in hepatitis B DNA, and conversion from e-antibody negative to positive. However, such tests are unlikely to be available in most resource-limited clinical settings.

**Risk Factors for IRIS**
Despite a lack of universal agreement on risk factors, a general consensus has emerged that patients with more advanced immunosuppression (i.e., those with lower CD4 count and higher VL prior to ART) and those with greater pathogen burden (indicated by disseminated disease, higher cryptococcal antigen titer, and indirectly by a shorter duration of OI therapy) are at a greater risk of IRIS.

Four published cohort studies of IRIS in all patients starting ART have examined potential risk factors for IRIS. The most consistent finding has been an association with a lower baseline CD4 cell count or CD4 percentage at ART initiation,\textsuperscript{22,30,55,56} with a hazard ratio of 1.39 for each 50 cells/mm\(^3\) decrease in baseline CD4 count in one study.\textsuperscript{56} Two other studies found odds ratios (ORs) for IRIS in patients with a baseline CD4 count below 100 cells/mm\(^3\) of 2.5 (95% confidence interval [CI], 0.9-6.4) and 3.1 (95% CI, 1.2-8.0) when compared with patients with higher CD4 counts.\textsuperscript{22,55} This may reflect the higher burden of viral or other pathogens or the increased susceptibility to immune dysregulation during immune reconstitution with more advanced immunodeficiency.

Other immunological risk factors include a baseline CD4 percentage of less than 10% (OR 3.0; 95% CI, 1.2-7.6) compared with a percentage greater than 15%,\textsuperscript{55} a baseline CD8 percentage greater than 65% compared with less than 52% (OR 3.1 on bivariate analysis; 95% CI, 1.2-7.6),\textsuperscript{55} and an increase in CD4 count at 12 weeks of less than 69 cells/mm\(^3\) compared with greater than 133 cells/mm\(^3\) (OR 2.6; 95% CI, 1.0-6.6).\textsuperscript{55} A final CD4 count greater than 400 cells/mm\(^3\) was a protective factor compared with patients with lower counts (OR 0.3 on multivariate analysis; 95% CI, 0.1-0.8).\textsuperscript{22} Other factors associated with the development of IRIS include a reduction in VL at 12 weeks of less than 2 log,\(_{10}\) compared with greater than 3 log,\(_{10}\) (OR 0.3; 95% CI, 0.1-0.7),\textsuperscript{55} younger age (median
of 33.7 years at baseline in IRIS cases compared with 35.6 years in controls, \( P=0.021 \), and baseline hemoglobin (10.95 g/dL in cases compared with 12.30 g/dL in controls).\(^71\)

**Patients Coinfected with Other OIs**

The most important risk factor for IRIS in patients with an existing OI in five out of nine cohort studies was shorter time between OI diagnosis and initiation of ART.\(^20,49,50,52,54\) In a South African outpatient setting, the relative risk (RR) for IRIS was 69.5 (95% CI, 9.94-485.6) in patients initiating ART within 30 days and 10.6 (95% CI, 1.88-59.5) in those starting after 31 to 60 days, compared with patients delaying ART more than 90 days.\(^52\) In patients treated for cryptococcosis, those diagnosed with an OI within one or two months of starting ART were at higher risk of IRIS than were patients delaying ART (OR 5.5; 95% CI, 1.0-29.6 and RR 1.7; 95% CI, 1.0-2.3).\(^20,54\)

Three studies also found an association with markers of pathogen burden—namely, cryptococcal fungemia at baseline (OR 6.1; 95% CI, 1.1-35.2),\(^10\) higher CSF cryptococcal antigen titer (1:4096 in patients with IRIS versus 1:1024 in those without IRIS, \( P=0.02 \)),\(^54\) and presence of extrapulmonary TB compared with pulmonary TB (OR 8.2; 95% CI, 1.8-37.9).\(^53\) Other risk factors include HIV diagnosis revealed by cryptococcosis (OR 4.8; 95% CI, 1.0-21.7),\(^20\) ART-naive status (RR 3.87; 95% CI, 1.01-14.88),\(^49\) and a more substantial drop in VL (a 2-log\(_{10}\) decrease in VL at 90 days gave an RR of 3.66 [95% CI, 1.55-8.64] compared with a lesser VL response in one study,\(^49\) and a -2.4 change in log\(_{10}\) VL in patients with IRIS compared with a +0.4 change in controls [\( P=0.02 \) found in another study].\(^50\)

The implications for resource-limited settings are significant. As a result of the global roll-out of ART across sub-Saharan Africa, South America, and southern Asia, large numbers of patients with advanced HIV disease and a high burden of serious OIs are initiating ART. It is therefore anticipated that IRIS will represent a significant problem in these settings, as a result of the increased prevalence of risk factors for IRIS such as high rates of prior OIs, lower baseline hemoglobin, lower CD4 count and percent, lower age at commencement of treatment, and greater pathogen burden.

**Clinical Outcomes**

The clinical outcomes of IRIS have not been well documented. The highest rates of morbidity and mortality are seen in cryptococcal disease. In one reported series, the mortality rate exceeded 50%,\(^60\) although it is unclear to what extent this reflects suboptimal management of the underlying cryptococcal infection. TB IRIS is associated with significant mortality, with reports ranging from 11% of individuals with paradoxical TB IRIS\(^52\) to 16%-25% in unmasking TB IRIS.\(^72,73\) Deaths from IRIS are mainly due to the consequences of raised ICP, widespread pulmonary disease, and lesions in critical anatomical regions such as the brain, spinal cord, and trachea.\(^74,77\) Sight-threatening lesions caused by immune responses against cytomegalovirus (CMV) have also been described.\(^23,24\) Dermatological IRIS is common and may have serious consequences for the patient in terms of symptoms, disfigurement, and general well-being. Although IRIS is often self-limiting, it may be prolonged, painful, or disabling and thus warrants prompt diagnosis and management.

Overall, findings from the ART-LINC (antiretroviral therapy in lower income countries) collaboration across multiple sites in sub-Saharan Africa indicate that IRIS might be a significant cause of death during the first few months of ART in resource-limited settings.\(^78\) Mortality was highest in the first year of ART, and mycobacterial disease and CNS infections were the main causes of death.
in a study from Senegal. In South Africa, where *M. tuberculosis* and cryptococcal infections are common, IRIS is estimated to account for around a quarter of deaths and one-fifth of hospital admissions within the first six months of ART.

**Case Definitions**
One of the greatest obstacles to research on the epidemiology and pathogenesis of IRIS has been the lack of a widely accepted case definition or clear diagnostic criteria for IRIS. This is due to the difficulty of establishing generic criteria for a diverse range of clinical conditions and both paradoxical and unmasking IRIS, and limitations in laboratory facilities to support a diagnosis (e.g., histopathological evidence of an inflammatory response). IRIS remains a diagnosis of exclusion, after consideration of adverse drug reactions, new OIs, anticipated disease progression, and microbiologic treatment failure, whether due to drug resistance or malabsorption. Differentiation of IRIS from these other diagnoses has important management implications, and is also necessary for assessing the impact of IRIS on clinical outcome.

Two generic case definitions have been proposed and are summarized in Box 3. The first definition outlines two major and three minor criteria for IRIS, with the requirement of the first major criterion plus either the second major or at least two minor criteria to fulfill the diagnosis. A second definition, proposed by the AIDS Clinical Trials Group (ACTG), is based on three criteria, all of which must be met to diagnose IRIS. The ACTG definition was evaluated in a study in

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**Box 3. Published Case Definitions for IRIS**

**Definition described by French et al**
Must meet both major A and major B criteria, or major A and any two minor criteria.

**Major Criteria A**
- Atypical presentation of opportunistic infections or tumors in patients responding to ART
- Localized disease (e.g., lymph nodes, liver, spleen)
- Exaggerated inflammatory reaction (e.g., severe fever, painful lesions)
- Atypical inflammatory response in affected tissues (e.g., granulomas, suppuration, necrosis, perivascular lymphocytic inflammatory cell infiltrate)
- Progression of organ dysfunction or enlargement of preexisting lesions after definite clinical improvement with pathogen-specific therapy before ART and exclusion of treatment toxicity and new diagnoses

**Major Criteria B**
- Decrease in VL greater than 1 log

**Minor Criteria**
- Increased CD4 T-cell count after ART
- Increase in an immune response specific to the relevant pathogen (e.g., delayed-type hypersensitivity response to mycobacterial antigens)
- Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of ART

**Definition cited by Robertson et al**
Must have all of the following:
- New onset or worsening symptoms of an infection or inflammatory condition following the initiation of ART
- Symptoms not explained by a newly acquired infection, the predicted course of a previously diagnosed infection, or the adverse effects of drug therapy
- Demonstration of a decrease of greater than or equal to 1 log in the number of HIV RNA copies
While the clinical features of IRIS are well documented, the immunopathogenesis (see Figure 2) remains poorly understood. IRIS is thought to be the consequence of restoration of an immune response against an opportunistic pathogen that is excessive and results in immunopathology detrimental to the host. As with the clinical presentation, the pathological and histological features of IRIS are diverse. The immunopathogenic mechanisms also appear to differ according to the type of pathogen. IRIS events associated with infections by intracellular pathogens, such as mycobacteria and fungi, are characterized by

**Figure 2. Summary of pathogenesis of and risk factors for infectious IRIS**

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and regulation of Treg cells in relation to IRIS remain poorly understood. A greater understanding of the immunopathogenesis is essential if prevention and treatment strategies are to be improved, particularly in resource-limited settings where rates of IRIS are high.

DIFFERENTIAL DIAGNOSIS AND INVESTIGATION OF SUSPECTED IRIS

In the absence of a diagnostic test or pathognomonic clinical features, the diagnosis of IRIS remains a process of exclusion. There are several possible explanations other than IRIS for a patient’s deterioration in clinical status after initiating ART (Box 4). The main differential diagnoses with possible paradoxical IRIS are suboptimal primary treatment of an OI (e.g., suboptimal antimicrobial therapy due to inappropriate drug selection or inadequate dosage, poor adherence, or reduced bioavailability resulting from malabsorption or drug interactions), resistance to the primary treatment regimen resulting in ART failure, natural history of underlying OI, newly acquired disease, and drug toxicity. The specific diagnostic workup will depend on the patient’s clinical presentation and the resources available.

Any patient presenting with symptoms suggesting a new OI or an HIV-related condition after ART initiation should be investigated for

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**Box 4. Differential Diagnoses in Patients Experiencing Clinical Deterioration after Initiating ART**

- IRIS—paradoxical reaction (deterioration of known condition that would otherwise be expected to improve)
- IRIS—unmasking (new clinical presentation of undiagnosed but preexisting condition)
- Failure of OI treatment because of drug-resistant organism
- Failure of OI treatment because of nonadherence to OI treatment or prophylaxis
- Failure of ART because of drug resistance
- Failure of ART because of nonadherence to ART
- Failure of OI treatment or ART for other reasons (e.g., malabsorption)
- Newly acquired OI or other condition
- Expected course of preexisting OI or other condition
- Adverse drug reaction

granuloma formation, hypercalcemia, suppuration, and features of a delayed-type hypersensitivity reaction, and have been associated with increased production of interferon gamma (IFN-γ)–secreting antigen-specific T cells. A CD8 T-cell response appears to predominate in IRIS associated with some viral pathogens, such as herpes zoster, CMV, hepatitis C, or HHV-8. Common features of some types of IRIS are the production of proinflammatory cytokines (such as IFN-γ and interleukin [IL]-6) and lower concentrations of mediators (such as IL-10 and IL-2), polymorphisms of cytokine genes and major histocompatibility complex (MHC) haplotypes have been identified as genetic markers of increased risk of IRIS.

It has also been proposed that IRIS may result from an imbalance of pathogen-specific effector and regulatory cellular immune responses shortly after initiation of ART. In particular, defective functioning of regulatory T cells (Tregs), the centrally important T cells in the regulation of cellular immune responses, may contribute to the immunopathogenesis of IRIS. For example, with TB IRIS, a slow reconstitution of *M. tuberculosis*–specific Treg cells as compared to the corresponding T effector cells may lead to the loss of control of inflammatory CD4 T-cell responses against active TB and lead to “paradoxical” TB-IRIS. However, the processes involved in the induction
treatment failure due to either nonadherence or drug resistance to both ART and other antimicrobial therapy. ART failure may be defined using clinical, immunological, or virological criteria and is covered in detail in the chapter entitled “Antiretroviral Treatment Failure, Drug Resistance, and Management of Therapy-Experienced Patients.” Although virological criteria provide the most objective assessment of treatment failure, VL assays are unavailable in many clinical settings, and so immunological criteria based on the absolute CD4 count are often used. However, this may be of limited value in discriminating between treatment failure and IRIS, as the latter can emerge in the absence of a good CD4 response. Overall, a rising CD4 count is more useful in supporting a diagnosis of IRIS than a falling CD4 count is in excluding it.

Exclusion of a clinical presentation consistent with the predicted course of a known OI as a differential diagnosis is problematic because some OIs (e.g., cryptococcal meningitis, progressive multifocal leukoencephalopathy [PML]) can deteriorate in patients despite appropriate antimicrobial therapy, as a result of overwhelming infection or poor immune status. In addition, conditions such as chronic diarrhea and eosinophilic folliculitis may undergo a relapsing/remitting course despite ongoing therapy.

The differential diagnosis of unmasking IRIS mainly includes newly acquired OIs and the emergence of latent infections due to immunosuppression. When dealing with infections that are endemic in the population, making that distinction can be challenging, even when sophisticated imaging or histology is available. A detailed clinical history and examination performed before starting ART may often identify minor or moderate symptoms that can be attributed retrospectively to a subclinical process that was unmasked by ART.

A temporal relationship with the initiation of ART is the most consistent feature of IRIS. Of 11 studies reporting the median time between the start of ART and the onset of IRIS, 9 studies reported an interval of less than three months. The two outlying estimates are 20 weeks and 34 weeks, the latter being in a cohort of patients with cryptococcal disease. It may be that some OIs, such as cryptococcosis, have long latencies before IRIS onset, whereas others, such as TB, occur much earlier (e.g., after a median of 2 weeks in two studies). As a general rule, IRIS should be considered as a possible diagnosis whenever a clinical problem presents less than three months after commencement of ART.

**PREVENTION OF IRIS**

At present, there are no evidence-based guidelines to treat or prevent IRIS. Given present knowledge, some recommendations to prevent IRIS can be made. A low CD4 count has been identified as a risk factor for IRIS in a range of clinical settings; therefore, initiation of ART at an earlier stage of disease would be associated with a lower rate of IRIS. This clearly presents challenges in resource-limited settings, where patients are often diagnosed with HIV and initiate ART at a late stage of disease.

A short duration of OI therapy at the start of ART has been identified as a further risk factor for IRIS in several studies. Therefore, delaying ART until at least two months of OI therapy have been completed would lower the pathogen burden and reduce the risk of IRIS. However, the potential benefits of delaying ART to prevent IRIS in patients receiving treatment for an OI need to be weighed against the risk of developing other OIs if ART is delayed. A recent trial in patients with non-TB OIs showed decreased rates of AIDS progression and death in patients initiating ART at a median of 12 days after initiation of OI therapy versus 45 days (14% vs. 24%, respectively) with
and life-threatening disease requiring temporary interruptions of ART and use of aggressive anti-inflammatory therapy. Because of the wide and varied clinical spectrum of IRIS, it is impossible to list all the possible scenarios and management steps required. Table 3 and Figure 3 provide a broad summary of the key considerations in the evaluation and management of IRIS.

**Decision to Continue ART**

Illnesses occurring early after initiating ART may have an impact on adherence. It is therefore important that patients are informed in advance about potential IRIS and advised that this is part of the process of immune recovery and not a reason to discontinue ART. ART will usually only need to be discontinued in exceptional circumstances of serious, life-threatening IRIS events. For patients with hepatitis, uncertainty may surround the relative contributions of drug toxicity and IRIS to the condition, because abnormal liver function tests may result directly from ART toxicity. Furthermore, patients with mycobacterial infections may present with liver enzyme abnormalities suggestive of hepatic infiltration caused by either disease progression or IRIS while taking hepatotoxic antimycobacterial drugs.

In cases of cutaneous eruptions, it is usually possible to distinguish the appearance of typical

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical approach</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Paradoxical IRIS (worsening of known infection or condition) | ■ Patient education  
■ Recognition of possible IRIS diagnosis  
■ Consider secondary diagnoses | ■ Continue ART; may stop if IRIS is life threatening  
■ Optimize pathogen treatment and complete course  
■ Consider steroids |
| Unmasking IRIS (emergence of undiagnosed infection or condition) | ■ Symptom-directed screening  
■ Patient education  
■ Expect atypical presentation | ■ Continue ART; may stop if IRIS is life threatening  
■ Treat new pathogen  
■ Consider steroids |

**Table 3. Clinical Management of IRIS**
Specific treatment of the OI or Inflammatory Condition

Antimicrobial therapy will depend on the nature of the causative pathogen and whether it is a paradoxical or unmasking event. Treatable OIs that may be unmasked by IRIS include mycobacterial diseases and fungal and parasitic infections. Although their presentations may be atypical, the treatments for these infections should follow standard local management. If IRIS is the most likely diagnosis, and OI therapy is already optimal, and the associated clinical manifestations are serious, consideration...
should be given to the use of corticosteroids or other immunomodulatory therapy (discussed in the next section). In cases of space-occupying lesions in the CNS (e.g., cryptococcomas or tuberculomas), raised ICP with a reduced level of consciousness or other neurological deficit, respiratory failure, lesions close to major airways, or other critical situations, it is wise to intensify antimicrobial treatment and add an immunosuppressant agent such as dexamethasone. Cryptococcal meningitis IRIS should not require intensification of antifungal therapy unless cryptococcal treatment failure is suggested by persistently positive CSF fungal cultures or India ink staining. Paradoxical cryptococcal peripheral lymphadenitis may be managed conservatively unless fluconazole resistance is suspected. Most cases reported in the literature have been managed by an increase in fluconazole dosage, although no evidence supports the practice.

OIs that result in latent or persistent infections, such as HSV, human papillomavirus, hepatitis B and C, and VZV, may present as IRIS. Genital HSV is often clinically indistinguishable from other ulcerating sexually transmitted infections (STIs), such as syphilis, chancroid, or lymphogranuloma venereum. Local antibiotic protocols for STIs should be used to manage these conditions. Both unmasking and paradoxical IRIS may be self-limiting and thus amenable to conservative management in less severe cases.

Inflammatory dermatoses, such as papular pruritic eruption and eosinophilic folliculitis, are often associated with IRIS. Treatment typically consists of mild to moderate topical steroids and an oral antihistamine. Treatment is usually continued for one to two months until the condition resolves. If an initial response to therapy does not occur and the dermatosis is disfiguring or disabling, dermatological advice should be sought.

**Role of Immune-Modulating Drugs**

Few data are available from randomized controlled trials on the use of corticosteroids or other immunomodulatory drugs in the treatment of IRIS. There are, however, several case reports of good response to different treatments, including non-steroidal anti-inflammatory drugs (NSAIDs) for cryptococcal lymphadenitis, thalidomide for TB and cryptococcal IRIS, montelukast for leukocytoclastic vasculitis and urticaria, and infliximab for a paradoxical reaction to CNS TB in an HIV-negative patient. High doses of corticosteroids (prednisone 0.5 to 1.5 mg/kg daily) have been used in a range of settings. In patients on ATT, an important pharmacokinetic interaction between rifampin and prednisone requires an increase in the dose of prednisone. The use of corticosteroids to suppress an immunopathological response as treatment for mild to moderate TB IRIS has also been examined in a randomized controlled trial. This South African study of 109 subjects found a significant reduction in the number of hospital days among patients treated with four weeks of high-dose prednisone compared to placebo (282 vs. 463 days of hospitalization and 29 vs. 38 procedures, respectively) with no overall difference in deaths or adverse drug reactions.
Box 5. Key Points

Chapter Key Points Summary

- IRIS occurs in 10%–40% of patients, usually within three months of starting ART.
- IRIS may occur in response to a wide range of infections and other diseases.
- There are two main scenarios of IRIS: paradoxical deterioration and unmasking of an undiagnosed condition.
- The epidemiology of IRIS in resource-limited settings is not well described.
- Risk factors for IRIS include advanced immunosuppression and short duration of treatment for an OI before initiation of ART.
- Alternative diagnoses include treatment failure, new infections, adverse drug effects, and expected course of a known condition.
- ART should be continued in most cases of IRIS.
- OI treatment may need to be intensified in some situations.
- Corticosteroids or other anti-inflammatory drugs are often used in severe or serious cases of IRIS; however, the evidence in support of their use is weak.
- IRIS may be prevented or anticipated by careful assessment before initiating ART and a good understanding of the risk factors.
Immune Reconstitution Inflammatory Syndrome: Color Plates

Plate 1: Mycobacterial lymphadenitis and abscess presenting as IRIS

Plate 2b. Chest X-ray after four weeks of ART, after complaints of night sweats, weight loss, and cough

Plate 2a. Chest X-ray prior to ART (patient was asymptomatic for TB)

Plate 3. Soft tissue swelling adjacent to the right breast that yielded Cryptococcus neoformans on microscopy and culture
Immune Reconstitution Inflammatory Syndrome: Color Plates (cont.)

Plate 4a.

Plate 4b.

Plate 4c.

Plate 5. Immune reconstitution oral herpes simplex presenting de novo in an adult patient with an otherwise good response to ART, four months into therapy.

Plates 4a–c. Eosinophilic folliculitis on the forehead and chest of three different patients, arising within the first three months of ART.
REFERENCE LIST


associated with unmasking and paradoxical presentations of TB IRIS. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, QC, Canada. Abstract 773.


INJECTION DRUG USE AND THE RELATED practices of sharing injection equipment are a major driver of the HIV epidemic in many parts of the world. One-third of new HIV infections outside sub-Saharan Africa are related to injection drug use. In the explosive epidemics seen in such regions as Eastern Europe and Central Asia, more than 80% of HIV cases are related to injection drug use.\textsuperscript{1,2} Injection drug use is also emerging as a public health concern in areas of Africa, particularly Kenya, Tanzania, South Africa, Nigeria, and Mauritius.\textsuperscript{3} In 2005, 90% of new HIV cases in Mauritius were related to injection drug use, up from 7% of cases in 2001.\textsuperscript{3} HIV prevalence among injection drug users in Mombasa, Kenya, and South Africa has been reported as 31% and 28%, respectively.\textsuperscript{1,3}

Sexual transmission from injecting drug users living with HIV to their sex partners is an important secondary route of spread, extending to perinatal transmission of HIV. Injecting drug users are often the conduit through which the virus moves from high-risk populations into the general population. Women who are not participating in any high-risk behaviors are often infected with an HIV-positive partner with a remote or recent history of injection drug use (while in a monogamous relationship). Injecting drug users who are incarcerated may also acquire HIV infection through sexual contact in prison, with subsequent exposure of their spouses, sexual partners, and children upon release. From a public health perspective, an important rationale for treating injecting drug users and keeping them in care is the role that high-risk behaviors play in the spread of HIV infection into the general population. Programs that reach out and engage injecting drug users and assist them in commencing drug or substitution therapy treatment can help reduce high-risk behaviors through better access to social services (housing, food). Such programs can also provide HIV-related services to this highly vulnerable population, which in turn can have a significant impact on limiting the growth of the HIV epidemic.

Injection drug use presents many challenges to the HIV health-care provider. Injecting drug users are often burdened by issues of adherence, addictive behavior, mental illness (depression more commonly than psychosis), and coinfection with hepatitis B, hepatitis C, and TB, along with recurrent bacterial infections. Limited availability of effective drug treatment in many resource-limited settings, and restrictive policy environments marked by harassment and social stigma, contribute to the
marginalization of injecting drug users and foster the silent expansion of the HIV epidemic. The complexity of these social, medical, and treatment issues often makes the injecting drug user difficult to identify and enter into and retain in care. For these reasons, targeted strategies are needed that foster unique alliances between medical treatment services, social services, drug treatment professionals, law enforcement, and civil society in order to create and sustain an effective interface with injecting drug users and address their HIV prevention and treatment needs over the course of disease.

There is abundant evidence that injecting drug users can be engaged and retained in medical treatment for HIV and that treatment outcomes on antiretroviral therapy (ART) are often equivalent to or better than those of non-injection-drug-using patients. Integrated approaches that involve knowledgeable medical providers, peer education and support, community services, and drug treatment (e.g., concurrent opioid substitution therapy), as well as various models of directly observed therapy, have all been shown to increase the adherence and retention of injecting drug users in care.

This chapter will address the issues that affect access to effective HIV treatment among injecting drug users, followed by a review of the medical management of HIV-positive injecting drug users, including the provision of ART. A summary of prevention strategies and the role of the medical provider in developing continua of prevention and treatment is also provided.

ACCESS TO HIV TREATMENT

Suboptimal access to effective ART and opportunistic infection prophylaxis by HIV-positive injecting drug users has been documented in numerous studies. Among the factors contributing to this lack of access are the negative attitudes of some medical providers toward injecting drug users and perceptions that they are unable to adhere to medication regimens. In a recent national survey of HIV-positive patients and their physicians (in the United States), 23% of patients were receiving care from physicians who harbored negative attitudes toward injecting drug users, reflected by their agreement with statements such as “treating injecting drug users seems futile” and “when given a choice, I would not treat injecting drug users with HIV infection.” Medical providers may hold the beliefs, commonly found in society at large, that drug users have brought their illness upon themselves, that drug users don’t care about their health, and that the injecting drug user is essentially a different type of person from the rest of the population. Allowing generalized thinking or biases toward a group to influence therapeutic decision making for an individual is fraught with ethical problems.

These personal biases are often compounded by a lack of professional training in substance abuse disorders, which can lead to misunderstanding and frustration on the part of physicians when dealing with the physiological and psychological aspects typical of chronic addiction. Many physicians fail to understand the chronic and relapsing nature of substance abuse and lack appreciation of substance abuse as a biological and medical disease that is compounded by a high rate of coexisting mental illness. Drug treatment strategies and the nature of addiction are generally not part of traditional medical training, and a climate of mutual distrust between providers and patients is common. For instance, patients may feel they are being intentionally mistreated or punished for their addiction by their provider. That perception must be modified by providing appropriate training to increase provider competence and confidence in working with injecting drug users, aided by a thorough understanding of the natural history of addiction that helps them to form realistic expectations for these patients.

It is imperative that health professionals realize the role an overtly judgmental attitude plays in
preventing injecting drug users from being engaged and retained in care. It is not the role of the provider to judge someone’s behavior, as civil society assumes this function. The attitude of medical providers related to drug abuse is critical to the development of a trusting relationship with their patients (see Box 1). Clinicians who openly diminish the needs, complaints, or requests of patients with addiction are frequently excluded from decisions that influence a patient’s ability to maintain adherence to or enter into long-term care. The injecting drug user must feel embraced and respected in the treatment setting, and it is the responsibility of the provider to make sure that occurs.

The ability of injecting drug users to access prevention services and medical treatment for HIV is also frequently limited by other structural factors, such as discrimination, poverty, and criminalization of drug-related behavior. When given equal access to care, injecting drug users are less likely to have undetectable viral loads; however, when adherence factors are adjusted for, injecting drug users and non–drug users who achieve viral suppression have similar rates of viral load suppression and rebound, suggesting that other barriers exist to successful treatment that must be taken into account when planning services. The presence of comorbidities such as mental illness and polysubstance use (including alcohol abuse) can affect housing stability, food security, and personal safety, resulting in immediate needs that may overshadow health-seeking behaviors or engagement in care. However, the data are clear that injecting drug users can effectively follow ART regimens and remain in care and treatment, with the same or better outcomes than people without a history of injection drug use.

Active drug use itself does not decrease the effectiveness of ART. Rather, among active users, the success or failure of treatment correlates to the degree to which active drug use results in disruption of the patient’s daily activities. Injecting drug users in supportive treatment environments have been shown to have comparable adherence rates, drops in viral load, and increases in CD4 lymphocyte counts as non-injecting drug users. When injecting drug users are successful in achieving durable undetectable viral loads, they experience the same positive clinical outcomes as non-injecting drug users. It is important to note that providers should not withhold ART or require ongoing treatment for substance abuse as a prerequisite for starting ART. When additional comorbidities, such as alcohol abuse and/or psychiatric illness, are present, special strategies need to be developed to identify, enter, and retain the patient in a continuum of medical care. That continuum can facilitate access to medical treatment, psychiatric care, social services, and harm-reduction strategies throughout the course of the patient’s illness.

Different models exist for delivery of primary care to HIV-positive injecting drug users. Medical care combined with psychiatric services, social

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Box 1. Principles to Enhance Patient-Provider Interaction

Providers should discuss the following key points with their patients regarding HIV and addiction:
- Physical/psychological effects of continued drug use
- Impact of drug use on the spread of HIV
- Benefits to the patient from both drug treatment and HIV treatment
- Impact of drug use on adherence

To foster a climate of mutual respect, the patient and provider should do the following:
- Agree on the respective roles of the patient and provider
- Set appropriate limits and, if needed, establish a patient-provider contract (e.g., “patient agrees to be truthful about concomitant drug use”)
services, and harm-reduction interventions are the core services needed, along with case management. Patients are often followed up with at a primary care clinic by case managers and/or counselors. Primary medical care can be provided on-site at drug treatment programs, or a substance abuse treatment component can be brought into an HIV primary care clinic. Integration of HIV treatment within opioid substitution therapy programs (i.e., methadone, buprenorphine) has also been implemented in some settings. Other approaches, such as directly administered antiretroviral therapy and modified directly observed therapy (MDOT) (i.e., three to five days of directly observed therapy [DOT], then self-administered two to three days per week), have been used to increase adherence and successful treatment outcomes among injecting drug users and others with substance abuse issues. However, both DOT and MDOT should be reserved for those who are not optimally adherent to ART, as such strategies are generally not needed for all injecting drug users. The role of peer educators and/or community support should be emphasized as well; HIV-positive injecting drug users on ART can be very effective in helping other patients live with their disease and manage their medications effectively.

**MEDICAL MANAGEMENT OF HIV INFECTION IN INJECTING DRUG USERS**

**Natural History of HIV Infection**

Most epidemiological data have found no difference in HIV progression between injecting drug users and non-injecting drug users in the pre-ART era. A study of 639 women over a seven-year period identified no difference in progression to AIDS between women who had past, current, or no history of injection drug use. Some in vitro and laboratory-based studies suggest that cocaine, methamphetamine, and heroin promote HIV replication, but the relevance of this to clinical outcomes has not been demonstrated. Two studies of a large urban cohort post-ART found that self-reported heroin and cocaine use were temporally associated with the development of new AIDS-defining conditions. The observation of more rapid HIV disease progression among injecting drug users relative to other risk groups may be related to the higher prevalence of comorbidities such as hepatitis B and C, late initiation of ART, or poor adherence. Early case identification combined with harm-reduction measures, drug treatment, and treatment of coinfections holds the potential to change this trajectory.

A prevention opportunity exists in the active using population of injecting drug users. A needle exchange strategy for HIV-negative active injecting drug users can reduce HIV transmission as well as transmission of hepatitis C virus (HCV) and hepatitis B virus (HBV). In addition, targeting HIV-negative active injecting drug users for early detection of primary infection provides an opportunity to prevent transmission before newly infected individuals seroconvert.

**Approach to the Patient**

Substance abuse often goes unrecognized by clinicians unless a careful history is taken along with a physical exam. The presence of a substance abuse diagnosis may reveal multiple comorbidities that bear on both diagnostic and care decisions. Medical systems are prejudicial toward the active injecting drug user, and the social and legal implications of a diagnosis of active substance abuse for the patient must be acknowledged. It is important to take the time to understand the unique characteristics of the injecting community and the social system of the injecting drug user, both to better inform medical care and to take advantage of the opportunity to promote prevention measures that can reduce health risks for sexual and injection-equipment-sharing partners.
Providing HIV care for active injecting drug users presents unique and sometimes overwhelming challenges. Many of the HIV epidemics in Russia, Ukraine, Vietnam, and some communities in Thailand have been driven by injection drug use. Providing HIV care is made all the more difficult by the stigmatization and criminalization of substance use in these settings. In many parts of the world, active substance use is not seen within the context of a medical condition, but rather within the context of criminal behavior that warrants punishment. This unfortunate reality makes providing HIV care to substance users all the more difficult and, paradoxically, can also make providing effective treatment for substance abuse more difficult.

First and foremost, individuals engaging in substance use need to be enrolled in a care program that emphasizes trust and builds a relationship with the patient based on compassionate care. This will lead to an open exchange of information in which the care provider can address the multiple ongoing issues facing substance users, including the need for substance abuse treatment, safer injection practices, and violence avoidance, as well as medical treatment for TB, bacterial infections, and HIV/AIDS. Care providers can begin to address the complex social challenges facing injecting drug users only after they have established trust and rapport with their patients.

Most injecting drug users who enter into care will be symptomatic with bacterial skin infections, pneumonia, active TB, or opportunistic infections. The priority is to treat the opportunistic infections and then to begin ART as soon as possible. TB may be the most common opportunistic infection in HIV-positive injecting drug users. The presence of TB infection will require diagnostic studies and initiation of anti-TB therapy that utilizes four drugs for patients with active disease.

Injecting drug users presenting with bacterial infections, TB, skin infections, or frank opportunistic infections should routinely be offered HIV testing. HIV testing should be offered frequently and routinely both for symptomatic and asymptomatic injecting drug users. Each HIV test represents an opportunity to reinforce risk-reduction messages as well as to inform both the individual patient and, through the patient, the substance-using community that effective treatment for HIV infection is available.

Although the challenges of providing HIV care for substance users are formidable, the rewards can be great. Many people with active substance use have never been treated with care, compassion, and respect. The provision of compassionate HIV care can serve as an impetus for such people to enter substance abuse treatment and turn around their lives. In this way, HIV treatment can be a transforming event that is highly rewarding for both the patient and care provider.
Empathy and a nonjudgmental approach are critical in obtaining a comprehensive and accurate history of substance abuse, including alcohol, illicit/recreational drugs, and prescription opiates and benzodiazepines. Understanding that addiction may involve multiple substances can make taking a history more complex. Medical schools often do not emphasize the complex medical and psychosocial aspects of treating the active injecting drug user who is HIV infected. The use of stimulants (i.e., sympathomimetics) and alcohol are associated with increased sexual activity, which can place the injecting drug user at an even greater risk of acquisition and transmission of HIV.

**History Taking and Physical Examination**

The key points to look for when taking the history of an injecting drug user are summarized in Box 2. Common findings to look for during the physical examination that will provide information about recent substance use, withdrawal status, and intoxication are provided in Box 3. Complications related to end organ damage to the heart, kidney, liver, and lungs may also be identified.

There are a number of physical findings seen in HIV-positive injecting drug users that can be due to HIV infection, HIV-related opportunistic infection, or substance abuse (see Table 1). Since the etiology of these findings can be difficult to differentiate, a careful history and physical examination, as well as clinical monitoring, may be required to arrive at an accurate determination of the cause.

**Bacterial Infection of the Skin and Heart Valves**

Bacterial infections, including pneumonia, endocarditis, and sepsis, are common among both HIV-positive and HIV-negative injecting drug users. Pneumonia is four times more common in HIV-positive injecting drug users than in those who are HIV-negative, with *Pneumococcus* and *Haemophilis influenzae* being the most common pathogens. There is an increased incidence of Gram-negative pneumonia among active injecting drug users, especially with concomitant alcohol use. Due to the potential for an altered mental status causing somnolence, opiate-addicted patients have a higher incidence of aspiration pneumonia with mixed aerobic and anaerobic infections. It is important to remember that the majority of patients respond well to appropriate antibiotic treatment guided by culture and sensitivity tests.

Generalized lymphadenopathy was a common clinical manifestation of HIV disease in the pre-ART era, and swelling of four or more lymph node groups is still a common clinical presentation of AIDS. Injecting drug users often have swollen lymph nodes as a result of chronic and recurrent antigenic stimulation of the regional lymph nodes (i.e., epitrochlear and axillary) that drain the most frequently used injection sites. Bacterial infection (lymphadenitis and subcutaneous abscess) must be ruled out in such cases.

During physical examination, the common manifestations of acute and subacute bacterial endocarditis should be looked for. Those include both immunological (e.g., Janeway lesions on the fingers or toes, Roth’s spots) and embolic phenomena (e.g., Osler’s nodes, splinters in the nail bed, hematuria, amaurosis fugax, etc.). Signs of hypotension, vasodilatation, and diminished renal output may be reflective of congestive heart failure due to a variety of causes (e.g., valvular heart disease).

**HIV and TB Coinfection**

The association of HIV and TB in the injecting drug user population has been well established worldwide. Before the emergence of the HIV epidemic, injection drug use was recognized as an independent risk factor for TB; low socioeconomic status, homelessness, poor nutrition, overcrowding,
of continuous anti-TB therapy. As with ART, the approach to TB treatment should be informed by the patient-provider partnership and tailored to the circumstances of the individual patient. In some cases, variations on the DOT model may be needed for patients having difficulty with adherence. It is generally recommended that treatment of active TB be continued for two months before initiation of ART, to avoid precipitating immune reconstitution inflammatory syndrome.23

Drug interactions associated with HIV-TB cotreatment include the potential interaction of rifamycin-based medications with both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). These interactions can result in subtherapeutic serum drug levels of various antiretroviral drugs (ARVs) (e.g., nevirapine, PIs, maraviroc, raltegravir). Further information on potential drug interactions can be found elsewhere in this volume.

### Box 2. History Taking for Injecting Drug Users

<table>
<thead>
<tr>
<th>Drug Use Patterns</th>
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</thead>
<tbody>
<tr>
<td>Screen for and/or identify multiple substances</td>
</tr>
<tr>
<td>Route of administration over time (e.g., intravenous, subcutaneous, inhaled, intranasal, oral, sublingual, anal, etc.)</td>
</tr>
<tr>
<td>Pattern of use (e.g., amount, frequency, most recent use, injection practices, sharing of needles or injection equipment)</td>
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<table>
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<tr>
<th>Treatment History (Inpatient and Outpatient)</th>
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</thead>
<tbody>
<tr>
<td>Drug treatment history</td>
</tr>
<tr>
<td>Pharmacologic treatment history, including opioid substitution therapies</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Complications of Substance Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle-induced: bacterial, viral, or fungal infections; peripheral vascular disease</td>
</tr>
<tr>
<td>Drug-induced: overdose, withdrawal, organ-specific complications (e.g., nephropathy due to heroin; cardiac ischemia due to cocaine; gastrointestinal, cardiac, and neurologic disease due to alcohol)</td>
</tr>
<tr>
<td>Other: hepatitis C, hepatitis B, sexually transmitted diseases (may be related to exchanging sex for drugs)</td>
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</tbody>
</table>

<table>
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<tr>
<th>Social Complications of Substance Abuse</th>
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</thead>
<tbody>
<tr>
<td>Unemployment</td>
</tr>
<tr>
<td>Family disruption</td>
</tr>
<tr>
<td>Legal problems</td>
</tr>
<tr>
<td>Homelessness</td>
</tr>
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</table>

Source: O’Connor et al.17

HIV-positive injecting drug users are at a much higher risk for TB infection, and for progression from latent infection to active TB, compared with HIV-negative injecting drug users and the general population.28 Although TB is predominately a pulmonary infection, up to 40% of HIV-positive patients may develop extrapulmonary disease.28 A full discussion of the diagnosis and treatment of HIV-TB coinfection is provided elsewhere in this volume. Adherence to TB medications for the full course of therapy is the most important factor in determining treatment outcomes, with excellent results expected within six to nine months of continuous anti-TB therapy. As with ART, the approach to TB treatment should be informed by the patient-provider partnership and tailored to the circumstances of the individual patient. In some cases, variations on the DOT model may be needed for patients having difficulty with adherence. It is generally recommended that treatment of active TB be continued for two months before initiation of ART, to avoid precipitating immune reconstitution inflammatory syndrome.33

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The choice of ARV regimens should be informed by the HBV and HCV status of HIV-positive injecting drug user patients. For patients ready to start ART, the antiviral effect of lamivudine and tenofovir is beneficial due to the anti-HBV activity of these drugs. Providers should be aware that the discontinuation or switching of these drugs can trigger a reactivation or flare of acute HBV.

Underlying hepatic disease in injecting drug users also complicates the diagnosis of liver function abnormalities that can result from toxicity to ART regimens and other commonly used medicines in HIV care (e.g., trimethoprim-sulfamethoxazole, rifampin, pentamidine, dapsone, isoniazid, pyrazinamide, etc.). Chronic HCV infection is associated with an increased risk of drug-induced hepatotoxicity, requiring closer monitoring of serum transaminases and patient symptoms until patients are stable on a specific ART regimen.

**HIV and Hepatitis Coinfection**

Injecting drug users are at high risk for all forms of infectious hepatitis and alcoholic hepatitis. HCV/HBV and HIV are all most efficiently spread through direct exposure to contaminated blood, which may remain on used needles or injection equipment. Incidence of HIV and HCV coinfection varies depending on individual risk behaviors, but prevalence rates of 70% to 80% have been reported among injecting drug users. Liver disease due to chronic HBV and HCV infection is becoming a leading cause of death among HIV-positive individuals worldwide, highlighting the need to pursue prevention strategies, including the supplying of single-use or sterilized injection equipment and, for those with a CD4 lymphocyte count of greater than 200 cells/mm³ (i.e., those able to mount a protective immune response), provision of hepatitis B vaccine.
infection on the rate of HIV disease progression are less clear cut, with conflicting study findings.31,33 The standard of care for HCV-HIV coinfected patients is pegylated interferon alfa plus ribavirin. All patients should be counseled to eliminate alcohol intake and acetaminophen use, and the emphasis should be on selecting an ART regimen with a lower hepatotoxicity profile and ramping up support for adherence.

### Hepatitis C Coinfection

The natural history of HCV infection is accelerated in patients living with HIV, with an increased rate of progression to cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death.31 Combination ART that results in restored immune function has been shown to decrease the rate of death due to HCV liver disease.32 However, the effects of HCV infection on the rate of HIV disease progression are less clear cut, with conflicting study findings.31,33 The standard of care for HCV-HIV coinfected patients is pegylated interferon alfa plus ribavirin. All patients should be counseled to eliminate alcohol intake and acetaminophen use, and the emphasis should be on selecting an ART regimen with a lower hepatotoxicity profile and ramping up support for adherence.

### Table 1. Possible Causes of Common Symptoms in HIV-Positive Injecting Drug Users

<table>
<thead>
<tr>
<th>Constitutional Symptoms</th>
<th>HIV-Related Causes</th>
<th>Substance-Abuse-Related Causes</th>
</tr>
</thead>
</table>
| Anorexia, weight loss, fever, night sweats, diarrhea | - Primary HIV infection  
- Mycobacterium avium intracellulare (MAI)  
- Tuberculosis  
- Cytomegalovirus (CMV) (gastrointestinal or pulmonary)  
- Early bacterial process | - Cocaine use  
- Acute bacterial endocarditis  
- Subacute bacterial endocarditis  
- Opiate withdrawal |
| Pulmonary Dyspnea, chest pain, cough | - Bacterial pneumonia  
- Pneumocystis pneumonia  
- Tuberculosis  
- Kaposi’s sarcoma  
- MAI  
- CMV of the lung  
- Lymphoma | - Cocaine use  
- Tobacco use  
- Aspiration pneumonia  
- Multiple pulmonary emboli  
- Right-sided subacute bacterial endocarditis |
| Neurologic Altered mental status, psychosis, seizures, focal deficits, peripheral neuropathy | - HIV infection  
- Cryptococcosis  
- Toxoplasmosis  
- CMV  
- Tuberculosis  
- Progressive multifocal leukoencephalopathy  
- Kaposi’s sarcoma  
- Lymphoma  
- Human T-cell lymphotropic virus type 1 | - Intoxication or withdrawal from opiates, cocaine, alcohol, or benzodiazepines  
- Drug-related chronic encephalopathy  
- Pyogenic central nervous system infections  
- Trauma  
- Alcoholic polyneuropathy |
| Dermatologic Pruritus, rash, purpura, vesicles | - HIV-related dermatitis  
- Psoriatic changes  
- HIV-related thrombocytopenia  
- Medication allergy, toxicity  
- Herpes simplex  
- Herpes zoster  
- Molluscum contagiosum  
- Cat scratch (toxoplasmosis) | - Drug-related pruritus  
- Cellulitis  
- Abscess (sterile/bacterial)  
- Alcohol- or heroin-induced thrombocytopenia  
- Lymphedema  
- Chronic hepatitis |

Source: Adapted from O’Connor et al.36
Hepatitis B Coinfection
HBV infection in HIV-positive persons increases the risk of cirrhosis, end-stage liver disease, and death, particularly in patients with a low CD4 lymphocyte count or alcohol use. Injecting drug users may contract HBV through blood-borne exposure from injection practices, or through sexual transmission. The prevalence of HBV-HIV coinfection is lower than that of HCV-HIV coinfection in the United States (5% to 10%) and Asia (20% to 30%), but may be higher within smaller communities of injecting drug users.\textsuperscript{30,31} Chronic HBV infection develops in 20% of HIV-positive adults following HBV exposure.\textsuperscript{31} HIV-positive patients should be vaccinated against both HBV and hepatitis A, due to the increased severity of hepatitis in patients with preexisting liver disease. For all nonvaccinated injecting drug users, vaccination is a critical primary care intervention before immune damage becomes severe. A more detailed discussion of HBV-HIV coinfection is provided elsewhere in this volume.

Sexually Transmitted Infections
Sexually transmitted infections (STIs) have long been associated with substance abuse, both due to the frequent exchange of sex for money and the sexual disinhibition that results from sympathomimetics (e.g., cocaine) and alcohol alone or in combination. Cocaine, crack, and alcohol use have been linked to an increased risk of syphilis and other ulcerative genital infections.\textsuperscript{34,35} Medical providers should remain alert to the risk of STIs in patients who may be engaging in transactional sex for drugs. There is also a high risk of cervical dysplasia and cancer associated with human papillomavirus. High false-positive rates of rapid plasma reagin in injecting drug users favor the use of the fluorescent treponemal antibody-absorption test to screen for syphilis in this population. HIV-positive injecting drug users with genital herpes may require longer therapy and suppressive dosing for symptom recurrence; fungal infections also require longer initial therapy, with continued suppression often needed due to the frequent recurrence of symptoms.

Cancer
There are reports that injecting drug users experience a more aggressive clinical course for cancer compared with non-injecting drug users at the same stage of disease. Cancer of the lung is seen in injecting drug users as young as 30 to 40 years of age and is particularly aggressive.\textsuperscript{36,37} Lack of recognition of Kaposi’s sarcoma by physicians who are not primed to recognize this condition may explain the low reported incidence of Kaposi’s sarcoma in injecting drug users; for instance, multiple skin lesions resulting from injection practices can complicate the detection of developing Kaposi’s sarcoma. At present, there are no data on the prevalence or outcomes of lymphoma in injecting drug users.

Psychiatric Illness and Cognitive Dysfunction
In developed countries, there is a significant coexistence of psychiatric disorders among HIV-positive injecting drug users, with disorders in this group occurring at a rate roughly 6% higher than in the general population. Among those with active addictions to opioids, the lifetime rate of major depression is greater than 53%, compared with greater than 40% among cocaine users, and greater than 35% among heavy alcohol users. Other affective disorders include antisocial personality disorders and anxiety. Providers working with injecting drug users must actively screen for suicidal tendencies among their patients, as well as be ready to intervene with multidisciplinary treatment plans when paranoia and psychosis are identified. These disorders can be difficult to differentiate from organic syndromes directly related to HIV infection or chronic secondary infections and malignancies. A higher index of suspicion should be maintained.
are consistent with the revised U.S. Department of Health and Human Services ARV guidelines, which recommend maximizing the preservation of immune function in HIV-positive individuals.23

Considerations guiding the selection of ARV regimens for injecting drug users include (1) presence of HBV and/or HCV coinfection; (2) side-effect profiles; (3) preexisting psychiatric illness (if efavirenz is being considered); (4) drug interactions, including ARV-methadone interactions; and (5) complexity of the regimen in terms of pill burden and dosing frequency. The benefit of lamivudine and tenofovir for patients with HBV-HIV coinfection has been previously discussed. Switching an HBV-positive patient off a regimen containing lamivudine or tenofovir can trigger a moderate to severe reactivation of HBV disease due to a rebound of HBV viral loads.

Due to the higher incidence of hepatic, renal, gastrointestinal, and hematologic diseases in injecting drug users, they are more likely to experience ARV-related side effects and toxicities. Baseline assessment of HBV and HCV status is required, along with serum transaminases at baseline and at frequent intervals during the first three months of therapy in HBV-positive or HCV-positive patients. Although nevirapine can be used safely in these patients with close monitoring, less hepatotoxic agents may be preferred where available. Use of nevirapine should, however, be avoided in women with baseline CD4 counts greater than 250 cells/mm³ and in men with baseline CD4 counts greater than 450 cells/mm³. Impaired renal function in patients with a history of glomerulonephritis would indicate caution in the use of tenofovir or indinavir.23 A common side effect when starting efavirenz is vivid nightmares for the first month of treatment, along with less frequently reported dizziness, hallucinations, and mood changes.23 More severe mental illness, including rapid development of psychosis, has rarely been reported. Clinicians...
should exercise caution when considering the use of efavirenz in persons with any history of mental illness, and patients need to be educated about possible symptoms and instructed to report them to their providers if they should develop.

Special attention should be given to the effect of methadone on ARVs, and vice versa. Among the nucleoside reverse transcriptase inhibitors (NRTIs), none have a clinically significant effect on methadone metabolism. Conversely, methadone has been shown to increase the area under the curve (AUC) of zidovudine by 43%, and providers should be alert to potential zidovudine toxicities (e.g., bone marrow suppression). A 27% decrease in stavudine blood levels is reported with methadone but no dose adjustments are needed. There are no clinically significant interactions of methadone with abacavir or tenofovir.

The NNRTIs are potent inducers of the p450 cytochrome system, which decreases methadone blood levels. Nevirapine has been reported to reduce methadone AUC by 46% and efavirenz has been reported to reduce methadone AUC by 50%-60%, commonly inducing opiate withdrawal symptoms within seven days of treatment initiation. Delavirdine inhibits the p450 cytochrome system and increases methadone AUC by 19%, but this rarely requires a dose adjustment.

Efavirenz and nevirapine decrease methadone levels by 43% and 46%, respectively, and often induce opiate withdrawal symptoms within seven days of treatment initiation. Such occurrences should be dealt with by increasing the methadone dose by 5 to 10 mg/day or until the patient no longer experiences withdrawal symptoms. Delavirdine inhibits the p450 cytochrome system and increases methadone levels, but this interaction rarely requires a dose adjustment.

PIs are generally not affected by methadone, with the exception of amprenavir. Amprenavir is reduced by 30% when taken with methadone, but the dose rarely needs to be increased. Nelfinavir, lopinavir/ritonavir, saquinavir, ritonavir, and amprenavir all reduce methadone AUC, but a clinically significant need for dose adjustments has not been shown. Buprenorphine is also widely used in drug substitution therapies for opiate addiction. It has not been shown to have any interactions with ARVs, or vice versa.

A summary of the data on methadone-ART interactions for ARVs is provided in Table 2. The AUC measures the blood level of a drug over a period of time.

The complexity of ART regimens in terms of pill burden and frequency of dosing is inversely related to successful adherence. The increased availability of effective fixed-dose combinations may offer significant benefits to injecting drug users in terms of simplifying the process of taking ARVs.

In addition to those routinely discussed, it is important to mention some additional barriers to adherence for injecting drug users. For active injecting drug users, addiction is a competing priority that overshadows their daily activities and motivations. The ability to develop routines or follow a time schedule for medications linked with a regular activity may be difficult, particularly for people without stable housing. Arrest or incarceration may also interrupt treatment. Yet one of the greatest barriers to successful treatment in this population is mistrust between the medical provider and the drug user, limiting the ability to discuss the patient’s injection drug use, the realities of his or her life and competing priorities, and potential strategies that can improve adherence. One of the most powerful factors supporting a patient’s adherence to ARV regimens is the health provider’s attitude toward the patient. When patients believe that a medical professional is truly working in their best interests and mutual respect exists between patient and health professional, it serves as a strong motivation for patients to follow recommended treatment.
HIV PREVENTION
The explosion of HIV/AIDS within populations engaging in injection drug use requires immediate action. A two-pronged approach is needed that both reduces the burden of drug addiction through prevention and drug treatment and reduces the health consequences of ongoing drug use for injecting drug users, their partners, and needle-sharing networks. The current situation is critical: the Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that only 8% of injecting drug users worldwide have access to HIV prevention services, although 80% coverage is required to effectively slow the epidemic.1

The sharing of contaminated injection equipment has become the primary mode of HIV transmission in many countries throughout Eastern Europe, the Commonwealth of Independent States (made up of 11 former Soviet republics), and significant regions in Asia.1 Needle and syringe exchange (NSE) programs have had documented effectiveness in reducing the sharing of used needles and syringes, as well as in reducing unsafe injection and disposal practices; NSE programs have also been associated with decreased frequency in injection practices.48 NSE programs typically include other prevention interventions such as counseling, education, condom distribution, and referrals to drug treatment and health care. For individuals who are actively injecting drugs, information coupled with the availability of sterile equipment can be a lifeline to reduce the risks of blood-borne transmission of HIV and hepatitis. Active users should also be educated about sterile injection techniques and the early recognition and care of abscesses. In recent years, naloxone has been introduced for use as a lifesaving intervention in the setting of a witnessed overdose. The use of predrawn syringes filled with naloxone, along with accompanying education, has been considered in some cities in the United States to reduce the number of deaths resulting from drug overdoses. Medical providers should become familiar with the availability of these risk-reduction services for their patients who are active drug users, regardless of HIV status.

There is strong and consistent evidence that opioid substitution treatment is effective in reducing use of opioids and increasing the retention of opioid-dependent individuals in drug abuse treatment and medical services.48 Methadone maintenance treatment reduces drug-related HIV risk behavior, including frequency of injections and sharing of equipment. Several studies have also shown a reduction in sex-related HIV risks among participants in methadone maintenance, but that effect has not been observed in all programs.48 There is an urgent need to increase the availability of methadone and/or buprenorphine substitution treatment wherever there is ongoing injection drug use, and to encourage patients to accept this approach to relieving the health and social burdens of their addiction. A recent study in 24 developing countries found that out of 9.2 million injecting drug users, only 33,000 had access to drug substitution programs.1 From a medical and public health perspective, all injecting drug users must have access to both NSE programs and drug substitution programs, as well as accessible Narcotics Anonymous treatment for those who want to stop.

INCARCERATION
It is impossible to talk about injection drug use and HIV without acknowledging the role of incarceration and prisons in fueling these twin epidemics. Injecting drug users are at great risk of being incarcerated for drug-related offenses or for engaging in illegal activities to obtain money for drugs. That leads to a high concentration of people living with or at high risk of HIV infection in prisons, where conditions are often
<table>
<thead>
<tr>
<th>ARV</th>
<th>Effect on Methadone</th>
<th>Effect on ARVs</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>None</td>
<td>Increased AUC 40%–43%&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>No adjustments in dosing; observe for AZT toxicity</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>None</td>
<td>Decreased AUC 27%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No adjustments needed; remain alert for virologic failure</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>None</td>
<td>No effect with enteric-coated ddI formulation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Use only enteric-coated formulation</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>Methadone AUC</td>
<td>None</td>
<td>Opiate withdrawal symptoms common by 7 days; titrate dose increase as needed</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Methadone AUC</td>
<td>None</td>
<td>Opiate withdrawal symptoms common by 7 days; titrate dose increase as needed</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Increased methadone levels 19%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>None</td>
<td>Unlikely to be clinically significant; no adjustments</td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir/ritonavir</td>
<td>Methadone AUC</td>
<td>Not significant</td>
<td>Unlikely to be clinically significant; no dose adjustments; monitor for withdrawal</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Methadone AUC</td>
<td>Not significant</td>
<td>No dose adjustments; careful monitoring for withdrawal symptoms</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>Not significant</td>
<td>AUC reduced 30%&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>No adjustments; unlikely to be clinically significant</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Methadone AUC</td>
<td>Decreased M8 active metabolite 48%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Usually no clinical significance; monitor for withdrawal</td>
</tr>
<tr>
<td>Tipranavir (TPV)</td>
<td>Methadone level</td>
<td>Not reported</td>
<td>No dose adjustments; careful monitoring for withdrawal with TPV/ritonavir</td>
</tr>
<tr>
<td></td>
<td>decreased 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1 study)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Panel on Antiretroviral Guidelines for Adults and Adolescents (Tables 22a, 22b, 22c).<sup>39</sup>
<sup>b</sup>Bruce et al.<sup>40</sup>
characterized by overcrowding, poor sanitation, inadequate medical care, injection drug use, and coercive sexual activity. When HIV infections are acquired in prison, the impact extends beyond the infected individual to his or her family and community upon release.

There is much that can be done to extend HIV prevention and treatment services into the prison setting through the extension of risk-reduction interventions and continuity of care for injecting drug users. Providing access to ART for HIV-infected individuals in correctional facilities is both necessary and feasible; when provided with care and access to medications, inmates who inject drugs respond well to ARV treatment, with adherence rates as high or higher than in the general population. The challenge is to sustain the gains in health status achieved during incarceration once a prisoner is released. That can be achieved through careful discharge planning and the creation of linkages with community care providers. The unmet demand for drug treatment programs in prisons represents an opportunity to implement substitution therapy, providing an alternative to illegal drug use while building a bridge to a mix of social services and support upon release.

**CONCLUSION**

Medical providers and the public health community have a vital part to play in recognizing the role of injection drug use in the expansion of the HIV epidemic, both locally and globally. Injecting drug users represent both a prevention opportunity through the use of needle-exchange and harm-reduction services and a treatment need for those who are already infected. The unique legal constraints facing active drug users often preclude their entry into and retention in medical, social, and psychiatric care services. Drug dependence is a complex medical and psychiatric condition often characterized by relapses, which can challenge and frustrate those working to help individuals overcome their addictions. Yet injecting drug users deserve to be afforded the same dignity, treatment, and support as HIV-positive non-injecting drug users, so that they may live full lives and protect their health and the health of their families and social networks. The critical role injecting drug users play in moving the virus into the general population must be acknowledged and aggressively responded to with a multidisciplinary approach supported by local ministries of health and civil society.
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35. Ellen JM, Langer LM. The link between the use of crack cocaine and the sexually transmitted...


HIV/AIDS and Nutrition in the Era of Antiretroviral Therapy: Programmatic Implications for Care and Treatment

Julia L. Finkelstein, Ferdinand M. Mugusi, Saurabh Mehta, and Wafaie W. Fawzi

The HIV pandemic continues to have a pronounced global impact on human health and development, particularly among the world’s poorest and most vulnerable populations. In resource-limited settings, chronic underlying malnutrition and its intersection with food insecurity, poverty, and co-infections pose a serious threat to efforts to combat HIV/AIDS. People living with HIV in resource-limited settings often cite food availability and security as their most immediate and critical concerns; at the same time, governments in developing countries grapple with a range of long-term programmatic, policy, and resource challenges relating to health, food, nutrition, and HIV/AIDS. The dual burden of HIV and malnutrition has a detrimental impact on population health and represents a significant challenge for healthcare professionals in these impoverished settings.

In developing countries, a high prevalence of HIV and malnutrition results in a vicious cycle of undernutrition, poverty, and disease. HIV increases metabolic needs, reduces appetite and dietary intake, and interferes with digestion and nutrient absorption. Poorer nutritional status affects the severity of HIV-related symptoms, immune reconstitution, disease progression, and survival. HIV/AIDS and undernutrition also lead to poverty and lowered nutritional status by reducing health resources, individual work capacity, agricultural and economic productivity, food security, and economic livelihood.

In the context of the rapid scale-up of antiretroviral therapy (ART) in resource-limited settings, an increased focus on nutritional management is urgently required to address the needs of people living with HIV. Among HIV-positive individuals at pre-ART disease stages, nutritional interventions can delay HIV disease progression, prolong survival, improve nutritional status and overall health, and mitigate the metabolic consequences of HIV infection. Nutritional interventions may also delay the onset of AIDS and ART initiation, thereby preserving first-line medications for use later in the course of disease. Similarly, nutritional management is an important adjunct to ART; improved nutritional status may confer benefits to ART safety and efficacy, limit the occurrence of side effects, and improve adherence to antiretroviral (ARV) regimens, patient survival, and quality of life.
HIV AND NUTRITION

The overlapping pandemics of HIV/AIDS and undernutrition have a severe impact on population health in resource-limited settings. According to the United Nations World Food Program, in 2008, an estimated 6.4 million people living with HIV were in need of nutritional support and HIV/AIDS care (i.e., ART, prevention of mother-to-child transmission [MTCT], assistance for orphans and vulnerable children, and palliative care); almost one million people urgently need food aid and ART. The estimated cost of nutritional support for HIV-positive individuals is relatively low, representing just 2% of the total estimated budget needed to target the HIV/AIDS pandemic.1,2

The interrelationship between HIV/AIDS and nutrition is dynamic and complex. HIV/AIDS is characterized by a progressive deterioration in immune function, while malnutrition, both in the form of protein-energy malnutrition and micronutrient deficiencies, also plays a major role in the etiology of immune dysfunction.3,4 Nutritional supplementation, due to its ability to improve humoral and cell-mediated immune function, may be effective in reducing morbidity in HIV-positive patients and decreasing vertical transmission. Improvements in immunological and nutritional status may also help to slow HIV disease progression and reduce the occurrence of opportunistic infections while improving the overall quality of life, an area of increasing importance, as HIV is becoming a manageable chronic disease.

HIV infection adversely affects nutritional status via several mechanisms, such as decreased appetite and food intake, increased caloric requirements (particularly during the symptomatic phase), greater nutrient utilization, and reduced nutrient absorption and bioavailability. Conversely, malnutrition is a risk factor for HIV transmission, disease progression, and mortality. For example, HIV-positive individuals who are severely malnourished at initiation of ART are six times more likely to die compared to those with adequate nutritional status.5 Undernutrition may also interfere with the safety and efficacy of ART and promote the rapid onset of full-blown AIDS.

Nutritional management is integral to comprehensive HIV care and treatment. Improved nutritional status and weight gain can lead to increased strength and enable patients to resume their normal daily activities, including attendance at work and caring for dependents. Increased mortality within the first three months of ART initiation, and concerns regarding ARV adherence, drug resistance, and side effects, reinforce the need for nutritional management. Additionally, the current treatment protocols for ART are associated with several metabolic complications, such as lipodystrophy, which can amplify the adverse effects of HIV infection on nutritional status.

NUTRITIONAL ASSESSMENT

Nutritional assessment is an integral component of nutritional management and HIV/AIDS care and treatment. Accurate, affordable, and feasible nutritional assessment methods are essential to program implementation. A comprehensive evaluation of nutritional status is composed of four main elements: (1) anthropometric assessment, including weight, height, and body composition; (2) biochemical measurements, including serum proteins, lipids, micronutrients, and immunological parameters; (3) clinical evaluation, including a comprehensive medical history and physical examination; and (4) dietary intake assessment.

Anthropometric Assessment

Anthropometric measurements are noninvasive, relatively low cost, and interpretable methods to assess nutritional status. The conventional anthropometric measures of weight, height, body mass index (BMI, kg/m²), and arm circumference can
be accurately measured with minimal training and expense, in even the most resource-limited settings. BMI and weight changes over time are particularly important for nutritional assessment of HIV-positive individuals, since these measures determine the clinical stage of disease and predict survival time. Use of the mid-upper-arm circumference (MUAC) index should be considered, particularly in situations in which it is difficult to collect weight and height, as it offers the operational advantage of being easily portable. However, there is a relatively large variability in MUAC measurements and an increased need for training and standardization of assessments. Accuracy of anthropometric measurements is also influenced by the type, condition, and calibration of the equipment, as well as the training of the individuals conducting the assessment.

Body composition assessment is particularly important in HIV-positive individuals, as both HIV disease and ART are associated with changes in body composition and metabolic complications. Since weight and BMI are crude measures of body composition, assessment necessitates the use of more sophisticated techniques. However, optimal methods to assess body composition, such as dual energy X-ray absorptiometry (DEXA) scans, are prohibitively expensive and operationally challenging to implement in resource-limited settings.

Bioelectrical impedance analysis (BIA) is a comparatively easier and less expensive method to assess body composition. Since BIA devices became available in the 1980s, this tool has become popular due to its ease of use, portability, and relatively low cost compared to other methods of body composition assessment. BIA relies on the difference in electrical conductance by fat and lean tissues to determine body composition after weight, height, sex, and age have been determined. BIA determines the opposition to the flow of an electric current (electrical impedance) of body tissues; electrical impedance can be used to estimate total body water, fat-free body mass, and body fat.

BIA has been used in HIV-positive populations, and BIA measurements have been shown to correlate with survival among people living with HIV. However, some data suggest that these measurements may not accurately reflect body composition in the context of HIV infection, and BIA has not yet been extensively validated in the era of ART. A recent pilot study was conducted to compare BIA, skinfold measurements, and DEXA methods to estimate percentage of body fat mass among 47 HIV-positive men receiving ART. Findings suggested that the level of bias and error in BIA and skinfold methods was relatively low compared to DEXA, and authors concluded that these techniques were acceptable methods of monitoring total body fat mass in HIV-positive male participants on ART. Further research is warranted to determine whether these findings are generalizable to women and children and to resource-limited settings.

Other anthropometric methods of assessing fat distribution include measurement of waist and hip circumferences, waist-to-hip ratio, and triceps skinfold thickness.

Biochemical Measurements
Biochemical measurements, including serum levels of proteins, lipids, micronutrients, and immunological parameters, represent important indicators of nutritional status and serve as valuable guides for clinical management of HIV and malnutrition. Among HIV-positive individuals, serum levels of albumin and vitamin A have been most extensively evaluated. The relative strengths and limitations of these methods are discussed in detail elsewhere.

Clinical Evaluation
Clinical evaluation, including a detailed medical history and physical examination, is essential in the assessment of nutritional status and overall health.
A comprehensive clinical evaluation includes history of weight changes, protein-energy malnutrition, micronutrient deficiencies, intercurrent illnesses, psychosocial health, level of functioning, and quality of life.

**Dietary Intake Assessment**
Dietary intake is optimally assessed by the use of food frequency questionnaires (FFQs), particularly for long-term evaluation. FFQs have been validated in studies in developed countries and in selected developing-country settings, and have become a well-established method of dietary assessment. However, FFQs have not been validated in all resource-limited settings, which may reduce their application. Self-reported dietary recall and diet record methods are useful for short-term dietary intake assessment, but may be more expensive to administer and require high levels of literacy. The relative advantages and disadvantages of these methods are reviewed in detail elsewhere.13,14

**HIV AND MACRONUTRIENT DEFICIENCIES**
Macronutrient malnutrition is common in HIV-positive individuals and is associated with accelerated disease progression, increased morbidity, and reduced survival. The following section reviews the effects of HIV/AIDS on weight loss and growth failure, metabolic disturbances, protein requirements, and fat metabolism.

**Weight Loss and Growth Failure**
HIV/AIDS was referred to as “slim disease” in many parts of Africa at the onset of the pandemic, due to the severe weight loss associated with it. Wasting, the hallmark of HIV disease in adults, is defined as involuntary loss of either 10% of body weight over 12 months, 7.5% over six months, or 5% over three months.15,16 Resting energy expenditure is approximately 10% higher in adults with asymptomatic HIV, compared with HIV-negative individuals; this increase is severalfold higher for individuals with active disease and secondary infections, and among children.17-23

**Weight Loss in Adults**
Weight loss can adversely affect HIV-related health outcomes and survival, particularly in adults at pre-ART disease stages. In a study in Gambia, BMI was a strong independent predictor of survival among HIV-positive patients.24 Baseline BMI of less than 18 kg/m² was associated with a 2.5-fold increase in risk of mortality, after adjusting for age, sex, wasting at diagnosis, baseline CD4 lymphocyte count, tuberculosis, and cotrimoxazole prophylaxis. Weight loss during the first four weeks of ART was also associated with increased risk of mortality in this study. Additionally, among HIV-positive individuals at pre-ART disease stages, as little as 5% weight loss has been associated with increased risk of opportunistic infections, hospitalizations, and mortality. BMI and changes in weight also determine the clinical stage of HIV disease and affect timing and initiation of ART.25-28

**Growth Failure in Children**
HIV infection is associated with poorer growth and development among infants and children. In a prospective cohort study of pregnant women (318 HIV-positive, 309 HIV-negative) and their infants in Rwanda, HIV-positive infants had significantly lower birth weight, head circumference, and weight-to-head circumference ratio at birth, compared to infants who were HIV-negative.29 Several studies in Africa have also found significant delays in linear and ponderal (weight-related) growth in HIV-positive infants less than two years of age.30-35 In a study of pre-pubertal male hemophiliacs, asymptomatic carriers of HIV were one quartile shorter in height for age, compared to HIV-negative children.36
Growth failure is also a powerful predictor of mortality in HIV-positive children, in studies in Malawi, Uganda, and Rwanda. In a study in Tanzania, wasting was an independent predictor of mortality among HIV-positive children but not among HIV-negative children.28

Pathogenesis of Wasting and Growth Failure

The etiology of wasting and growth failure in HIV/AIDS is complex; HIV may contribute to severe weight loss and deficits in growth via several mechanisms, including decreased dietary intake, reduced absorption and bioavailability of nutrients, and increased resting energy expenditure and metabolic demands.

Reduced dietary intake is likely the major contributor to weight loss and wasting in HIV disease in adults39 and growth failure in HIV-positive children.40 Decreased intake and appetite loss may be due to metabolic consequences of HIV disease,41 opportunistic infections (particularly those affecting the oropharynx and gastrointestinal tract), and repeated infections.28 Reduced dietary intake may also be due to poverty-related conditions such as inadequate food intake, food insecurity, decreased agricultural productivity, lack of resources for food preparation and storage, and poor social support at mealtime. The burden of HIV/AIDS is disproportionately higher in the low-income countries, where unhygienic conditions, overcrowding, and infectious diseases are prevalent; these factors increase the likelihood of exposure to repeated infections and further reduce appetite, food security, and dietary intake.

Reduced absorption and bioavailability of nutrients also contribute to weight loss and growth failure, due to intestinal dysfunction and HIV enteropathy. Diarrhea and intestinal malabsorption contribute to the chronic weight loss observed in people living with HIV, due to secondary infections, such as cryptosporidiosis.42-49 Further, HIV may have a direct effect on the intestinal surface and villi, thus altering intestinal absorption and transit.28

Increased metabolic demands associated with HIV infection also contribute to weight loss and growth failure. For example, HIV increases resting energy expenditure, protein turnover, caloric needs, and nutrient utilization. Increased metabolic requirements are also the result of opportunistic infections, other concurrent infections (e.g., malaria and other parasitic diseases), and hormonal deficiencies.

Metabolic disturbances that lead to wasting appear to represent an adaptive response to a generalized inflammatory state, and are mediated by increased secretion of pro-inflammatory cytokines, including tumor necrosis factor (TNF-α), interferon gamma (INF-γ), and interleukins (IL) 1 and 6.50,51 Both TNF-α and INF-γ are known to inhibit myosin expression in muscle cells,52 and TNF-α also induces anorexia.53

Maternal HIV infection also affects fetal growth and development. In a meta-analysis of 17 studies, the risk of low birth weight was twofold higher among infants born to HIV-positive women, compared to infants born to HIV-negative women.54 A recent study in Nigeria found a fivefold higher risk of low birth weight among infants born to HIV-positive women (P<0.0001).55

Reduced dietary intake is likely the major contributor to growth failure in HIV-positive children. In particular, decreased protein intake and increased nutritional requirements during childhood may exacerbate the risk of growth failure. Nutritional deficiencies and related infectious diseases, such as persistent diarrhea, fever, and pneumonia, are also more prevalent in HIV-positive children, further contributing to deficits in growth and development. Social factors, such as parental smoking or illicit drug use during pregnancy, may increase the risk of growth failure in HIV-positive
Micronutrient deficiencies are widely prevalent in HIV-positive populations. In cross-sectional studies, low serum concentrations of various micronutrients have been observed in people living with HIV; injecting drug users, pregnant women, and children seem to be at the highest risk of micronutrient deficiencies. Low serum levels of vitamin A, provitamin A carotenoids, niacin, vitamin B-6, folate, vitamin B-12, vitamin C, vitamin D, vitamin E, iron, zinc, selenium, and magnesium have been well documented.

Micronutrient deficiencies impair systemic immune function, and may accelerate disease progression and increase the risk of vertical transmission. Improved micronutrient status may confer benefits with regard to humoral and cell-mediated immunity, disease progression, and immune reconstitution. Micronutrient supplements can delay disease progression and reduce mortality, particularly among HIV-positive individuals at pre-ART disease stages. Nutritional supplementation may also prolong the pre-ART stage in HIV-positive patients and preserve first-line ART regimens for later use. In the context of ART, improved micronutrient status may also reduce the occurrence of adverse events, mitigate the impact of ART on nutritional outcomes, and improve ART adherence.

**HIV Seroconversion**

A few observational studies have been conducted to examine the role of vitamin A in heterosexual transmission of HIV in resource-limited settings. In a nested case-control study in Rwanda, low serum levels of vitamin A, carotenoid, or vitamin E were not associated with risk of HIV seroconversion. Similarly, a nested case-control study in Tanzania found no significant relationship between vitamin A levels and risk of HIV infection. However, findings from other observational studies have been divergent. Low serum vitamin A and carotenoid levels were associated with increased risk of HIV infection in India. In contrast, low vitamin A levels were protective for HIV seroconversion in a study in Kenya.

**HIV Disease Progression**

Several observational studies have been conducted to examine the role of micronutrients in...
HIV disease progression and immune reconstitution. In the United States, two cohorts were established to assess HIV disease progression in relation to multiple factors, including vitamin intake: the Multicenter AIDS Cohort Study (MACS)^97-100 and the San Francisco Men’s Health Study (SFMHS)^101; nutrient intake was assessed using FFQs. Investigators examined the relationships of various micronutrients with HIV disease progression to clinical AIDS^98,101 and death. In the MACS cohort, a U-shaped relationship was observed between vitamin A intake and HIV disease progression and mortality, whereas in SFMHS, vitamin A intake was directly associated with CD4 lymphocyte counts without any apparent effect on clinical progression. However, B-vitamin intake and/or supplementation in MACS and multivitamin use in SFMHS were associated with reduced risks of disease progression and mortality. Similar benefits of B-complex vitamin supplementation on disease progression and death were observed in a large cohort of 2,179 HIV-positive patients in South Africa.102

Other observational studies have examined the relationships between serum micronutrient levels and HIV disease progression and mortality. Low serum vitamin A was associated with low CD4 counts,83,103-105 accelerated disease progression,105 and increased mortality.103,104,106 Reduced serum vitamin D (1,25-dihydroxyvitamin D) was also associated with low CD4 counts84,107 and increased risk of mortality84 in studies in Germany and Norway, respectively. Lower maternal plasma selenium levels were associated with significantly increased risk of mortality in HIV-positive pregnant women in Tanzania.108

**Maternal and Child Health Outcomes**

Several observational studies have been conducted in sub-Saharan Africa to examine the role of micronutrients in MTCT of HIV and other perinatal outcomes. Low maternal vitamin A status was associated with increased risk of vertical transmission and other adverse pregnancy outcomes in studies in Malawi^100,110 and Rwanda. However, findings regarding maternal vitamin A status and pregnancy outcomes in the United States have been divergent. Low maternal vitamin A levels were associated with increased risk of vertical HIV transmission in one study in the United States.112 However, in other studies no associations were observed between maternal serum levels of vitamin A,113,114 beta-carotene,113 or vitamin E113 and risk of vertical HIV transmission.

In an observational study in Haiti, lower serum zinc levels were associated with increased risk of vertical HIV transmission, although this finding was not statistically significant.115 Low maternal selenium status was also associated with increased risk of intrapartum HIV transmission, fetal death, and child mortality in a study in Tanzania. In an observational study in Uganda, low serum vitamin A and carotenoid concentrations were associated with reduced weight and height velocities in HIV-positive children, suggesting a role for these micronutrients in child growth in the context of HIV.117

It should be noted that observational studies have a few limitations that warrant caution when interpreting findings. The observed associations between micronutrient deficiencies and adverse HIV-related outcomes may be due to reverse causation. For example, HIV infection may lead to decreased nutrient absorption and increased excretion, resulting in lower serum micronutrient levels and an apparent deficiency. Reduced levels of micronutrients may also be attributable to the acute phase response to infection rather than being a marker of actual micronutrient status. There may also be residual confounding due to factors not accounted for in the study design or analyses, such as other nutritional deficiencies, micronutrient supplement use, opportunistic infections, other
coinfections, and access to health care. Therefore, residual confounding of the relationship between micronutrient status and outcomes by these covariates may lead to biased results and constrain interpretability of findings.

**NUTRITIONAL INTERVENTIONS IN HIV-POSITIVE POPULATIONS**

The findings and limitations of the aforementioned observational studies prompted the undertaking of several intervention studies to investigate the effects of micronutrient and macronutrient supplementation on health outcomes in HIV-positive populations.

**Macronutrient-Based Interventions**

The efficacy of macronutrient-based interventions in improving HIV-related outcomes has been examined in several studies. Many of these interventions have focused on providing protein or amino acid supplements to HIV-positive patients.

In a study in France, a complete amino acid infusion was administered to HIV-positive patients; the authors found that deficiencies of essential amino acids (threonine and methionine) were a limiting factor for whole-body protein synthesis. A similar study in Brazil focused on the role of glutamine, an amino acid mobilized from muscle tissue in states of severe stress or catabolic states as an energy substrate; low levels of glutamine were correlated with increased morbidity and mortality among HIV-positive individuals. In another study, 41 HIV-positive adults were randomized to glutamine, alanyl-glutamine, or placebo supplementation; glutamine and alanyl-glutamine both significantly reduced the occurrence of gastrointestinal symptoms and increased the levels of ART medications, compared with the placebo.

A study in Germany found that supplementation with whey proteins led to a sustained increase in glutathione levels in HIV-positive patients. In a randomized trial in Zambia, the effect of amino acid supplementation on health outcomes was examined among children. In this study, 200 children (106 HIV-positive, 94 HIV-negative) with persistent diarrhea-malnutrition syndrome were randomized to receive either an exclusive diet of amino-acid-based elemental feed or standard nutritional rehabilitation (based on skim milk and soya) for four weeks. Significant improvements in weight gain and hemoglobin levels were observed in the elemental feed group; however, there were no differences in mortality between the two groups.

Interventions in several other studies have involved a dietary counseling component, either alone or in combination with a macronutrient supplement. In a study in the United States, investigators conducted a retrospective chart review for 119 HIV-positive patients, to examine the effect of a macronutrient intervention on nutritional status. The intervention included a dietary assessment, intake analysis, appropriate counseling, follow-up, and provision of supplements as needed. Patients who received the intervention had a significantly greater average weight gain, of 0.5 (±5.2) kilograms, while patients who did not receive the intervention lost an average of 1.6 (±5.8) kilograms (P= .02). In another study in the United States, dietary counseling was provided to 17 HIV-positive patients; counseling consisted of recommendations to consume a high-protein diet (1.5g/kg ideal body weight) and at least one high-energy, high-protein nutrition supplement daily. A total of 12 of the 17 patients gained or maintained their weight, leading the authors to propose that a nutritional supplement containing high levels of energy, protein, and nutrients should be the first-line nutrition treatment for malnourished, HIV-positive patients.

In a study in Spain, 74 HIV-positive patients were randomized to receive standard enteral formula (54.5% carbohydrate, 31.5% fat, and 14% protein) or an enterotrophic peptide-based formula,
enriched with omega-3 fatty acids and dietary fiber (65.5% carbohydrate, 15.8% fat, 18.7% protein, 9.46 g/mL omega-3 fatty acids, 8.9 g/L dietary fiber); all patients also received dietary counseling. A significant and sustained increase in weight was observed in both groups after three months. Furthermore, a significant increase in CD4 counts was observed in the group supplemented with the enterotrophic peptide-based formula, but not in the standard formula group.126

In Switzerland, 15 HIV-positive individuals with a BMI of less than 21 kg/m² or a CD4 count under 500 cells/µL were randomized to receive either (1) oral nutritional supplements (complete macronutrient and micronutrient supplementation; 2,510 kJ [~600 kcal]) and dietary counseling or (2) standard of care follow-up, which included identical clinical monitoring but no supplements or specific nutritional advice. In the intervention group, protein catabolism and whole-body protein turnover significantly decreased, as marked by leucine oxidation and whole-body leucine flux, respectively. Lean body mass increased in the intervention group, whereas fat mass decreased, compared to the control group.127

In a placebo-controlled randomized trial in the United States, 68 HIV-positive patients with a history of at least a 5% weight loss in the past three months were randomly assigned to receive either a nutrient mixture or placebo daily for eight weeks. The nutritional supplement consisted of beta-hydroxy beta-methylbutyrate, glutamine, and arginine, and was expected to slow muscle proteolysis. Patients in the intervention group had significantly greater weight gain, increased CD3 and CD8 counts, and lower viral load, compared to the placebo group.128 In a similar study in Chile, 46 HIV-positive malnourished adult outpatients were randomized to receive either a polymeric diet or regular foods for two consecutive 45-day periods, using a crossover design. Weight, fat-free mass, energy balance, and nitrogen balance increased significantly with the polymeric mixture, compared with the standard diet; however, there were no effects on CD4 or CD8 counts or plasma albumin levels.129

A few studies have explored the effect of anabolic hormones on the marked catabolic state associated with HIV infection. Miller et al reported a positive effect of testosterone on body composition in HIV-positive women with AIDS wasting syndrome.130 A large multicenter randomized trial was conducted to examine the impact of recombinant human growth hormone (rhGH) (daily vs. alternate day vs. placebo; dose: 0.1 mg/kg) on treatment of wasting and weight loss, among HIV-positive men and women on ART (88%). A total of 757 participants were randomized across 56 sites in eight countries; 548 individuals were included in the final analyses. Over the 12-week course of therapy, daily rhGH was superior to the placebo in improving physical function (P<.0001), body weight (P<.0001), body composition (P<.0001), and quality of life.131

Findings from randomized trials regarding the effect of anabolic steroids on lean body mass have been inconsistent. A systematic review of eight randomized trials found that testosterone therapy may increase lean body mass in HIV-positive patients.132 However, findings from other trials suggest that anabolic steroids may not confer any benefit to lean body mass in the context of HIV. For example, in a multicenter placebo-controlled randomized trial (14 AIDS clinical trial units), 79 HIV-positive men with at least a 5% weight loss or a BMI of less than 20 kg/m² were randomized to receive megestrol acetate (800 mg) plus testosterone enanathate (200 mg) or megestrol acetate alone, biweekly, for a 12-week period. Increases in weight, lean body mass, and fat were observed in both groups; co-administration of testosterone did not enhance accrual of lean body mass but preserved
sexual functioning.\textsuperscript{133} A placebo-controlled randomized trial was conducted in the United States among HIV-positive women with more than 5% weight loss in the past six months and low testosterone levels (<33 ng/dl); investigators did not observe any improvements in whole-body fat mass, regional fat distribution, insulin sensitivity, or markers of inflammation and thrombolysis with testosterone therapy.\textsuperscript{134}

In a more recent Cochrane review of 13 trials, administration of anabolic steroids resulted in a small increase in lean body mass and body weight, compared with the placebo. However, overall findings from the trials were heterogeneous; the authors concluded that there was insufficient scientific evidence to inform treatment recommendations for the use of anabolic steroids in HIV-positive individuals.\textsuperscript{135} Additionally, potential development of adverse events with the long-term use of steroids is a cause for concern.

The role of other macronutrient supplements, such as enzymes and fatty acids, has been examined in several small studies. As part of the Swiss HIV Cohort Study, 64 HIV-positive patients were enrolled in a double-blind randomized controlled trial and followed for six months. All patients received a daily oral nutritional supplement (606 kcal supplemented with vitamins, minerals, and trace elements), and half were randomized to additionally receive arginine (7.4 g) and omega-3 fatty acids (1.7 g). Body weight increased by a similar magnitude in both intervention and control groups.\textsuperscript{136} Another study was conducted in Italy to evaluate the effectiveness of open-label oral pancreatic enzyme therapy on lipid absorption in 24 HIV-positive patients. Pancreatic enzyme supplementation effectively reduced fecal fat loss among HIV-positive individuals with fat malabsorption.\textsuperscript{137} Modest improvements in fat absorption have also been observed with the use of high-fat diets\textsuperscript{138} and probiotics.\textsuperscript{139}

In a recent Cochrane review of macronutrient interventions in HIV-positive populations, macronutrient supplementation, with or without nutritional counseling, resulted in significant increases in energy and protein intake. However, reviewers found no effects of macronutrient supplements on body weight, fat mass, fat-free mass, or CD4 lymphocyte counts.\textsuperscript{140}

### Micronutrient-Based Interventions

Most micronutrient supplementation studies have examined micronutrients’ effect on two primary outcomes: HIV disease progression and perinatal outcomes, including HIV transmission. We discuss these studies in the two sections that follow, according to their primary focus.

#### Effects on HIV Disease Progression

Several intervention trials have been conducted to examine the effect of micronutrients such as beta-carotene; vitamins A, B-complex, C, and E; zinc; and selenium on HIV disease progression, either singly or jointly as part of a multiple micronutrient formulation. Two trials to examine the effect of beta-carotene supplementation on CD4 counts, one conducted in the United States and one in France, found no association.\textsuperscript{141,142} Vitamin A supplementation also had no effect on CD4 counts or viral load in trials in Kenya,\textsuperscript{143} South Africa,\textsuperscript{144} and the United States.\textsuperscript{145,146}

A multicenter clinical trial in Canada randomized 331 patients with AIDS on conventional management to receive either (1) multivitamins alone (including vitamin A and trace elements) or (2) multivitamins plus carotenoids (120,000 IU of carotene; equivalent to 72 mg of beta-carotene) daily. In multivariate analyses, individuals with higher baseline serum carotene concentrations had significantly improved survival ($P=.04$). A statistically non-significant increase in mortality was observed among participants who did not receive carotenoids
supplementation, compared to those who did; this increase became significant after adjustment for baseline CD4 counts and serum carotenoid concentrations \((P=.03)\). However, a major limitation of this study was the markedly reduced potency of the carotenoid supplement administered; authors reported that the daily dose of carotenoids was equivalent to only 9.2 milligrams of beta-carotene, instead of the intended 72 milligrams.

In a zinc supplementation trial in Peru, 159 HIV-positive adults with at least seven days of diarrhea were randomized to receive either zinc (100 mg) or a placebo daily. Zinc supplementation had no effect on either duration (persistence of diarrhea at day 14) or remission (time to cessation) of diarrhea. However, deficient serum zinc concentrations were observed in a high proportion of patients during follow-up (i.e., 66% of supplemented patients and 94% of nonsupplemented patients were deficient). Therefore, the regimen dose, duration, or adherence may have been insufficient to observe any potential beneficial effect of zinc supplementation in this population.

In the Trial of Vitamins study in Tanzania, 1,078 HIV-positive pregnant women were randomized to receive daily supplementation of (1) vitamin A (30 mg beta-carotene and 5,000 IU of preformed vitamin A), (2) multivitamins (20 mg thiamine, 20 mg riboflavin, 25 mg B-6, 100 mg niacin, 50 μg B-12, 500 mg C, 30 mg E, and 0.8 mg folic acid), (3) both vitamin A and multivitamins, or (4) placebo, using a 2-x-2 factorial design. At delivery, women in the vitamin A supplemented groups received an additional oral dose of vitamin A (200,000 IU) (vs. placebo). All women also received iron (120 mg ferrous iron) and folate (5 mg folic acid) supplementation daily. Maternal multivitamin supplementation resulted in significant increases in CD4, CD8, and CD3 counts, and significantly decreased viral load. Multivitamins also delayed the progression of HIV disease to World Health Organization stage IV or AIDS-related death by 30%, and significantly reduced manifestations of HIV disease such as oral thrush, oral ulcers, difficulty in swallowing, fatigue, rash, and acute upper respiratory infections. Multivitamin supplementation demonstrated a protective effect on maternal wasting and improved hematological status \((0.59 \text{ g/dL increase})\) during follow-up \((P=.0002)\), compared with placebo. However, vitamin A had no significant effect on any of these outcomes.

Multiple-micronutrient supplementation had no effect on CD4 counts in randomized trials in Thailand (vitamins A, B-1, B-2, B-6, B-12, C, D, E, and K; beta-carotene; folate; iron; zinc; and selenium) and Zambia (vitamins A, C, and E; selenium; and zinc). However, the trial in Thailand reported a nonsignificant decrease in mortality in the micronutrient supplemented arm; this decline was significant among individuals with CD4 cell counts of less than 100 cells/µL.

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trials used identical multiple-RDA micronutrient supplementation (vitamins B-complex, C, and E), apart from the addition of selenium in the Kenyan trial. The trials in Kenya and Tanzania identified beneficial effects of micronutrient supplementation on CD4 and CD8 counts. However, the Kenyan trial also identified an increased risk of viral shedding with supplementation. Since both trials used identical micronutrient supplementation regimens (except the addition of selenium) and genital viral shedding was greatest among women with normal selenium levels at baseline, the potentially harmful effect on HIV transmission via increased genital viral shedding observed in the Kenya study may be attributable to selenium.

Selenium-only supplementation studies in HIV-positive populations have had divergent findings. A selenium supplementation trial was conducted in Nigeria among individuals with advanced AIDS on ART; patients receiving selenium supplementation had higher rates of CD4 cell increase, fewer hospital visits, and greater weight gain, compared with the patients on ART alone. In a randomized controlled trial among 262 HIV-positive adults, serum selenium concentrations increased significantly in the selenium-treated group, compared with the placebo-supplemented group ($P<.001$). Increased serum selenium levels significantly reduced HIV viral load ($P<.02$) after adjusting for age, sex, ethnicity, income, education, illicit drug use, HIV symptom classification, time since HIV diagnosis, ARV regimen, adherence, and hepatitis C coinfection. Selenium-treated participants whose serum selenium increase was greater than 26.1 µg/L demonstrated excellent treatment adherence, no changes in HIV viral load, and increased CD4 counts. However, in a selenium trial in HIV-positive pregnant women in Tanzania, there were no differences in maternal CD4 counts, plasma viral load, or mortality between selenium- and placebo-supplemented groups.

**Effects on Maternal and Child Health Outcomes**

Randomized trials have primarily focused on the role of vitamin A status in pregnancy outcomes among HIV-positive pregnant women and children. In trials in Malawi and South Africa, maternal vitamin A supplementation did not have any beneficial effect on the risk of MTCT of HIV. However, contrary to a priori hypotheses, maternal vitamin A supplementation significantly increased the risk of vertical HIV transmission in trials in Tanzania and Zimbabwe.

In the ZVITAMBO trial in Zimbabwe, administration of the vitamin A regimen to either the mother (400,000 IU) or infant (50,000 IU) significantly increased the risk of vertical HIV transmission and infant mortality. However, vitamin A administered to both the mother and the infant did not increase the risk of these outcomes, compared with the placebo. Additionally, all three vitamin A regimens resulted in a twofold increase in the risk of mortality among infants who were HIV-negative at six weeks postpartum, compared with the placebo arm ($P\leq.05$).

In a randomized trial in South Africa, 118 infants born to HIV-positive women were randomized to either vitamin A or placebo supplementation. Vitamin A reduced diarrheal morbidity by 50% among HIV-positive infants with diarrhea; no effect was observed in HIV-negative children. In another trial in South Africa among HIV-positive children, vitamin A supplementation prior to influenza vaccination blunted the increase in HIV viral load typically observed post-immunization. In a randomized trial in Tanzania, vitamin A reduced all-cause mortality by 63% and decreased AIDS-related deaths by 68% in HIV-positive children. Vitamin A supplementation was also associated with reduced risk of respiratory infections and increased average length gain in HIV-positive children. A protective effect of vitamin A supplementation on
mortality was also observed among HIV-positive children in a randomized trial in Uganda.\(^{168}\)

Other single-nutrient trials have examined the role of zinc and selenium supplements in maternal and child health outcomes. In a randomized trial in Tanzania, maternal zinc supplementation had no effect on the risk of fetal death, preterm birth, infant low birth weight, vertical HIV transmission, or neonatal mortality.\(^{169,170}\) In a trial in South Africa, HIV-positive children were randomized to receive either oral zinc supplementation or a placebo daily for six months. There were no differences in viral load, CD4 counts, or hemoglobin concentrations in the two groups; however, zinc supplementation reduced the incidence of watery diarrhea.\(^{171}\) In a trial in HIV-positive pregnant women in Tanzania, maternal selenium supplementation had no effect on neonatal or overall infant mortality but reduced the risk of child mortality after six weeks, suggesting a survival benefit for breastfeeding children.\(^{157}\)

In the trial of vitamins study in Tanzania described earlier, maternal multivitamin (vitamins B-complex, C, and E, at multiple-RDA levels) supplementation did not affect the risk of MTCT of HIV in the overall population; however, multivitamins significantly reduced the risk of vertical HIV transmission among infants born to women who were nutritionally and/or immunologically compromised at baseline.\(^{161}\) Maternal multivitamin supplementation also reduced the risk of severe preterm birth by 39%, low birth weight by 44%, small size for gestational age by 43%, and fetal death by 39%.\(^{149}\) In contrast, vitamin A supplementation had no effect on pregnancy outcomes, but increased the risk of vertical HIV transmission by 38%.\(^{161}\)

In the Trial of Vitamins study, multivitamin supplementation significantly increased maternal weight gain and reduced the risk of developing hypertension during pregnancy.\(^{172,173}\) Maternal multivitamin supplementation also improved child psychomotor development and decreased the risk of developmental delay.\(^{174}\) Children born to mothers who received multivitamins also had improved hematological status, with a 63% lower risk of macrocytic anemia, compared with the placebo group (\(P=.01\)).\(^{152}\)

In accordance with WHO guidelines, daily folate and iron supplementation is the standard of prenatal care in most settings, and includes 400 mg folate and 60 to 120 mg iron for a duration of six months, regardless of HIV status.\(^{175}\) These recommendations are based on the demonstrated benefits of folate in preventing neural tube defects\(^{176}\) and of iron in preventing maternal anemia and related complications.\(^{177-180}\)

The safety and efficacy of folate and iron supplementation have not been extensively evaluated in HIV-positive populations. There is a lack of evidence to suggest that folate supplementation should differ among HIV-positive women. However, there are some concerns regarding the safety of iron supplementation in HIV-positive individuals. For example, iron is an acute-phase reactant, akin to vitamin A and zinc, and may therefore have similar adverse effects. Additionally, although there is some evidence to suggest that iron supplementation may exacerbate malaria outcomes, its potential risks for HIV-positive individuals residing in malaria-endemic regions are unknown. Further research is needed to elucidate the role of iron supplementation in HIV-positive individuals and to establish specific iron-folate recommendations for HIV-positive pregnant women and malaria-endemic settings.\(^{181-184}\)

**HIV, NUTRITION, AND ART**

As access to ART is rapidly scaled up worldwide, addressing the role of nutrition in the context of ART is an increasingly critical component of HIV/AIDS care and treatment. Among HIV-positive individuals on ART, enzyme systems (e.g., mixed function oxidase in the liver) and nutrient cofactors...
are essential for efficient metabolism, uptake, and utilization of medications. Malnutrition affects medication absorption, safety, efficacy, and adherence. Nutritional interventions may confer benefits with regard to ART-related side effects and metabolic complications. Conversely, ART may also contribute to further improvements in nutritional status by alterations in appetite, dietary intake, nutrient absorption, metabolism, and excretion. Potential nutrition-ART interactions also warrant consideration in the development of evidence-based HIV/AIDS programs in the ART era.

**Effects of ART on Macronutrient Status**
The occurrence of HIV/AIDS-related wasting appears to have diminished in the ART era; it is postulated that ART reduces HIV-associated weight loss and wasting by decreasing viral load. There is, however, limited evidence regarding the specific impact of ART on macronutrient status at the individual level. For example, a recent study in India found that the majority of HIV-positive patients who received nevirapine-based ART gained weight and retained body shape symmetry with no changes in waist-to-hip ratio; however, several patients lost weight despite initiating ART. Similarly, in an analysis of 469 HIV-positive individuals in the Nutrition for Healthy Living cohort, more than 50% of the cohort was receiving ART at the time that they met clinical criteria for wasting.

Several studies have examined the effect of ART on child growth. Miller et al found that exposure to non-protease-inhibitor ART before three months of age was a risk factor for failure to thrive in HIV-positive infants. Similarly, Goldstein and colleagues found a higher rate of low birth weight in infants born of HIV-positive women who received either zidovudine (AZT) or protease inhibitors (PIs). In contrast, Morris et al found that intrauterine exposure to maternal PI therapy (for the prevention of MTCT of HIV) had no effect on birth outcomes. In utero or neonatal exposure to AZT had no adverse effects on intrauterine and postnatal growth of HIV-negative children followed for up to 5.6 years. Tuomala et al found no association between the use of combination ART and low birth weight. In a study among HIV-positive children, ART positively influenced height and weight, reduced viral load, and increased CD4 cell counts. Most of these studies, however, were conducted in developed countries, where the risk of poor nutrition is relatively low. Furthermore, these studies had methodological limitations that constrain interpretability of findings, including small sample sizes, use of different endpoints and proxy measurements for child growth, and limited assessment of dietary intake and nutritional status.

**Effects of ART on Micronutrient Status**
ART may also alter the micronutrient status of HIV-positive individuals. Abnormalities in zinc and selenium plasma levels were observed following ART initiation in a study in France. Lower levels of circulating vitamin D (1,25D) have also been found in some observational studies and are more commonly reported among individuals on PI therapy. This finding is cause for concern due to the increased occurrence of bone-related disorders with HIV infection, such as osteoporosis, osteopenia, and osteodensity.

**Metabolic Complications of ART**
HIV-positive individuals on long-term ART may experience a variety of metabolic abnormalities. These complications can be severe and fatal, interrupt adherence, and reduce the quality of life of the affected individual. Metabolic complications of ART include fat redistribution, dyslipidemia, insulin resistance, lactic acidemia, mitochondrial toxicity, and abnormalities in bone mineral metabolism. Each class of ARV medication has been associated with metabolic complications;
Abnormalities in fat distribution are common among individuals on ART. Lipodystrophy, the loss of peripheral and subcutaneous fat and accumulation of central fat, is observed within 7 to 22 months after ART initiation in most patients. Men are more likely to accumulate dorsocervical fat (buffalo hump) and present with fat depletion, whereas women more commonly accrue fat in the waist and breasts. In a study in Italy, investigators examined adipose tissue alterations in 2,258 HIV-positive adult men and women; men had a significant 0.47 times lower risk of presenting with adipose tissue alterations compared to women ($P<.0001$).

In a recent observational study in the United States, researchers examined the relationship between dietary intake (four-day food records or 24-hour recall) and serum lipid levels in 356 HIV-positive patients and 162 community-based HIV-negative controls. HIV-positive patients had significantly greater intake of total fat, saturated fat, and cholesterol, and a greater percentage of calories from saturated fat and trans fat, compared to controls at similar levels of caloric intake. Greater saturated fat intake was predictive of increased serum triglyceride levels. In a subsequent analysis, visceral adiposity was increased among nonobese HIV-positive men and women, compared to controls. Abdominal subcutaneous adiposity was reduced in HIV-positive men in normal and overweight categories, but increased among HIV-positive obese women, relative to control participants. Findings were similar when limiting the analysis to individuals without metabolic syndrome.

Lipodystrophy contributes to insulin resistance in HIV-positive patients, and is associated with a constellation of metabolic abnormalities such as impaired glucose tolerance, insulin resistance, and type 2 diabetes. An estimated 6% to 10% of patients receiving ART will develop type 2 diabetes in their lifetime. Conversely, insulin resistance may also be a primary feature underlying the etiology of lipodystrophy syndrome, as it often precedes fat redistribution. ARV medications stavudine, indinavir, ritonavir, and lopinavir, but not atazanavir or amprenavir, are known to acutely induce insulin resistance; however, long-term effects are not known. Several studies have demonstrated the efficacy of insulin-sensitizing medications in lipodystrophy management. A randomized trial was conducted to examine the effects of exercise training and metformin on body composition and cardiovascular indices among HIV-positive patients on ART with hyperinsulinemia and fat redistribution. Findings demonstrated that exercise training in combination with metformin significantly improved cardiovascular and biochemical parameters, compared to metformin alone.

Nucleoside reverse transcriptase inhibitor (NRTI) drugs may lead to a range of adverse metabolic effects, such as fat wasting, peripheral neuropathy, lactic acidosis, cardiomyopathy, and pancreatitis. These diverse NRTI side effects may be mediated by a common physiological mechanism of mitochondrial toxicity. In a case-control study, cases were HIV-positive patients with lactic acidosis or hyperlactatemia; controls were randomly selected (two per case) from treated patients and matched by center and calendar year. After adjusting for age, gender, and current CD4 count, lactic acidosis/hyperlactatemia was associated with exposure to didoxynucleosides and advanced immunosuppression (CD4<200 cells/µL). This association remained across all categories of didanosine exposure but was greatest at shorter durations of exposure (less than 12 months), suggesting a potential susceptibility in a small percentage of HIV-positive individuals. Lactic acidosis, although relatively uncommon, can be potentially life-threatening,
with an estimated 60% mortality rate. This is of particular concern in resource-limited settings where NRTIs are more frequently used, and other risk factors for lactic acidosis (e.g., lower CD4 counts) are likely to be more prevalent. A potential mechanism for the observed decrease in HDL might be the impairment of cholesterol efflux from macrophages by HIV itself, therefore promoting atherosclerosis in HIV-positive patients.

A clinical trial was conducted to compare the effects of three ARV regimens—didanosine (ddI, Videx) and stavudine (d4T, Zerit), plus either efavirenz (Sustiva), nelfinavir (Viracept), or both—on metabolic complications. A total of 234 patients (out of 881) progressed to develop metabolic syndrome, as defined by criteria of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Third Report; ATP-III), and a total of 178 patients met International Diabetes Federation criteria for metabolic syndrome. The development of metabolic syndrome during ART was a significant risk factor for cardiovascular disease and diabetes; however, no significant differences were observed in rates of progression to metabolic syndrome between the randomized treatment arms.

Several studies have been conducted to examine the effects of ART on cardiovascular parameters. In the Strategies for Management of Antiretroviral Therapy (SMART) treatment interruption study, investigators evaluated electrocardiograms of 4,831 HIV-positive patients with no prior ischemic heart disease and found that more than 10% had asymptomatic ischemic heart disease. A marginally significant reduced risk of asymptomatic heart disease was observed in patients who were using a non-nucleoside reverse transcriptase inhibitor (NNRTI) \( (P = .05) \); however, no association was observed between ART duration and asymptomatic ischemic heart disease. In a large prospective observational study of 23,437 HIV-positive patients, longer duration of exposure to PIs was associated with increased risk of myocardial infarction, whereas no such relationship was observed with NNRTIs. Findings were consistent with prior studies that found an increased incidence of coronary artery disease and myocardial infarction in HIV-positive patients receiving ART.

In the context of increased use of ARV medications that have less impact on lipid metabolism, however, the occurrence of ART-related lipodystrophy and cardiovascular risk factors are decreasing. In a recent report from the Swiss HIV Cohort Study, the likelihood of developing lipodystrophy decreased as the percentage of patients receiving stavudine, didanosine, and nelfinavir declined; the percentage taking lopinavir, nevirapine, and efavirenz remained stable; and the percentage taking atazanavir and tenofovir increased. Other factors that may be contributing to this observed decline include the increased use of lipid-lowering drugs and lower prevalence of smoking.

**NUTRITION AND ART: SAFETY, EFFICACY, AND ADHERENCE**

Nutritional interventions may affect the safety and efficacy of ART and enhance adherence. Nutritional interventions may also have beneficial effects on HIV-related outcomes among individuals receiving ART, including reduced rate of disease progression, enhanced immune function, reduced viral load, and decreased mortality. Malnutrition at the time of starting ART has been identified as a significant independent predictor of reduced survival. Additionally, improvements
ARV-food interactions have been reviewed in further detail by Nerad et al.241

In patients receiving ART, micronutrient supplementation may help to correct ART-associated adverse effects. For example, iron may help reduce AZT-associated hematologic toxicity and anemia.242 Vitamin E may help reduce metabolic abnormalities associated with ART, including body fat redistribution, dyslipidemia, insulin resistance, and serum lactate.243 Vitamin B-12 has been identified as a potential adjunct to reduce AZT-associated hematologic toxicity,244 and B-complex vitamins may attenuate NRTI-associated lactic acidosis. Antioxidant supplementation (including vitamin E, beta-carotene, N-acetylcysteine, selenium, gingko biloba extracts, and nutritional supplements) has demonstrated benefits in asymptomatic stable chronic hyperlactatemia in HIV-positive patients taking NRTIs.245 Antioxidants, such as selenium, Vitamin C, and Vitamin E, may also reduce NF-κB activation, which is implicated in viral transcription.

Nutritional interventions and ART may interact through a number of potential mechanisms: (1) nutritional status may affect ART absorption, metabolism, distribution, and excretion; (2) ARVs may affect nutrient absorption, metabolism, distribution, and excretion; (3) ART side effects may reduce dietary intake; and (4) ARVs and certain nutrients may lead to side effects.

Nutrition-ART interactions may adversely affect the safety and efficacy of ART. For example, significantly decreased plasma concentrations of the PI saquinavir were observed in healthy volunteers with long-term use of garlic supplements.256 Decreased cytochrome P450 activity and reduced expression of P glycoprotein were observed with the ingestion of the African potato (Hypoxis hemerocallidea) and Sutherlandia frutescens, which are commonly used for symptom relief in HIV-positive patients in some resource-limited settings. These cofactors are important components of medication transport; therefore, Hypoxis hemerocallidea and Sutherlandia frutescens likely increase ARV toxicity.237,238 St. John’s wort (Hypericum perforatum), a popular herbal supplement, may significantly reduce plasma levels of NNRTIs and PIs.239 Similarly, in a small study in HIV-negative healthy volunteers, concomitant administration of high doses of vitamin C reduced steady-state indinavir plasma concentrations.240

in nutritional status may reduce the occurrence of adverse events associated with ART, including diarrhea, nausea, peripheral neuropathy, anemia, and fatigue, and mitigate ART-related metabolic complications. Reducing the occurrence of these side effects may lead to significant improvements in safety, efficacy, and adherence to ART and enhance survival and overall quality of life. Preservation of first-line regimens would also contribute to improved virological suppression and clinical success and have considerable cost implications in resource-limited settings.

Nutritional management is an integral part of care and treatment of HIV-positive patients on ART. Effective management of macronutrient and micronutrient undernutrition may alleviate ART-related adverse effects. Improved nutritional status and overall health may also have beneficial effects on adherence, immune reconstitution, survival, and quality of life.242 For example, in a randomized trial in Zambia, provision of monthly household food rations (micronutrient-fortified corn-soya blend) to food-insecure HIV-positive patients initiating ART increased adherence by 40%, compared with nonparticipants, although there were no significant differences in weight gain between the two groups.246

The majority of research on ART and its related complications has been conducted in developed countries, among well-nourished HIV-positive individuals. However, some studies have demonstrated
similar adverse effects of ART in less-developed settings. For example, in a cross-sectional study in India, 46% of patients taking first-line ART for more than one year had significant fat redistribution. Dyslipidemia and hyperglycemia were also more commonly reported among HIV-positive patients on ART; lipodystrophy was particularly prevalent among patients receiving stavudine-based ART regimens.\(^2\) This finding is of particular concern, as stavudine is the most widely utilized ART regimen in resource-limited settings, due to its comparatively lower cost.\(^2\)–\(^4\)

**PROGRAMMATIC IMPLICATIONS**

Comprehensive programs that concurrently target HIV/AIDS and nutrition are central to fostering long-term improvements in population health. Essential to this comprehensive approach is the training of health-care providers, community health workers, and caregivers on nutritional assessment, counseling, food-drug interactions, and adherence. It is also critical to involve patients and caregivers in the planning and development of individual nutritional and medication plans. In order to strengthen home- and community-based programs, provision of nutritional tool kits (e.g., dietary plans, medications, and meal schedules) and integration of nutritional management, specific nutritional-ARV interactions, and adherence into nutritional counseling, staff training, and supervision systems are recommended.\(^3\)

Establishment and strengthening of linkages to governmental and nongovernmental actors, as well as the private sector, are needed to develop sustainable, long-term improvements in the health and nutritional status of HIV-positive populations. Forging linkages with nongovernmental organizations and the private sector may ensure that foods and supplements are tailored to meet the specific needs of people living with HIV and are manufactured in-country. Public-private partnerships may also inform the development of cost-effective and sustainable nutritional interventions. To ensure greater food security, it is critical to incorporate poverty alleviation strategies, microfinance opportunities, and intersectoral collaboration, in order to maximize programmatic integration and long-term sustainability.

**NUTRITIONAL ASSESSMENT AND COUNSELING**

Assessment of nutritional status is an essential component of HIV care and treatment and should be conducted as part of routine screenings in HIV/AIDS programs. Some nutritional assessment techniques, such as DEXA, are optimal under controlled environments but remain prohibitively expensive and challenging to implement in field settings. However, even in the most resource-limited contexts, screening for nutritional status can be achieved through assessment of anthropometry (e.g., MUAC), dietary intake, and clinical examinations, with minimal training and financial resource investment. Initial assessment of dietary intake patterns, food security, and type and seasonal availability of local foods should also be paired with an evaluation of individual-level nutritional needs, ARV regimens, and specific nutritional-ART interactions. Although BIA and biochemical methods are excellent measures of body composition and micronutrient status, these assessment techniques are comparatively more resource intensive and pose programmatic and operational challenges for large-scale implementation in developing regions. Additionally, BIA needs to be further validated among HIV-positive populations in resource-limited settings in the ART era.

Nutritional counseling can enable health-care professionals to identify and address barriers to nutritional management. Dietary counseling can also provide information and support to HIV-positive individuals and their caregivers regarding
specific dietary intake, nutritional needs, nutritional requirements of medications, and contraindicated foods, in order to achieve optimal nutritional status and ARV safety and efficacy.

In integrated nutrition and HIV programs, it is important to consider poverty-related factors that fuel the dual epidemics of undernutrition and HIV/AIDS. Consideration of household- and community-level factors such as food security, type and seasonal variation of foods, patterns of household food utilization and distribution, potential gender inequalities, and protection of vulnerable populations should be incorporated into nutritional counseling related interventions.

**NUTRITIONAL INTERVENTIONS FOR PEOPLE LIVING WITH HIV**

In addition to dietary assessment and counseling, nutritional interventions are warranted to meet the nutritional requirements of people living with HIV.

**Adult Men and Women**

Based on current scientific evidence, the major macronutrient recommendation for HIV-positive adults is to increase energy intake by 10% among asymptomatic individuals and by 20% to 30% in symptomatic adults. These energy requirements should be achieved through food-based approaches whenever possible; there is currently no evidence to support specific increases in protein or other macronutrients or for changes in the usual composition of a balanced diet.29

In HIV-positive adults, multivitamin supplementation of vitamins B-complex, C, and E is recommended to slow HIV disease progression and reduce the risk of associated mortality.250 Micronutrient supplementation may also be beneficial as an adjunct to ART. There is currently no conclusive epidemiological evidence to support the specific use of other micronutrient supplements in HIV-positive adults.251

**Pregnant and Lactating Women and Children**

Multivitamin supplementation (vitamins B-complex, C, and E) is strongly recommended for HIV-positive pregnant women, based on its demonstrated effect on pregnancy outcomes, such as low birth weight and fetal death. Vitamin A supplementation should be avoided for HIV-positive pregnant and lactating women, due to the associated increased risk of MTCT as identified in some randomized trials. However, dietary intake of vitamin A by these women should remain adequate and consistent with recommended dietary allowances. In accordance with WHO guidelines, daily folate and iron supplementation is recommended for HIV-positive pregnant women to reduce the risk of neural tube defects, maternal anemia, and other adverse pregnancy outcomes. However, the safety and efficacy of iron supplementation urgently needs to be established in HIV-positive pregnant women.182 There is currently no strong epidemiological evidence to support the use of other micronutrient supplements, such as zinc and selenium, among pregnant and lactating HIV-positive women.252

As per the recommendations of WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS), HIV-positive pregnant women should receive ARV prophylaxis for prevention of MTCT. HIV-positive mothers should avoid breastfeeding “when replacement milk is acceptable, feasible, affordable, sustainable and safe.”253,254 In settings where alternatives to breastfeeding are not viable, exclusive short-course (six month) breastfeeding and early weaning are recommended, followed by appropriate introduction of complementary foods; mixed feeding is to be avoided.

Children represent another vulnerable group warranting particular attention in the context of HIV and nutrition. Adequate nutritional support for HIV-positive children is 20% to 30% greater than the total energy intake requirements for
HIV-negative children. Vitamin A supplementation should be avoided in the first months of life, due to increased risk of MTCT of HIV. However, periodic vitamin A supplementation for children older than six months (preferably at the time of early weaning) is recommended regardless of infant HIV status, based on its benefits in reducing all-cause morbidity and mortality.\textsuperscript{255} Nutritional support for the infant (e.g., micronutrient-fortified foods) is also suggested, starting at the time of early weaning through 30 months of age, in order to reduce the risk of stunting.

**Monitoring and Evaluation**

Monitoring and evaluation are essential to effective delivery of nutrition and HIV/AIDS services. Food aid programs are currently being implemented in many developing countries, with a focus on the provision of nutritional support for people living with HIV; however, there is limited scientific evidence to support the nutritional composition of many of these interventions and a lack of evaluation of these food aid programs. This poses challenges to the development of recommendations for universal nutritional programs for a broad range of contexts.\textsuperscript{256} Incorporation of operational research initiatives and program evaluation are needed to provide a stronger evidence base for integrated HIV and nutrition programs, and to inform effective delivery of services to HIV-positive populations in resource-poor settings.

**RESEARCH GAPS AND FUTURE DIRECTIONS**

There is a paucity of evidence-based interventions that concurrently target HIV and undernutrition among individuals on ART in developing countries. Most nutritional intervention studies to date have been conducted in developed countries and among HIV-positive patients with relatively better immunological and nutritional profiles. Studies have been characterized by methodological limitations such as small sample sizes, short duration of follow-up, lack of nutritional supplementation, and inadequate assessment of HIV-related outcomes.

There is an urgent need for clinical, epidemiological, and operational research on nutrition and HIV/AIDS in the ART era to inform HIV/AIDS care and treatment in resource-limited settings. Specific nutritional recommendations are needed for HIV-positive adults at pre-ART disease stages and for individuals on ART. The effect of nutritional interventions on ART safety and efficacy needs to be evaluated to ensure ART adherence, quality of life, long-term retention, and survival in HIV/AIDS care and treatment programs.

Areas for further research include nutrition and HIV, nutrition-pharmacological interactions, and vulnerable populations, such as pregnant and lactating women and children.

**Nutrition and HIV**

- Further research is warranted to establish the appropriate nutritional content and form of aid that can be provided to people living with HIV in resource-limited settings. Dietary supplements using a range of locally available foodstuffs are needed to overcome severe weight and nutritional loss during acute illness.
- Research is needed to develop palatable, affordable, available, and acceptable nutritional interventions, with ongoing feedback from individuals, caregivers, and health professionals. Identification of locally appropriate, sustainable methods of increasing dietary intake to meet the additional energy and micronutrient requirements of HIV-positive individuals in resource-limited settings is also needed.
- Further research is warranted to determine if specific protein or amino-acid-based interventions are efficacious in reducing morbidity and mortality among HIV-positive individuals.
Specifically, additional research is needed to elucidate the role of particular proteins or amino acids, including threonine, methionine, and glutamine, in HIV-positive patients.

- Additional research is needed to evaluate the potential long-term benefits and adverse effects of anabolic steroids, optimal doses, and methods of administration. Furthermore, the correlation of improved lean body mass with more clinically relevant endpoints, such as physical functioning, morbidity, and mortality, needs to be determined.\(^\text{135}\)

- There is insufficient evidence regarding the relative benefit of administering single versus multiple RDA levels of micronutrients to HIV-positive individuals or the exact doses required. Although multiple-RDA multivitamin supplementation (including B-complex, C, and E) has demonstrated a consistent beneficial effect on immunological function among HIV-positive individuals, the generalizability of findings to HIV-positive individuals on ART has not yet been established.

- Due to concerns regarding iron supplementation among HIV-positive individuals, the efficacy and safety of routine iron supplementation—in HIV-positive individuals in general and in HIV-positive pregnant women in particular—urgently needs to be examined.

- Additional research is warranted to examine interactions between foods and nutrients among of HIV-positive individuals on ART. Micronutrients can have synergistic or antagonistic effects; for example, iron supplements may decrease zinc absorption,\(^\text{257,258}\) and high doses of zinc can interfere with the absorption of iron and copper.\(^\text{259,260}\) Further research is warranted to examine nutrient-nutrient interactions and evaluate complementary dietary approaches, such as food fortification as adjuncts to ART and nutritional supplementation.

### Nutrition-Pharmacological Interactions

- Additional research is warranted to develop evidence-based recommendations for specific nutrition-pharmacological interactions, and consideration of the role of traditional medicine and local diets in these settings. Greater understanding of the interactions between ARVs and traditional medicines will help to promote optimal medication safety and efficacy and to reduce the risk of adverse interactions and side effects.

- The generalizability of findings in the aforementioned studies, which have primarily been conducted in developed countries, to resource-limited settings characterized by chronic undernutrition has not been established. The effects of preexisting nutritional deficits on ARV safety and efficacy and the metabolism of nutrients and ARVs are unknown. Malnutrition may adversely affect the efficacy of certain ARVs; therefore, specific nutritional interventions may play a profound role in mitigating these effects. Conversely, the impact of ARVs on the nutritional and immunological status of chronically malnourished individuals has not been well documented.

- There are limited data regarding the prevalence of metabolic complications in long-term use of ART in resource-limited settings. However, as ART access is scaled up in these settings and the average lifespan of HIV-positive individuals increases, there is growing need for evidence regarding prevention, diagnosis, and management of the metabolic consequences of ART. Many metabolic complications associated with ART may potentially be corrected with nutritional modifications; for example, a high-fiber diet may help with improving lipodystrophy, and vitamin D and calcium supplementation may help to correct derangements in bone mineral metabolism.
Vulnerable Populations: Pregnant and Lactating Women and Children

- Additional research is needed regarding nutrition and ART in HIV-positive pregnant women; specifically, the potential impact of ART on the nutritional needs of pregnant women and the optimal nutritional supplementation during pregnancy. There is insufficient evidence to suggest that iron-folate recommendations should differ for HIV-positive pregnant women; however, the safety and efficacy of iron supplementation among HIV-positive pregnant women needs to be established.

- Additional research is needed regarding the potential effect of ART on the nutritional needs of lactating women, particularly in resource-limited settings where breastfeeding is ubiquitous. ARVs affect nutritional status, body composition, breast growth, and lipid metabolism; however, the impact of ART on breast milk composition in HIV-positive lactating women is unknown.

- Further research is urgently needed to examine the potential impact of ART on the growth, development, and nutritional status of HIV-positive and negative children born to mothers living with HIV in regions characterized by extensive malnutrition and overlapping epidemics of HIV/AIDS and undernutrition.

CONCLUSION

Nutritional management and universal access to ART are essential weapons in the arsenal against HIV/AIDS. Nutritional management represents an important adjunct to ART, and may improve ART safety, efficacy, and adherence; reduce the impact of ARV side effects; alleviate the nutritional consequences of ART; and increase survival and quality of life. In the context of rapid scale-up of ART, comprehensive HIV/AIDS care and treatment programs including integrated nutritional management are of paramount importance.

Nutritional status coupled with dietary counseling should be considered by governments and external aid agencies involved in providing health services and evidence-based programmatic recommendations for people living with HIV. This would facilitate the rapid identification and resolution of nutritional problems and confer benefits such as improved nutritional status, improved health, and reduced disease progression in affected populations. However, ensuring access to ART should remain the top priority of these agencies, as treatment has the single largest beneficial effect on nutrition and survival in individuals with HIV/AIDS.

There is an urgent need for further research to inform optimal clinical and nutritional management of the HIV-positive individual. Areas in need of further study include: nutritional assessment, nutrition-ART interactions, safe and efficacious dosages of multivitamin supplementation (single-dose RDA vs. multiples of the RDA) to delay disease progression, nutritional composition of macronutrient supplementation, identification and development of palatable and locally available foods to improve nutritional status, and effects of ART on growth and development in HIV-positive children.

The overlapping pandemics of HIV/AIDS and undernutrition pose serious clinical and programmatic challenges to health-care providers in resource-limited settings. As access to ART is rapidly scaled up, commensurate increases in nutritional management are urgently needed to ensure the health and well-being of all those living with HIV.
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HIV Postexposure Prophylaxis: General Recommendations and Lessons Learned from Jos University Teaching Hospital, Nigeria

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Jos University Teaching Hospital (JUTH) is situated in Jos, the capital city of Plateau State in the north-central region of Nigeria. It is a tertiary health facility serving a region comprising six states. Plateau State has an HIV prevalence rate of 6.3%, which is above the national rate of 4.4%. The antiretroviral therapy (ART) clinic at JUTH cares for about 12,000 patients living with HIV, representing one of the largest ART clinics in Nigeria. The hospital’s laboratory is equipped to perform HIV antibody screening, Western blot (for confirmatory testing), and tests for viral load, CD4 lymphocyte count, hematology, liver function, pancreatic amylase, electrolytes, and creatinine. The HIV postexposure prophylaxis (PEP) program has access to the same laboratory services used for HIV patient care. An infection prevention and control team at JUTH oversees the provision of PEP. Members of that team include a physician, laboratory scientist, nurse counselor, patient tracker (for patient follow-up), and pharmacist. The team is also responsible for the sensitization of hospital staff on safety measures to prevent exposures to HIV in the course of their work.

In an attempt to reduce the spread of HIV infection among health-care workers at JUTH, a committee was set up to oversee and manage cases of accidental occupational and non-occupational exposure that carried a risk of HIV infection. Over three years, we monitored health-care workers (occupational) and others (nonoccupational) who were exposed to the blood, tissue, or body fluids of patients who were HIV positive or of unknown status. Exposed individuals received risk assessment, counseling, HIV testing, and, if deemed appropriate, HIV PEP to prevent HIV infection.

The information presented in this chapter is based on lessons learned from the provision of PEP at JUTH, as well as general guidelines and recommendations for PEP in resource-limited settings. Although many of the recommendations in this chapter may be applicable to settings other than JUTH, it is important to modify approaches to PEP based on local conditions and the patient population being served.
DEFINITION OF POSTEXPOSURE PROPHYLAXIS

HIV PEP is drug therapy given to prevent HIV infection after direct contact with blood, tissue, or body fluids believed to be from an HIV-positive source. PEP is aimed at preventing HIV from invading sites of the human body known as “sanctuaries,” which include the lymph nodes and testes. Within the first 72 hours of HIV exposure, these sites are thought to be invaded by the virus, which remains there permanently. Therefore, administering HIV PEP within 72 hours of exposure to HIV is the most effective way of preventing HIV infection.

TYPES OF HIV EXPOSURE WARRANTING PEP

There are basically two types of exposure that may warrant PEP: occupational and nonoccupational.

**Occupational exposure** occurs when, in the course of his or her work, an individual is exposed to blood, tissue, or body fluids from an individual who is confirmed or believed to be HIV positive. This type of exposure is more common in hospitals and clinics but can occur anywhere as long as the exposed individual was performing work duties at the time of the incident.

**Nonoccupational** exposure, as the name implies, occurs outside the workplace and is not associated with the individual’s job. This type of exposure includes rape and sexual assault, condom breakage during sexual intercourse with an HIV-positive individual, and contact with HIV-contaminated blood or body fluids outside one’s place of work (e.g., at an accident scene).

Other instances of nonoccupational exposure include human bites, fights that involve the shedding of blood, and rituals and other practices that involve the exchange of blood and blood products. Practices such as scarification, female genital mutilation, and local surgeries in which equipment sterility cannot be guaranteed may also lead to nonoccupational exposure.

Nonoccupational exposure cases from rape and sexual assaults are commonplace and frequently go unreported because the survivor fears molestation and embarrassment from the public and relatives. Most referrals of rape cases are received from peripheral health facilities. Thus, it is important that health-care providers at all levels are fully aware of the availability of PEP services and the short response time required for effective treatment. Health-care workers should also be able to assess the patient’s risk of exposure according to the type of contact that has occurred. Sexual assault and rape are violent acts that can result in cuts and abrasions— Injuries increase one’s risk of exposure to HIV and should therefore be treated with the utmost seriousness. In addition to PEP, survivors of rape and sexual assault should be offered antibiotics to protect them from other sexually transmitted infections and should receive extensive psychological counseling.

CRITERIA FOR RECEIVING HIV PEP: DEFINITION OF LOW AND HIGH RISK

**Occupational Exposures**

The following occupational exposures are at high risk for HIV infection:

- Severe percutaneous deep injury (e.g., cut during amputation, piercing by bone speckle, deep penetrating injury during a medical procedure)
- Direct contact with a large amount of blood (e.g., blood splash)
- Visible blood of the source person on the invasive device
- Needle-stick injury from a needle that has been in contact with the source patient’s artery or vein
• Source patient known to be in the acute seroconversion stage or advanced stage of HIV disease

The following circumstances constitute a low risk for HIV infection:
• Contact with mucous membrane or nonintact skin
• Contact with a small amount of blood (i.e., a drop of blood)
• No blood from the source person visible on the invasive device
• An abrasion with no significant bleeding
• Source person with asymptomatic HIV infection and/or low viral load

When mucous membrane or nonintact skin is exposed to a large amount of blood (e.g., blood splashing into the eye), it is considered a high risk for HIV infection because of the quantity of blood involved and the susceptibility of the exposure site. Exposures to other body fluids, such as pleural, pericardial, peritoneal, and amniotic fluids, though they may lead to HIV infection, are termed low risk because they contain a lower viral count compared with that of blood or blood products. In all cases of potential exposure, the source blood or body fluid must be confirmed as being from an HIV-infected individual whenever possible.

The key issue in deciding whether a person should receive PEP is the determination of whether a potential exposure to the infectious material has occurred (see Tables 1 and 2). For potential exposure to occur, there has to be a break in the lining of the skin, as with a needle-stick injury, cuts by sharps contaminated with HIV-positive fluid, or a spill or splash of contaminated fluid over an open wound. A mere splash or spill of contaminated fluid over intact skin is not considered a potential exposure.

If the HIV status of the source patient is unknown or has not been verified by a trustworthy source, that patient will have to be screened for HIV antibodies after appropriate counseling to confirm his or her status. If the screening test is negative and the patient is not at high risk for HIV infection, the injury may be considered not a risk for HIV infection and therefore may not require HIV PEP, especially in a low-prevalence setting. However, in JUTH and many other settings in sub-Saharan Africa where there is a high prevalence of HIV, PEP may be considered even though the source patient is found to be negative for HIV antibodies.

Polymerase chain reaction (PCR) testing of the source person when available may be advised after a negative screening test if that person meets any of the following criteria:
• Child under 18 months of age born to an HIV-positive mother
• Recent history of unprotected sexual intercourse with a person of unknown HIV status (an earlier clinical history to elicit this is important)
• One of a discordant couple
• An indeterminate result from a Western blot test (PCR can be used as a tiebreaker)

Nonoccupational Postexposure Prophylaxis

In cases of potential nonoccupational exposure, risk should be assessed based on the HIV status of the source (if known) and the type of exposure. Figure 1 (next page) provides a basic algorithm for the assessment and management of nonoccupational exposure risk. As with all HIV PEP, the exposure must have occurred less than 72 hours from the initiation of treatment in order for non-occupational postexposure prophylaxis (nPEP) to be effective.

PROCEDURES FOR ADMINISTERING PEP

Administering PEP after a potential exposure is a relatively straightforward process. HIV screening of the exposed person is done within the first hour of presentation. If the exposed person is found to be HIV negative and it is determined that there is
The PEP officer will usually ask preliminary questions about the nature of injury to rule out “assumed injury.” Whenever possible, it is essential to verify whether the source person is HIV positive. Instances abound when PEP that was commenced outside the hospital had to be stopped because the source patient was confirmed to be HIV negative. Some health-care workers are not aware that PEP is given only when the source person is known to be HIV positive or of unknown status, regardless of the severity of the worker’s injury.

**Figure 1. Algorithm for evaluation and treatment of possible non-occupational HIV exposures**

Source: Smith DK et al.
CRITERIA FOR PROVISION OF PEP

The question of who should access PEP continues to be discussed in the medical community because of the serious consequences of seroconversion. The following guideline is based on the Nigerian national guidelines for administration of ARVs for both occupational and nonoccupational exposure.

For an individual to access HIV PEP, the following criteria must be met:

- Patient has been exposed to HIV-contaminated fluid, blood, or tissue within 72 hours of initiation of therapy.
- There is confirmation that actual exposure is highly likely to have occurred (i.e., patient has had low- or high-risk contact with blood, tissue, or other body fluids from source person known to be HIV positive or of unknown status).
- Exposed individual has been screened for HIV antibodies and found to be seronegative.

COUNSELING FOR HIV PEP

A brief counseling session takes place before the exposed person is sent for HIV screening. Counseling provides reassurance and is also needed to obtain consent for an HIV screening test. After screening, posttest counseling is provided, and the results are reviewed by the same doctor who prescribes ARVs. If the patient is found to be eligible for PEP, the physician and the pharmacist provide drug adherence counseling. Possible adverse effects
of the drugs and ways to manage them are also explained at this time. A dedicated phone number is given in case the patient has questions about side effects or other treatment issues, and HIV prevention counseling is provided. The patient is advised to abstain from unprotected sexual intercourse and blood donation during the treatment period.

**SELECTION OF ARV DRUGS FOR HIV PEP**

ART for HIV PEP consists of drugs known to be efficacious while producing minimal side effects. The goal is to give the most effective ART within the shortest time and with the least chance of adverse reactions. For HIV PEP, two or three drugs from one or two classes of ARVs are used. Two drugs from the same class are used for low-risk cases, while three drugs from two classes are used for high-risk cases. JUTH offers three ARVs when it cannot be determined whether the exposure was low or high risk. The most widely used drugs for PEP are zidovudine (AZT), lamivudine (3TC), indinavir (IDV), and lopinavir (formerly called ABT-378).

ARV selections are ideally based on whether exposure is deemed to be high or low risk. In high-risk situations, we offer two nucleoside reverse transcriptase inhibitors, usually AZT and 3TC (Combivir) and IDV/r (a ritonavir-boosted protease inhibitor). Nevirapine is avoided because of the risk of hypersensitive reactions, which are more common among patients with high CD4 counts (males >400 cells/mm$^3$ and females >250 cells/mm$^3$).

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**Table 2. Recommended HIV Postexposure Prophylaxis after Mucous Membrane and Nonintact Skin Exposures**

<table>
<thead>
<tr>
<th>Exposure Type</th>
<th>Infection Status of Source$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV Negative</td>
</tr>
<tr>
<td>Small Volume (e.g., a few drops)</td>
<td>No PEP warranted</td>
</tr>
<tr>
<td>Large Volume (e.g., a major blood splash)</td>
<td>No PEP warranted</td>
</tr>
</tbody>
</table>

$^a$For skin exposures, follow-up is indicated only if evidence exists of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).

$^b$HIV positive (class 1): asymptomatic HIV infection or known low HIV RNA viral load (e.g., <1,500 copies/mL); HIV positive (class 2): symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load; unknown HIV status: for example, a deceased source person with no samples available for HIV testing; unknown source: for example, a needle from a sharps disposal container.

$^c$The recommendation “consider PEP” indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the doctor regarding the risks versus benefits of PEP.

$^d$If PEP is offered and administered, and the source is later determined to be HIV negative, PEP should be discontinued.

Source: Clinical Manual for Management of the HIV-Infected Adult.$^h$
The decision to prescribe ARVs for PEP is also based on whether the source patient (and/or the patient’s mother in the case of a pediatric source patient) is responding well to a particular ART regimen. For example, if the source patient has failed first-line therapy, the transmitted HIV strain may be drug resistant. This would necessitate elaborate investigation, including an HIV drug resistance test, to establish the most effective therapy. In the absence of these tests, the choice of drugs for PEP should be based in part on empiric HIV drug resistance data of first-line therapy failures. A complex case such as this, while possible, is a rare occurrence.

**EXPERIENCES FROM JUTH**

Accessing HIV PEP begins at the point of exposure. All the wards, theaters, and dressing/injection rooms in JUTH have notices on where and how to access PEP after exposure. Health-care workers have also received training on injection safety and universal precautions, and have attended a sensitization workshop on PEP. When a potential exposure occurs, the officer in charge of the unit is notified, and then the PEP officer is informed. The PEP officer has an open telephone number that is widely circulated to allow for unrestricted access. The hospital PEP team is headed by a physician assisted by a pharmacist. Other members of the team include a counselor and a laboratory scientist. This team is on call 24 hours a day, and all have one another’s phone numbers for ease of communication.

PEP drugs are always available for dispensing on instruction. The time to complete all needed steps varies from 15 to 20 minutes. However, universal precautions are usually undertaken even before notification (i.e., the site of injury is washed with clean running water using soap or liquid detergent). Because of panic, some health-care workers use bleach to wash their hands; this may not be necessary because clean water and soap are sufficient. When the conjunctiva is involved, the exposed person should use only clean water to irrigate the eyes; using soap on the eyes could increase the chances of infection and irritation.

We have found that it can be challenging to counsel health-care workers to receive HIV tests, the prerequisite for receiving HIV PEP. In some instances, health-care workers have refused HIV screening for fear of being diagnosed as HIV positive. This fear can often be allayed through reassurance that testing is voluntary and confidential. Exposed persons who refuse counseling and testing at the facility where they work are referred to another facility to receive the necessary intervention. In practice, it is difficult to deliver an HIV-positive result to a co-worker. Physicians are sometimes the most difficult cases; often they are willing to take PEP to prevent infection but do not want to be screened for HIV infection. Despite these difficulties, the policy at JUTH is that refusal to have HIV testing at baseline does not delay initiation of PEP. PEP is begun while the health-care worker receives further counseling on the need for the test, as PEP is usually not adequate to treat HIV infection if the HIV test is positive at baseline.

Challenges also arise when the source patient refuses HIV screening. In such cases, we proceed to manage the health-care worker or other potentially exposed individual as a case of high-risk exposure. It is also important to take a thorough history from the source patient to determine whether the risk of exposure is high and, if so, the anticipated window of opportunity. If the risk for recent exposure is high but the source person is found to be seronegative, a repeat screening test should be provided at a later date. In that case, the exposed person is still offered HIV PEP because of the high HIV prevalence in the JUTH setting.

Needle-stick injury occurring in the course of pediatric care when the mother is known to be HIV infected is followed by mandatory PCR on the
child if under 18 months of age, because an antibody test is not reliable for young infants (in settings that cannot offer PCR, the exposed individual should be offered PEP). For children older than 18 months, an antibody test should be done on the child after the parents receive counseling.

Preliminary investigations are usually done before commencement of PEP to establish a baseline for monitoring any abnormalities in organ functions caused by drug side effects. These include a liver function test (liver enzymes such as alanine and aspartate transaminases, total proteins, and alkaline phosphatase), serum urea and creatinine (for renal function), and pack cell volume or hemoglobin (for anemia and to possibly exclude the use of AZT). These investigations are repeated if the patient presents with symptoms suggesting an adverse reaction to the drugs. Patients are encouraged to report any side effects to the PEP team directly or to call a dedicated telephone line for further assistance.

CHALLENGES AND NEXT STEPS
Based on our experiences, some challenges related to the effective use of PEP include the following:

- Mandatory HIV screening prior to PEP initiation may not be widely acceptable.
- PEP is not 100% effective, so seroconversion could occur regardless of adherence to the PEP regimen.
- People who have been exposed to ARVs and subsequently seroconvert may develop resistance if the initial dose was suboptimal or if less than three ARV drugs were given.
- Not enough studies have been done on PEP in humans. PEP knowledge to date is largely based on animal studies.
- Follow-up for cases of HIV PEP is poor, and cases of rape and sexual assault are often reported very late, making ARVs less efficacious.
- JUTH is short staffed and therefore overburdened by this additional responsibility, particularly when patient follow-up is required. Creating a database to track patients receiving PEP could be helpful.
- We observed that poor communication was one of the problems associated with delivery of PEP services. Therefore, a dedicated telephone line was created to provide information about PEP and how to receive it.
- Drug stock-outs should be anticipated because the number of PEP cases cannot be accurately forecasted. We aim to stock three times the number of drugs we expect to use. For example, we see an average of eight cases every month, so we have 24 doses in stock. For centers that do not provide free ART, this might be a major constraint. Help from donors could be sought in these cases.
- There is general underreporting of exposure cases because of many factors, including lack of knowledge about the availability of PEP services. We are tackling this issue through sensitization workshops.

CONCLUSION
HIV PEP should be incorporated into all health-care facilities and coordinated by a team that responds to both nonoccupational and occupational exposures. There should be an enhanced public awareness campaign notifying the public and health-care workers alike about HIV PEP services and how to access them. Adequate resources, drugs, and staff should be provided at health facilities to care for individuals exposed to HIV. Improved HIV PEP data collation and interpretation will also help educate the medical community and the public on better ways of managing HIV exposure. Toward that end, the provision of PEP should be accompanied by routine data collection.
REFERENCE LIST


OPPORTUNISTIC INFECTIONS, CANCERS, AND COINFECTIONS
THE CENTRAL NERVOUS SYSTEM (CNS) is one body system significantly affected by HIV infection. In addition to the direct invasion of the CNS by HIV, which is a neurotrophic virus, the gradual deterioration in the host’s immune function indirectly leads to the colonization of the CNS by opportunistic infections (OIs).¹ The spectrum of CNS disorders ranges from mild self-limiting conditions to severe life-threatening infections and malignancies. There is significant overlap in the presentation (i.e., signs and symptoms) of HIV-associated CNS disorders.² To reduce the high morbidity and mortality associated with delayed or missed diagnosis of life-threatening CNS disorders, the clinician must have the capacity to make a prompt, accurate diagnosis and to initiate immediate therapeutic measures. Clinical skills, laboratory support and, where available, neuroimaging tools (e.g., computerized axial tomography [CAT] scans) are all helpful in achieving the best possible outcomes.

The clinician in resource-limited settings faces considerable challenges in promptly diagnosing and managing CNS disorders in people living with HIV. The high prevalence of HIV in parts of Africa and other resource-limited settings has led to a significant increase in the burden of CNS infections and malignancies.³ The limited expertise of clinicians in neurological assessment, coupled with the widespread lack of laboratory capacity for cerebrospinal fluid (CSF) analysis, may lead to unnecessary delays in the diagnosis of CNS disorders. CAT scans and magnetic resonance imaging (MRI) technologies, which are both key diagnostic tools for CNS disease, are rarely available, even at tertiary levels of care. These difficulties are compounded by the fact that in many instances, CNS disease may be the initial indication of HIV infection.⁴ Thus, there is a real need for more accessible and affordable diagnostic tools to support clinicians in the timely management of CNS disorders in resource-limited settings.

Decision rules, or algorithms, constructed from an understanding of the presentations of the most common diagnoses, are one such diagnostic support tool that clinicians in resource-limited settings may find useful.⁵ The algorithms are stepwise pathways that start with categories of diseases (by cause) based on readily available skills and tools (i.e., physical diagnosis and basic tests), followed by further subcategorization based on more specific laboratory investigations (e.g., CSF...
approach to the hIV-poSItIVe patIent wIth headache

The Etiology of Headaches in the Setting of HIV Infection

Headache is one of the most common complaints among HIV-positive patients in outpatient settings. Among HIV-negative individuals, headache is rarely due to significant intracranial pathology, even when patients present in an emergency setting. In the HIV-positive individual, however, the complaint of headache must always be taken seriously. In the setting of HIV infection, headache may indicate the presence of life-threatening infections that, if not promptly diagnosed and treated, can lead to death or severe disability. Causes of such fatal headaches include meningitis due to Cryptococcus neoformans, Mycobacterium tuberculosis, Streptococcus pneumoniae, and Toxoplasma gondii encephalitis. HIV-positive individuals also suffer from headaches with etiologies similar to those suffered by HIV-negative individuals, including sinusitis, aseptic meningitis, vascular headaches, and tension headaches. Drugs such as zidovudine (a commonly used antiretroviral agent) are also known to cause headache. The differential diagnosis of headache in the HIV-positive individual is therefore quite wide.

Algorithmic Approach to Differential Diagnosis

An algorithmic approach can be employed to support clinicians in resource-limited settings who are faced with HIV-positive individuals presenting with headache. The algorithm presented here (Figure 1) was constructed with the following assumptions in mind:

- Individuals presenting with headache are already known to be HIV-positive.
- The complaint of headache has been voluntarily brought to the attention of a health-care worker rather than being elicited.
- The algorithm is not exhaustive; rather, it is a tool that enables the diagnosis of the most common, and perhaps most life-threatening, conditions.

The recommendations in the following algorithm are based on an understanding of the common causes of headache in people living with HIV in ambulatory and inpatient facilities in resource-limited settings. The algorithm employs increasingly sophisticated methods to differentiate the etiologies of headache, starting with the most basic approaches (e.g., history taking, examination, basic tests), moving through to lab-based approaches (e.g., CSF examination and chest radiographs), and then to specialized tests (e.g., neuroradiological imaging, serum cryptococcal antigen [sCRAG] tests, and blood cultures). These three levels of sophistication mirror the capabilities commonly found in primary, secondary, and tertiary levels of care. What follows is a detailed description of the diagnostic process.
The Diagnostic Process

The HIV-positive individual who presents with headache should always undergo an initial clinical evaluation consisting of a detailed history, physical examination, and some basic tests (including malaria smear in malaria-endemic regions). This basic evaluation may immediately yield some readily identifiable causes of the headache, including sinusitis, migraines, dental carries, hypertension, malaria, and other infectious processes (e.g., typhoid fever, yellow fever).

Where such a cause is identified, appropriate therapy should be instituted. If there is no readily identifiable cause, the next step in the diagnostic process is to determine whether there are focal neurological symptoms and signs associated with the headache. These include weakness of one side of the body (hemiplegia/hemiparesis), cranial nerve deficits, unstable gait (ataxia), speech disorder (aphasia), and convulsions (seizures). If an HIV-positive individual presents with a headache associated with focal neurological findings, empiric treatment for toxoplasma encephalitis (TE) should be initiated immediately. Because the presence of TE, which is a treatable diagnosis, represents an important opportunity to reverse neurological deficits, TE
should always be considered in patients with focal findings. Seven days after the empiric trial of therapy, the patient should be evaluated for a response. Reduction of weakness should warrant completion of antitoxoplasma therapy for at least six weeks. If after seven days the weakness does not significantly change or worsens, further diagnostic workup is warranted.

If the individual has no readily identifiable cause for the headache (on the initial basic evaluation) and has no focal neurological findings, the clinician should determine whether any of the following are present:
- Altered state of consciousness (confusion, stupor, or coma)
- Neck stiffness
- Hypotension

If any are present, an immediate lumbar puncture (LP) for CSF analysis, followed by empiric broad-spectrum antibiotics (given intravenously to cover bacterial meningitis), should be performed. If a CSF examination is not possible, empiric broad-spectrum antibiotics should be given immediately, and the patient should be referred, if possible, to a center where CSF analysis can be done. The choice of antibiotics should be informed by the local sensitivity patterns of the common isolates of bacterial organisms that cause meningitis and bacteremia in HIV-infected individuals.

Following CSF analysis, a number of diagnoses may become apparent, including the following:
- Cryptococcal meningitis (CM)
- Acute bacterial meningitis
- Aseptic (viral) meningitis
- Tuberculous meningitis
- Neurosyphilis/syphilitic meningitis

If any of these meningitides are diagnosed, the appropriate antimicrobial therapy should be instituted. (The management of CM is described in more detail later in this chapter.)

The CSF analysis may not reveal a specific diagnosis in individuals who do not have any focal findings. These individuals should be reassessed 48 hours after the initial assessment. For those who show improvement in their general conditions, further clinical observation should be done with symptomatic management. The clinician should consider performing one or more of the following when he or she follows up with individuals who experience either no improvement or a worsening of their condition:
- Repeat LP with CSF culture
- Blood cultures for fungal and mycobacterial isolation
- Chest X-ray
- Empiric antifungal and/or antimycobacterial therapy

If no further insight or improvement occurs after instituting the above measures, additional diagnostic workup is warranted (see below).

The clinician may be faced with a situation in which the patient without focal findings does not have any of the findings that require immediate LP (Figure 1). Such individuals should be managed symptomatically with analgesics and reassessed within 48 hours for progress. Individuals with improved symptoms should be observed further until they are fully well.

If no improvement occurs or if the symptoms worsen, an LP with CSF exam is recommended. Further management depends on the CSF findings, with any isolated organism being treated with appropriate antimicrobials. Further diagnostic workup is warranted for those individuals without any positive findings on CSF examination.

**Further Diagnostic Workup**

As noted previously, three instances warrant further diagnostic workup. The individual under investigation will need to undergo tests that may
only be available at a tertiary care facility, requiring referral to such a facility. The following tests are suggested at this stage to facilitate a more accurate diagnosis:

- CD4 lymphocyte count: Counts below 200 cells/mm³ are strongly suggestive of an OI.
- CAT scan: Can demonstrate structural lesions of varied etiology.
- Serum/CSF CRAG: Will aid diagnosis when India ink is negative (20% of cases) and when the CSF culture for *Cryptococcus neoformans* may take a while to grow yeast cells.

**MANAGEMENT OF SELECTED CNS DISORDERS THAT PRESENT WITH HEADACHE**

**Cryptococcal Meningitis**

CM is the most common life-threatening fungal infection among people living with HIV globally and is now the leading cause of meningitis among adults in areas of high HIV prevalence.¹ The causative organism, *Cryptococcus neoformans*, is a capsulated fungus that is commonly isolated from pigeon droppings and is widely distributed in soils. The infection is acquired via the lungs through inhalation of aerosolized organisms, which then establish a pneumonitis in the lungs followed by dissemination throughout the body in immunocompromised individuals. The organism has a predilection for the CNS; in a setting of profound immunosuppression resulting from HIV infection, this organism can lead to fungal meningitis.¹²

The onset of symptoms due to CM is insidious, with headache being by far the most common symptom. The headache is usually reported as frontal in location and occasionally as radiating to the occipital (back) region of the head. If the condition is not treated, the initially mild headache will gradually become severe and incapacitating. The headache may be associated with sixth-cranial-nerve palsies (an indicator of raised intracranial pressure) and changes in mental state. HIV-positive CM patients do not commonly report seizures. Compared with HIV-seronegative individuals with CM, up to 50% of HIV-associated CM patients may not have symptoms and signs of meningeal irritation (e.g., neck stiffness, positive Kernig’s sign).¹³ The non-specific presentation of CM in HIV-positive individuals requires that clinicians have a high index of suspicion to readily diagnose the condition and significantly reduce the high mortality associated with it.

The diagnosis of CM is established by examining CSF using India ink stain (through demonstration of a thick capsule around the fungal organism) or fungal cultures for the causative organisms using Sabouraud’s agar. Screening for CM among symptomatic individuals is best done with an sCRAG test, an agglutination assay that requires limited laboratory infrastructure. The sCRAG assay has a very high positive predictive value (99%) for CM in symptomatic individuals (i.e., those with headache).¹⁴

In summary, HIV-positive individuals with headache—particularly those in high-prevalence areas—have a very high likelihood of developing CM. Despite the high positive predictive value of the sCRAG test, patients with a positive result should nevertheless undergo LP for several reasons. First, LP offers the opportunity for a definitive CM diagnosis through CSF analysis. Second, LP in CM patients with raised intracranial pressure (ICP) offers some therapeutic benefit by relieving the pressure through CSF drainage. Finally, in some instances, HIV-positive individuals may have multiple CNS infections; the only way to detect this is by analyzing the CSF.

Management of CM consists of the following steps:
1. Initiation of specific antifungal therapy

Antifungal therapy occurs in three phases. Table 1 lists both the preferred and the alternative treatment regimens.15

2. Management of raised ICP

CM in people living with HIV is very often associated with elevated ICP; this is particularly true in resource-limited settings, where patients presenting at a health facility may be at a late stage of disease. Because of the association of raised ICP with high mortality, the Infectious Diseases Society of America (IDSA) guidelines for the management of HIV-associated CM recommend the management of raised ICP as an integral part of CM management.15 ICP management is achieved through serial drainage of CSF directly from the diagnostic LP. In settings where CSF manometers (for measurement of CSF pressure) are not readily available, it is advisable to perform generous drainage of CSF (>10 mL) in patients with focal neurological deficits. The safety of this procedure has been demonstrated in a small study in Uganda among HIV-positive patients with CM.16

3. Exclusion of concurrent OIs

The high mortality observed in CM patients may partly result from concurrent OIs. For example, one study found that as many as 27% of patients with HIV-associated CM also had active tuberculosis.17 Therefore, active screening for common OIs is recommended in CM patients.

4. Initiation of antiretroviral therapy

CM occurs in severely immunosuppressed individuals, and a CM diagnosis implies advanced HIV disease (World Health Organization [WHO] stage IV). Following the management of the acute episode of CM, it is imperative that patients be prepared for and initiated on antiretroviral therapy (ART). However, very early ART initiation may be associated with immune reconstitution inflammatory syndrome (IRIS; see section later in this chapter).

**Toxoplasma Encephalitis**

TE is the most common cause of focal neurological deficits among HIV-infected individuals.18 TE is caused by *Toxoplasma gondii*, a highly prevalent parasitic infection of the brain that is usually latent but is reactive in immunosuppression settings. The reactivated infection leads to clinically apparent disease.19

The common presentations of TE include hemiparesis or hemiplegia, unilateral facial weakness (i.e., cranial nerve lesions), ataxia, and seizures, as well as aphasia, depending on the part of the CNS affected. The onset of symptoms is usually insidious rather than sudden, even though TE

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**Table 1. Phased Antifungal Therapy for Cryptococcal Meningitis**15

<table>
<thead>
<tr>
<th>Regimen type</th>
<th>Acute phase (2 weeks)</th>
<th>Consolidation phase (8 weeks)</th>
<th>Maintenance phase (lifelong)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred regimen</td>
<td>Amphoterin B (0.7 mg/kg/day for 14 days +/– Flucytosine</td>
<td>Fluconazole (400 mg/day)</td>
<td>Fluconazole (200 mg/day)</td>
</tr>
<tr>
<td>Alternative regimen</td>
<td>Fluconazole (400 mg/day)</td>
<td>Fluconazole (400 mg/day) Or Itraconazole</td>
<td>Fluconazole (200 mg/day) Or Itraconazole</td>
</tr>
</tbody>
</table>
lesions involving the cerebral vasculature can lead to sudden presentation.20

The diagnosis of TE is initially made on clinical grounds (i.e., focal neurological deficit in a setting of profound immunosuppression) and is augmented by serological evidence of active Toxoplasma gondii infection (i.e., elevated serum antitoxoplasma IgG titers). Definitive diagnosis is made using neuroradiological imaging. Typically, the contrasted CAT scan shows ring-enhancing lesions that may be multiple and that are usually in the area of the basal ganglia. In settings without access to CAT scan technology, diagnosis can be made when the patient responds to antitoxoplasma therapy (Table 2).21

Because the diagnosis of TE in resource-limited settings is usually presumptive (i.e., based on the clinical presentation), patient response to antitoxoplasma therapy is essential for confirming the presence of TE. Patients are assessed after two weeks of empiric antitoxoplasma therapy, and responsive individuals continue the treatment regimen as indicated. Individuals with minimal or no improvement should undergo evaluation for other HIV-associated conditions that present with features similar to TE, including primary CNS lymphoma (PCNSL), progressive multifocal leukoencephalopathy (PML), and meningovascular syphilis.22

PCNSL is a neoplasm of B-cell origin that affects HIV-infected individuals who have advanced immunosuppression. The Epstein-Barr virus (EBV) has been implicated as a cause for PCNSL. Patients with PCNSL present with focal neurological findings, including weakness on one side of the body, facial weakness, or speech defects, depending

<table>
<thead>
<tr>
<th>Table 2. Antimicrobial Management of Toxoplasma Encephalitis21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen type</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td><strong>Preferred regimen</strong></td>
</tr>
<tr>
<td><strong>Alternative regimen</strong></td>
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</table>
of the part of the brain affected. Diagnosis is aided by CAT scan imaging, which usually shows a solitary, deep (subcortical) brain lesion that minimally enhances on contrast. These features may help distinguish PCNSL from toxoplasmosis, particularly if the patient does not respond to empiric antitoxoplasma therapy within two weeks. Treatment of PCNSL consists of radiotherapy and chemotherapy, either singly or combined. Even with treatment, however, median survival ranges from two to four months.

PML, an OI that affects the brain, is caused by the John Cunningham virus (JCV; a human polyomavirus). Like PCNSL, PML presents with focal neurological symptoms and signs in advanced HIV disease; it is easy to distinguish PML from PCNSL and TE with neuroimaging. Lesions seen on a CAT scan are usually limited to the white-matter portion of the brain and are not ring enhancing on contrast. There is no known effective treatment for PML, though in a few individuals, use of cytosine has resulted in some improvement. There have also been some documented cases of spontaneous remission.

Meningovascular syphilis usually occurs in early HIV disease and, in this regard, is relatively easy to distinguish from PML, TE, and PCNSL.

**Immune Reconstitution Inflammatory Syndrome**

Between December 2003 and June 2006, the estimated number of individuals receiving ART in low- and middle-income countries increased fourfold. This increase has led to tremendous reductions in morbidity and mortality from HIV-associated OIs. Unfortunately, this restoration of immune function can also lead to an abnormally heightened response to antigens in some patients, resulting in a clinical presentation characterized by inflammatory symptoms and signs. This situation is referred to as the immune reconstitution inflammatory syndrome (IRIS).

The manifestations of IRIS are diverse, depending on the body system affected. The scope of presentations includes meningeal symptoms, abscesses, fevers, cutaneous lesions, and chest symptoms, as well as hepatic liver enzyme abnormalities. In the CNS, IRIS may present as a meningeal syndrome, headache, or space-occupying lesion. The prevalence of IRIS in resource-limited settings ranges from 10% to 25% among individuals initiating ART. The most common antigens associated with IRIS in these settings are *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, and herpes simplex virus; however, IRIS has also been described for most opportunistic pathogens.

Most IRIS episodes are self-limiting, and only rarely is the syndrome life threatening. Unfortunately, the CNS is one system in which IRIS events can be fatal, because IRIS in the CNS may be associated with raised ICP as a result of inflammation. In CNS IRIS due to *Cryptococcus neoformans*, fungal CSF cultures are usually negative, despite the presence of cryptococcal antigen. The diagnosis of other CNS antigens that cause IRIS can be difficult in resource-limited settings due to limited laboratory capacity for mycobacterial and viral culture, including polymerase chain reaction (PCR) assays. Where CNS IRIS is associated with raised ICP, LP and drainage of CSF are recommended as part of the patient’s management. A further discussion of IRIS can be found elsewhere in this text.

**Approach to the HIV-Positive Patient with Visual Loss**

Visual loss and ocular diseases are a common complication among people living with HIV worldwide. In North America and Europe, it is estimated that 50% to 75% of HIV-positive individuals develop visual loss at some point during the course of their illness. In Africa, the prevalence of ocular disease...
among HIV-positive individuals is estimated to be between 30% and 45%. Visual loss is important because it can be the first manifestation of a life-threatening systemic disease process in the person living with HIV. The ocular diseases that cause vision loss result in irreversible blindness if not treated promptly and effectively.

The three main mechanisms that result in ocular manifestations of HIV and visual loss are as follows:

1. The depressed immunity in patients with advanced HIV disease predisposes them to OIs and malignancies that affect the eye.
2. Ocular allergic and toxic drug reactions are a complication of some of the medications used for treatment of OIs or the virus itself.
3. The HIV virus can have a direct effect on ocular tissues.

The pattern of ocular diseases affecting HIV patients in the African region, however, is different from that found in developed countries. Ocular tumors and OIs due to organisms such as *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, and *Toxoplasma gondii* are more frequent causes of ocular morbidity and visual loss in Africa, but in developed countries, cytomegalovirus (CMV) retinitis and immune recovery uveitis remain the leading causes of visual loss.

In the following section we review some of the common causes of visual loss seen in developing countries and the approach to patients presenting with these conditions.

**OPPORTUNISTIC INFECTIONS AND MALIGNANCIES**

Opportunistic ocular and systemic infections are the most common causes of visual impairment in people living with HIV/AIDS worldwide. These commonly occur in advanced stages of the disease when the patient’s CD4 T cell count falls below 100 cells/mm³.

**CMV Retinitis**

CMV is the number one cause of ocular morbidity and visual loss in HIV-positive individuals. The prevalence of CMV retinopathy in people living with HIV in developed countries before the introduction of combination ART was about 30% to 50%. It is documented that the prevalence of CMV retinitis is decreasing to 7.5% with the advent of ART in developed countries.

The prevalence of CMV retinitis reported in different African centers, however, is 0% to 8.5%. The mean CD4 T cell count at the time of CMV diagnosis is typically less than 50 cells/mm³, and diagnosis is rare with CD4 T cell counts greater than 200 cells/mm³. CMV retinitis was reported to be lower in Africa because of lack of effective treatment of OIs and ART; therefore, few patients survive long enough to develop CD4 T cell counts of less than 50 cells/mm³. However, more recent studies in Africa are documenting an increasing number of patients presenting with CMV retinitis over the past six years as ART is becoming more readily available.

Visual loss or blindness is the most common presenting symptom for CMV retinitis in developing nations like Africa because of late presentation and lack of routine ophthalmologic examinations of those at risk, which are a constraint due to limited resources.

In the early stages of retinitis, when lesions start away from the macula, patients may be totally asymptomatic or may have symptoms of floaters due to a vitreous reaction. Such patients can only be diagnosed by routine dilated fundoscopy. It is only in the advanced stages of the disease when a large area of the retina or the macula is affected that patients present with varying degrees of visual loss in the affected eye.

Diagnosis of CMV retinitis is largely made by the clinical appearance of the retinitis on ophthalmic evaluation with the supporting low CD4 T cell count.
levels. Serum antibody titers are not helpful; there is a 50% to 90% prevalence of seropositivity in the general adult population, and there is no relationship between antibody titers and the development of CMV retinopathy in people living with HIV.41

Table 3 summarizes the different diagnostic options that are used in different centers, depending on the resources available.

CMV retinitis responds to antiviral drugs such as ganciclovir, foscarnet, cidofovir, and valganciclovir.42-44 These drugs do not eradicate the virus from the eye. Patients therefore must receive chronic low-dose (“maintenance”) therapy to prevent the immediate reactivation of the disease. Recent studies also show that ART improves the patient’s immune system enough to control CMV retinitis.

Antiviral drugs for CMV retinitis are expensive and hardly available in developing countries. In such resource-limited settings, weekly intravitreal injections of ganciclovir or foscarnet are given to individual affected eyes together with ART until the patient’s CD4 T cell count improves to 200 cells/mm³ or more. This does not treat systemic CMV infection. In resource-limited settings, a typical fundus lesion, a supporting low CD4 T cell count, and a positive response to anti-CMV treatment and ART are the major parameters used to support diagnosis of CMV retinitis.

**Herpes Zoster**

Herpes zoster ophthalmicus (HZO) is a dermatome skin eruption along the distribution of the ophthalmic branch of the trigeminal nerve due to varicella-zoster virus. It may occur at any stage of the HIV infection but is often the first sign of the disease. Studies done in Africa reveal the prevalence of HZO in HIV-positive individuals to be 5% to 10%.45 Visual impairment occurs when there is an associated keratitis, anterior uveitis, or viral infection of the retina (progressive outer retinal necrosis [PORN]). Sixty-five percent of patients with HZO develop corneal complications and will become visually impaired.46 No data are currently available on the prevalence of PORN in the developing world. It has been reported in African patients, and risk factors include a low CD4 T cell count (less than 50 cells/mm³) and a recent or current cerebral or visceral herpes zoster infection.47

The associated clinical symptoms of cornea and anterior segment involvement include pain, redness, photophobia, and tearing. PORN presents as sudden, painless loss of vision in the affected eye. Diagnosis is made on clinical grounds. Patients with HIV infection and HZO should be treated with systemic acyclovir to promote healing of skin lesions and to reduce the incidence and severity of ocular lesions.

Antibiotic cover for secondary infection is usually required. HZO is another common cause of visual loss in developing countries because of poor referral systems to ophthalmologists. Traditional eye medicines are often applied to treat pain associated with the different stages of the disease, and these contribute to secondary infection, corneal ulcers, scars, and, many times, endophthalmitis.

**Herpes Simplex Virus**

Herpes simplex virus type 1 is a common cause of prolonged visual impairment in patients living with HIV.48 Vision-impairing lesions are a result of corneal involvement, anterior uveitis, and retinal infection. The keratitis is associated with pain and redness of the affected eye, and the retinal infection is painless with occasional floaters. Diagnosis is usually made on clinical grounds by identifying the characteristic dendritic or geographic corneal ulcers or disciform keratitis on slit lamp examination. Herpes simplex virus infection of the retina occurs in HIV-positive patients, causing acute retinal necrosis and PORN. Corneal lesions respond to topical antiviral therapy, but recrudescence may
<table>
<thead>
<tr>
<th>Etiology of Visual Impairment</th>
<th>Ocular Manifestations</th>
<th>Definitive Diagnosis</th>
<th>Highly Probable</th>
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<tr>
<td><strong>Opportunistic infections</strong></td>
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<td>Varicella zoster</td>
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<td><strong>A. Anterior segment disease</strong></td>
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<td>C5 sensory distribution of skin rash/scars</td>
<td>Virus isolation from skin rash vesicles (culture, polymerase chain reaction [PCR])</td>
<td>1. Demonstration of multinucleated giant cells on Tzanck smear 2. Typical C5 dermatomal vesicular skin rash or scars +/- other ocular manifestations</td>
<td>Typical C5 dermatomal vesicular skin rash or scars +/- other ocular manifestations</td>
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<td>Keratopathies</td>
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<td>Pupil abnormalities</td>
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<td>Uveitis / iris atrophy</td>
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<td><strong>B. Posterior segment disease</strong></td>
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<td>Vitritis</td>
<td>1. Virus isolation in vitreous or retinal tissue (culture, PCR)</td>
<td>1. A rapidly progressing discrete peripheral necrotizing retinitis +/- other postsegment manifestations 2. Response to anti-viral treatment</td>
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<td>Vitreous hemorrhage</td>
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<td>Progressive outer necrosis</td>
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<td>Acute retinal necrosis</td>
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<td><strong>C. Neurophthalmic disease</strong></td>
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<td>Postherpetic neuralgia</td>
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<td>Extraocular muscle palsy</td>
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<td>Facial nerve palsy</td>
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<td>Cerebral vascular accidents</td>
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<td>Hemiplegia</td>
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<td>Herpes simplex</td>
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<td>Dendritic corneal ulcer</td>
<td>Isolation of virus in corneal scrapings (culture, PCR)</td>
<td>Typical clinical corneal lesion +/- other ocular manifestations</td>
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<td><strong>Opportunistic infections (cont.)</strong></td>
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<td>Herpes simplex</td>
<td>B. Posterior segment disease</td>
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<td></td>
<td>■ Acute retinal necrosis</td>
<td>1. Virus isolation in vitreous or retinal tissue</td>
<td>1. A rapidly progressing discrete peripheral necrotizing retinitis</td>
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<td></td>
<td>■ Progressive outer necrosis</td>
<td>2. Viral antibodies in intraocular fluids and serum</td>
<td>2. Response to antiviral treatment</td>
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<td>Cytomegalovirus (CMV)</td>
<td>■ CMV retinitis</td>
<td>1. Detection of cytomegalic inclusion bodies in retinal tissue</td>
<td>1. Typical clinical full thickness retinitis spreading along blood vessels</td>
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<td>■ Vitreous hemorrhage</td>
<td>2. Isolation of virus in retinal tissue, aqueous/vitreous</td>
<td>2. CD4 count less than 50 cells/mm³</td>
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<td></td>
<td>■ Retinal detachment</td>
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<td>■ Optic neuritis</td>
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<tr>
<td>Toxoplasma gondii</td>
<td>■ Anterior uveitis</td>
<td>1. Isolation of organism in ocular tissue (culture, PCR)</td>
<td>1. Typical clinical toxo lesion +/- positive toxo antibody titers</td>
<td>Atypical toxo lesion with evidence of systemic toxo</td>
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<td></td>
<td>■ Optic neuritis</td>
<td>2. Detection of toxo antigen in aqueous and serum</td>
<td>2. Response to antiparasitic drugs</td>
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<td>■ Vasculitis</td>
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<td>■ Chorioretinitis</td>
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<td>■ Retinal scars</td>
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<td>■ Retinal detachment</td>
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<td>Treponema pallidum</td>
<td>■ Interstitial keratitis</td>
<td>1. Direct observation of organism by darkfield illumination</td>
<td>1. Positive VDRL or rapid plasma reagin (RPR) and positive T. pallidum hemagglutination (TPHA) test in serum or CSF</td>
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<td>■ Anterior/posterior uveitis</td>
<td>2. Direct fluorescent antibody T. pallidum test</td>
<td>2. Fall in VDRL/RPR titers after treatment</td>
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<td>■ Argyll Robertson pupil</td>
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<td>■ Optic atrophy</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
<td>■ Anterior/posterior uveitis</td>
<td>Isolation of mycobacterium in involved tissue (culture, PCR)</td>
<td>1. Clinical and radiological evidence of systemic TB + ocular manifestations</td>
<td>Response to therapeutic trial of isoniazid</td>
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<td>■ Retinitis</td>
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<td>■ Complicated cataract</td>
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<td><strong>Allergic/toxic drug reactions</strong></td>
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<td>Mucocutaneous skin reaction</td>
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<td><strong>Toxic optic neuropathy</strong></td>
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<td>Impaired red/green color vision</td>
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<td>Random amplification of polymorphic DNA</td>
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<td>Optic neuritis</td>
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<td>Optic atrophy</td>
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<td>1. History of use of offending drug prior to onset of symptoms listed</td>
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<td>2. Resolution on withdrawal of drug / response to steroids</td>
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<td><strong>Immune recovery uveitis</strong></td>
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<td>Anterior/posterior uveitis</td>
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<td>Cystoid macular edema</td>
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<td>Epiretinal membranes</td>
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<td>Retinal neovascularization</td>
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<td>Vitreous reaction</td>
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<td>1. A patient with diagnosis of CMV retinitis on antiretrovirals with evidence of immune reconstitution prior to onset of signs/symptoms listed</td>
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<td>2. Lab tests negative for other causes of uveitis</td>
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<td><strong>Orbital/ocular tumors</strong></td>
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<td>Squamous cell carcinoma</td>
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<td>Abnormal raised vascular conjunctival growth</td>
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<td>Corneal infiltration</td>
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<td>Globe perforation</td>
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<td>Carcinoma cells confirmed in ocular specimen at histology</td>
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<td>Orbital lymphoma</td>
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<td>Proptosis</td>
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<td>Exposure keratitis</td>
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<td>Compressive optic neuropathy</td>
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<td>Tumor cells identified at histology of ocular biopsy tissue</td>
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### Table 3. Diagnostic Criteria for Common Causes of Visual Impairment in the HIV-Positive Patient (cont.)

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<tr>
<th>Etiology of Visual Impairment</th>
<th>Ocular Manifestations</th>
<th>Definitive Diagnosis</th>
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<tr>
<td>Orbital/ocular tumors (cont.)</td>
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<tr>
<td>Orbital cellulitis</td>
<td>Fever</td>
<td>1. Positive blood culture</td>
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<td></td>
<td>Periorbital pain and swelling</td>
<td>2. Abscess formation</td>
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<td>Proptosis</td>
<td>3. Response to specified sensitive antibiotic</td>
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<td>Abscess formation</td>
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<th>Neuroophthalmic/intracranial disease</th>
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<tr>
<td>Meningitis/encephalitis (bacterial, crypto, TB, viral)</td>
<td>Cranial nerve palsies</td>
<td>Demonstration of causative organism in CSF (culture, PCR)</td>
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<td>Space-occupying lesion (lymphoma, toxo, crypto, TB)</td>
<td>Internuclear ophthalmoplegia</td>
<td>1. Radiological evidence of space-occupying lesion (CAT scan, MRI, skull X-ray)</td>
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<td></td>
<td>Papilledema</td>
<td>2. Typical visual field defect</td>
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<td>Optic atrophy</td>
<td>1. Characteristic CSF abnormalities for specific causative agent</td>
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<td>Pupillary abnormalities</td>
<td>2. Response to treatment</td>
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<td>Visual field defects</td>
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<td>Cortical blindness</td>
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People living with HIV are at risk for serious, disseminated *Toxoplasma gondii* infections, including toxoplasmic retinochoroiditis. This commonly occurs when a patient's CD4 T cell count falls below 100 cells/mm³. Visual impairment occurs as a result of reactivation of the infection within the retina or in the CNS. Zumla et al. found the seroprevalence for toxoplasma among people in Uganda and Zambia to be 34% among those who were HIV positive and 27% in those who were HIV negative. For reasons that are unclear, ocular toxoplasmosis is much less common than intracranial lesions. In developed countries, toxoplasmosis probably accounts for only 1% to 3% of all intraocular infections in HIV-positive patients.

Patients with ocular toxoplasmosis experience progressive and painless loss of vision. The retinitis can present as a focal necrotizing retinitis with an overlying vitreous reaction or with diffuse or multifocal lesions with minimal vitreous reaction. Such variations in presentation make diagnosis very challenging, especially in resource-limited settings. Those with intracranial lesions may report double vision and a squint, with reduced visual field due to involvement of cranial nerves or the visual pathway.

Diagnosis is made by ophthalmologic examination and positive antibody titers. CAT scan is necessary for suspected intracranial involvement. Lesions will respond to antiparasitic therapy consisting of pyrimethamine, sulfadiazine, and folic acid. Clindamycin, tetracycline, and spiramycin are also effective, but continued treatment is
necessary to prevent reactivation of disease. A positive response to therapeutic trial with a conventional combination of antibiotics is used to support diagnosis in resource-limited settings.

**Ocular Syphilis and TB**

Many patients living with HIV are also at high risk for syphilis because it is a sexually transmitted infection. Vision-impairing disease manifests as a prolonged uveitis, optic neuritis, or interstitial keratitis. Several epidemiological surveys show a high prevalence of active syphilis among HIV-positive patients in sub-Saharan Africa; however, there is no published information on the prevalence or clinical presentation of ocular syphilis in HIV-positive individuals in sub-Saharan Africa. A 1% prevalence of syphilitic uveitis has been reported in HIV-positive patients in Brazil. It is possible that complications leading to blindness attributable to syphilis do occur in developing countries but are probably underdiagnosed.

Diagnosis requires a positive plasma reagin test (VDRL or rapid plasma reagin) and a T. pallidum hemagglutination test (TPHA). Both tests are important in diagnosis and follow-up to monitor response to treatment. They are readily available in resource-limited settings. Treatment for ocular syphilis in HIV-positive patients requires the regimen used for neurosyphilis regardless of the CNS examination. This consists of intravenous penicillin or oral doxycycline. A decline in the VDRL titer to 1:4 occurs within six months. Long-term therapy may be required in some patients.

**Mycobacterium tuberculosis** can infect most tissues of the eye and is a well-known cause of uveitis in HIV patients. The most common form of ocular tuberculosis is a multifocal chorioidopathy. There are no features that are pathognomonic for tuberculosis, and lesions must be differentiated from other mycobacterial infections, *Pneumocystis carinii* infection, syphilis, and lymphoma. Choroidal infections can be complicated by scleral extension, serous retinal detachment, and a severe secondary granulomatous anterior uveitis. Response to anti-TB treatment supports diagnosis, but steroids are usually required to control inflammation.

**Neurophthalmic Disease and Ocular Tumors**

**Cryptococcal Meningitis**

Cryptococcal meningitis is a common complication in people living with HIV. Forty percent of patients with cryptococcal meningitis develop vision-impairing complications such as papilledema, optic atrophy, extraocular muscle paresis, and cortical blindness. Decreased vision has also been reported as the result of chiasmal or optic tract involvement and intraocular infections causing endophthalmitis, uveitis, and chorioretinitis. It is estimated that 8% to 10% of people living with HIV in developed countries develop multifocal choroidal lesions that result from *Pneumocystis carinii* and *Cryptococcus neoformans*. Other forms of meningitis such as bacterial meningitis do occur and would cause similar vision-impairing complications.

**Other Neurophthalmic Diseases**

A variety of other neurophthalmic abnormalities in people living with HIV may present as cranial nerve palsies, visual field defects, pupillary abnormalities, optic atrophy, and papilledema. They are commonly caused by disseminated intracranial infections, as mentioned above, or tumors that result in space-occupying lesions. Burkitt’s lymphoma may develop in the orbit of HIV-positive individuals. Proptosis, lid swelling, or ocular motility disturbances can be the first manifestation.

**Carcinoma**

Conjunctival squamous cell carcinoma and carcinoma in situ have a strong association with HIV infection. Studies show a prevalence of 70% to 86% seropositivity among African patients with
Squamous cell carcinoma can affect the eyelids, conjunctiva, or orbit. Early excision of this tumor is curative. Vision is lost in advanced stages when the tumor infiltrates the eyeball. This is a common finding in resource-limited settings, mainly because of lack of awareness at HIV treatment sites about the presentation of this tumor and late referral to an ophthalmologist.

**Sarcoma**

Kaposi’s sarcoma (KS) is a vascular tumor also commonly associated with AIDS. In the pre-ART era, ocular adnexal KS was found in 2% of patients with AIDS. It rarely causes visual loss when the tumor is large enough to cross the visual axis. The incidence of KS has declined in the ART era.

**DIRECT EFFECT OF HIV**

HIV has been recovered from most ocular tissues, including the retina and cornea. It has been proposed as the possible cause of the conjunctival microvasculopathy, cotton-wool spots, and retinal hemorrhages commonly seen in HIV patients. These are, however, asymptomatic and do not cause visual loss.

HIV is also believed to cause nonspecific intraocular inflammation and serve as a contributing factor in the pathogenesis of secondary disorders in some patients. This presents as a chronic iridocyclitis that cannot be attributed to any secondary intraocular infection or systemic inflammatory disease. The iridocyclitis resolves rapidly in some patients with ART (e.g., zidovudine), suggesting a direct relationship to HIV. Alternatively, inflammation might be the result of an unidentified infectious agent of low virulence that is successfully suppressed with improvement in the patient’s immune function.

The virus also acts as a cofactor in CMV retinopathy. Both viruses have been found in the same retinal cells at autopsy. Interactions between the two viruses, which are known to occur in vitro, may enhance the activity of CMV in coinfected cells and may be one reason that CMV retinopathy is more severe in some patients.

**OCULAR ALLERGIES AND TOXIC DRUG REACTIONS**

People living with HIV are usually on numerous medications for treatment of OIs and the virus itself. This predisposes them to drug toxicity and hypersensitivity reactions. When the eye is affected, it results in impaired vision and sometimes blindness. Stevens-Johnson syndrome is a blinding hypersensitivity reaction common to sulfur-containing antibiotics such as Septrin, antimalarials such as sulfadoxine/pyrimethamine (Fansidar), and thiacetazone in HIV-positive individuals. It causes an aggressive mucocutaneous inflammation, which causes the conjunctiva to adhere to the cornea, a condition referred to as symblepharon. One study done in Malawi showed 75% of patients admitted with Stevens-Johnson syndrome were HIV positive. Many of these patients were taking pyrimethamine. Other drugs associated with Stevens-Johnson syndrome in HIV-positive patients include phenytoin and nvrapine.

Ethambutol causes optic neuritis that can result in irreversible blindness if the drug is not withdrawn early. Cidovir, used to treat CMV retinitis, and rifabutin have been reported to cause severe vision-threatening uveitis. These are more commonly used in developed countries.

Immune recovery uveitis has also been reported in 18% to 63% of patients with a history of CMV retinitis who experience immune reconstitution while on ART. Drug toxicity and hypersensitivity reactions are managed by withdrawal of the offending drug and treatment with steroids.
A DIAGNOSTIC APPROACH TO THE PATIENT WITH LOSS OF VISION

Essential steps in examining the HIV-positive patient with impaired vision are presented in Figure 2 and include the following:

1. **History related to visual impairment.** A detailed history of the patient’s complaints should be taken. The mode of onset, duration, and description of his or her visual impairment will be noted. Any associated symptoms such as pain, redness, or double vision should be noted.

2. **Medical history related to visual impairment.** A history of past or current systemic illnesses that could cause visual impairment should be elicited. These include conditions such as diabetes mellitus, hypertension, rheumatoid arthritis, tuberculosis, and syphilis among many others. The patient’s past and current medication should be elicited to rule out the use of drugs that are toxic to the structures of the eye and can cause visual impairment.

3. **HIV-related history.** The patient’s past and present CD4 lymphocyte count should be determined. Most of the ocular diseases are diagnosed clinically, and a low CD4 count supports the diagnosis. The duration of use of antiretroviral drugs should be noted. The patient’s history of OIs and their treatment should be elicited such as tuberculosis, cryptococcal meningitis, toxoplasmosis, and so forth.

4. **Ophthalmic examination.** A complete ocular examination to determine the presence of eye disease should be carried out. It involves documentation of visual acuity and visual field testing. All patients should be refracted to rule out the presence of refractive error as the cause of reduced vision. Eyeball movements are tested in all directions of gaze. Pupillary function is also assessed. A slit lamp examination to view the structures in the anterior and posterior segment of the eye should be performed. Direct and indirect ophthalmoscopes are used to assess the fundus.

5. **Investigations.** Photography of clinical findings, visual field plotting, and CAT scan are done where indicated. Appropriate laboratory investigations to confirm diagnosis are performed. Table 2 summarizes diagnosis of some of the common causes of visual loss in the patient living with HIV.
# REFERENCE LIST


Kaposi’s Sarcoma (KS) is an AIDS-defining cancer that occurs with advanced immunosuppression associated with HIV. The causative underlying viral infection is human herpesvirus type 8 (HHV-8), also known as Kaposi’s sarcoma-associated herpesvirus (KSHV).1 Long before the AIDS pandemic, KS existed in the Mediterranean and Central Africa and in organ transplant recipients. Patients coinfected with both HIV and KSHV infection are 10,000 times more likely to develop KS compared with HIV-uninfected persons, and 50% of coinfected patients will develop a KS tumor within 10 years of HIV infection.2 The increased risk in HIV-infected patients is caused by immunosuppression associated with lowering CD4 counts. HIV-1 replication produces transactivating (tat) protein from the virally infected cells. The tat protein has pro-angiogenic (blood vessel proliferating) properties and with the aid of cytokines, sets the stage for the development of KS lesions.3 These factors, in conjunction with HHV-8 infection, cause proliferation of vascular lesions on the skin and viscera.

**CLINICAL PRESENTATION**

HIV-associated KS most commonly involves the skin, gastrointestinal tract, respiratory tract, and lymph nodes. Although cutaneous lesions are a source of much disfigurement and stigmatization, they are not associated with mortality; however, visceral lesions involving the respiratory or gastrointestinal tract are associated with mortality.4 KS presentation also varies depending on age, with adults usually presenting with cutaneous involvement and children typically presenting with the lymphadenopathic form of the disease.5

The lesions of Kaposi’s sarcoma are distinctively characteristic. They are violet-colored plaques directed along the cleavage lines of the skin and are usually symmetrical (Plate 1). They can occur at all sites: face, upper limbs, trunk, and lower limbs. However, many conditions can mimic these lesions; these are described in Box 1 (next page). The limbs are often the first sites to be involved (Plate 2). There they can present with nonpitting edema, which signifies lymphedema. Early-stage lesions can present as bruises or macules, which are merely discolorations of the skin (Plate 1), progressing to elevated, solid, violet-colored plaques and nodules (Plate 3). The lesions are asymptomatic and may go unnoticed by both patient and caregiver; identification is particularly difficult in dark-skinned individuals. Thus, thorough examination

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in adequate light is essential. As the lymphedema progresses, it is associated with extreme pain.

Late-stage aggressive lesions may progress to fungating tumors (Plates 4 and 5). Because of the vascular nature of the tumors, lesions are prone to bleeding, which may be the primary cause for concern in the patient presenting for care. Regression of KS lesions is characterized by decrease in size (i.e., flattening and shrinking), usually accompanied by residual hyperpigmentation, even when lesions have disappeared. In some cases, plaques and nodules may disappear completely.

Oral involvement is commonly associated with cutaneous lesions and may occur in the absence of skin lesions (Plate 6). These appear as violet-colored macules, plaques, and nodules on the hard palate, gingiva, and tongue. The mouth may be the presenting site in approximately 20% of patients, and lesions there may herald a more rapidly progressive form of the disease with higher mortality than disease confined to the skin. They may also be a marker of pulmonary involvement.

Other commonly involved sites are the gastrointestinal tract, lungs, and lymph nodes. Lesions similar to those on the skin can be identified in all segments of the bowel and respiratory tree and can cause symptomatic gastrointestinal and respiratory disease. Bowel involvement will present as obstruction or blood loss, while respiratory involvement will present as cough and dyspnea (labored respiration), with or without fever and occasionally with hemoptyis (expectoration of blood from the respiratory tract). Systemic gastrointestinal and pulmonary involvement may occur in the absence of skin lesions. Gastrointestinal bleeding requires confirmation with a fecal occult blood test, but only endoscopy allows for an accurate diagnosis. If the patient presents with chest symptoms, sputa to exclude an infectious etiology and a chest X-ray are the first steps to identifying pulmonary KS. Suggestive findings on the chest X-ray are mediastinal enlargement and diffuse reticulonodular shadowing, and occasionally effusions. A definitive diagnosis requires bronchoscopy.

**DIAGNOSIS OF KS**

The approach to examination and investigation of a patient with KS is outlined in Box 2.

If a patient has an abnormal chest X-ray, sputa microscopy and culture are mandatory to exclude tuberculosis and *Pneumocystis carinii* pneumonia (PCP). If the patient has an effusion, a pleural tap is essential to exclude infective causes like tuberculosis. A hemorrhagic effusion is suggestive of KS. If the chest X-ray is abnormal, the patient has been treated empirically for a chest infection, and sputa are negative, a bronchoscopy should be considered. If the patient complains of passing blood from the rectum or has abdominal symptoms or melena stools, endoscopy and/or colonoscopy is necessary.
The importance of assessment for other opportunistic infections cannot be overemphasized, because Kaposi’s sarcoma is AIDS defining and patients presenting with KS suffer marked immunosuppression. Another reason assessing for opportunistic infections is essential is that they may cause progression of KS by way of proinflammatory cytokines. Corticosteroids have also been known to exacerbate KS lesions and should be avoided in patients with HIV KS. A good history of all current drugs is vital, especially antituberculous and antiretroviral medications. It will influence planning of therapies, especially when current chronic medication might interact with chemotherapy.

ANTIRETROVIRAL THERAPY AND KS

Because Kaposi’s sarcoma is an AIDS-defining condition associated with advanced immunosuppression, all HIV-infected patients require antiretroviral drugs (ARVs). ARVs have been shown to decrease the incidence of new KS cases among HIV patients and are associated with the resolution of KS lesions. The ability of ARVs to cause regression is thought to be linked to reduction in HIV-1 viral load and hence the HIV transactivating gene (tat), induction of spindle cell growth, improved immune response to HHV-8, and the direct antiangiogenic activity of some protease inhibitors (PIs). Thus, the basic workup for initiation of ARVs is the starting point for any patient with HIV KS.

Although ARV regimens differ from country to country, any potent regimen that leads to CD4 restoration and HIV viral load suppression will suffice. A review of antiretroviral therapy (ART) in advanced HIV infection found that non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens achieved a higher rate of durable viral suppression compared with nonboosted PIs. Whether a regimen containing PIs is superior to an NNRTI-based regimen in HIV KS is unknown. A response rate of 20% was reported in a recent study using mainly protease inhibitor–based therapy in HIV KS.

Intimately linked with initiation of ARVs is the development of immune reconstitution inflammatory syndrome (IRIS). KS IRIS refers to the worsening of existing KS or the development of new KS lesions (cutaneous or visceral) in the first two months after initiating ARVs. This is in association with rapidly declining HIV viral load and improving

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**Box 2. Steps to Diagnosing a Patient with Kaposi’s Sarcoma**

- Patient complains of skin lesions, or lesions are found incidentally during routine consultation.
- Examine skin for violet-colored macules, plaques, nodules, and tumors that are firm and nontender (Plate 1).
- Look at oral mucosa and conjunctivae (Plate 6).
- Palpate skin of limbs for nonpitting edema (lymphedema) (Plate 7).
- If lesions are fungating, they have typical odor caused by superinfection (Plate 5).
- Examine chest and abdomen; feel for lymph nodes, liver, and spleen.
- Assess for other opportunistic infections (e.g., PCP).
- Certain basic investigations are essential to confirm diagnosis and assess extent of disease. They are important for staging the disease so that appropriate therapy can be identified. These investigations are:
  - biopsy,
  - stool sample for occult blood,
  - chest X-ray,
  - HIV test,
  - CD4 count, and
  - full blood count.
It is well established that HIV-associated KS is not a curable disease. Therefore, the main objectives of therapy in patients with HIV Kaposi's sarcoma are as follows:

- Palliation and symptomatic management in patients with disseminated disease
- Improvement of pain associated with lymphedema
- Maximum possible resolution of disfiguring cutaneous lesions
- Resolution or slowing growth of visceral lesions
- In all cases, improving the patient’s quality of life

Figure 1 illustrates the approach to therapy of a patient once diagnosed with KS.

### STAGING OF KAPOSI’S SARCOMA

KS can be divided into good or poor prognosis disease according to AIDS Clinical Trials Group (ACTG) criteria that classify disease stage according to the extent of tumor, immune status, and severity of systemic illness (Table 1). When these criteria were first validated, it was found that the combination of tumor state and immune status (as quantified by CD4 count) were predictive of patient survival. However, a more recent evaluation of the ACTG criteria in the context of ART found that the combination of advanced tumor state and systemic disease were predictive of a poor prognosis.

For practical purposes, it is helpful to divide patients with Kaposi’s sarcoma into the following two categories so that appropriate and specific therapy can be planned:

- Localized disease—restricted to the skin only or skin and lymph nodes; lymphedema restricted to distal extremities or KS sites; nonobstructive or asymptomatic oral or other visceral disease
- Advanced disease—lymphedema of entire limb; symptomatic or obstructive visceral involvement

### THERAPY

It is well established that HIV-associated KS is not a curable disease. Therefore, the main objectives of therapy in patients with HIV Kaposi’s sarcoma are as follows:

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Figure 1 illustrates the approach to therapy of a patient once diagnosed with KS.

### Localized Therapy

For disease localized to skin and mucous membranes, the aim is to treat the patient with ART alone for as long as possible. If the disease is still in an early stage, improvement can be expected after approximately six months once the CD4 count has increased. Initially, it is important to review patients at least monthly and advise them to return if the lesions are increasing in size. Increasing size of existing lesions and development of new lesions should be monitored because they can signal the
manifestation of IRIS. If IRIS occurs, patients will require chemotherapy while continuing to take ARVs.

For disease that does not respond to ART alone and is localized to the skin and mucosa, localized forms of therapy are indicated. It should be noted that intralesional chemotherapy with vinblastine, cryotherapy, or alitretino in gel are purely for cosmesis and do not control the underlying disease.

Vinblastine is one of the most widely used intralesional agents. It is cheap and effective, with a response rate of approximately 70%. Small, localized, cutaneous lesions as well as some mucosal lesions (e.g., on oral mucosa and eyelids) are amenable to therapy. Diluted with local anesthetic in a solution of 0.2 mg/mL and injected into the lesions, vinblastine induces necrosis and regression over a few days. A topical antibacterial cream used prophylactically prevents secondary infection. Among the drawbacks of most local therapies, including vinblastine, are that their effect is temporary and lesions may recur. In addition, patients should be advised of the postinflammatory hyperpigmentation that occurs as a result of therapy.

Cryotherapy using liquid nitrogen can be effective for small, isolated, disfiguring cutaneous lesions. Two freeze-thaw cycles applied to the lesions induces regression over a few days. The response rate is in the range of 80%, but associated complications include pain, secondary bacterial infection, relapse, and postinflammatory hypopigmentation. In dark-skinned individuals, the postinflammatory hypopigmentation is more obvious than the hyperpigmented violet-colored plaques, which blend in easily with the patient’s skin color.

Alitretinoin gel is a topical retinoid (9-cis-retinoic acid) preparation shown to be effective in inducing response four to eight weeks after treatment. However, it is expensive and induces
irritation, causing secondary leucoderma in dark-skinned patients. Thus, it is considered impractical in most resource-limited settings.

Radiotherapy
When patients have localized fungating tumors, localized lymphedema, or localized disfiguring cutaneous lesions that have not responded to the previously listed therapies, radiotherapy in addition to ART is appropriate. Radiotherapy is an important addition to ART and indicated when local KS-specific therapy cannot control the disease, yet the disease is not extensive enough to warrant chemotherapy.

A recent Cochrane Review assessed the effectiveness of current therapeutic regimens for HIV KS, with a focus on options available in resource-limited settings. The major selection criteria for this review were randomized controlled trials for HIV KS in adults. The main conclusions were that data from randomized controlled trials on effective treatments for HIV KS are scarce, particularly among people who are also taking ART. However, the review did show that alitretinoin gel is effective for therapy of cutaneous lesions, pegylated liposomal doxorubicin is effective for advanced KS, and radiotherapy is effective for treating cutaneous lesions. Apart from a randomized trial of radiotherapy, no trials applicable to resource-limited settings were identified.

With respect to radiation, the response to dosages of 20 gray (Gy) given in 10 fractions and 40 Gy given in 20 fractions were similar, and both dosages were slightly superior to treatment of lesions with a single dose of 8 Gy. In addition, radiotherapy is given to palliate patients with low CD4 counts (less than 50 cells/mm³) who require systemic chemotherapy but will not tolerate the side effects. It is also used as an adjunct to chemotherapy for localized tumors and painful lymphedema.

Systemic Therapy
For extensive lymphedema, symptomatic visceral disease, and KS immune reconstitution, chemotherapy is the treatment of choice. Therapy can be given as either single-agent vincristine (2 mg) or, if available, a combination of vincristine, doxorubicin (10 mg/m²), and bleomycin (10 mg/m²), also known as ABV therapy. Chemotherapy can be administered at two to three weekly intervals until response is achieved. Drug availability, cost, and patient CD4 count will dictate which regimen is chosen. One study used the following guide in the absence of ARVs:
- CD4 count greater than 100 cells/mm³: ABV, as described
- CD4 count of 30 to 100 cells/mm³: vinblastine 6 mg/m² and bleomycin

Etoposide
The effectiveness of oral etoposide as a treatment for systemic KS in resource-limited settings has been documented. Its activity may be antiangiogenic and used over a long period at low doses, and it can be given as metronomic therapy. Low doses can be given orally at 50 to 100 mg daily, depending on body mass, continuously for three weeks of the month; patients should be reassessed monthly. This regimen is especially appropriate in resource-limited settings where intravenous chemotherapy is expensive and labor intensive. For ABV therapy, patients require cardiac assessment prior to doxorubicin infusion. Patients respond well to this regimen over time, and for the nonresponders, etoposide phosphate can be used. ABV chemotherapy also remains an option.

In our center in Durban, South Africa, chemotherapy is withheld when a patient’s CD4 count is less than 200 cells/mm³. These patients continue on ARVs until their CD4 count improves, when they are better able to tolerate chemotherapy and
Paclitaxel
Paclitaxel is a relatively new agent shown to be effective and safe for HIV KS patients who require chemotherapy. It is administered in a dose of 100 mg/m² over three hours every two to three weeks and must be administered with intravenous dexamethasone to avoid allergic reactions. Concerns regarding its use include long infusion time, side effect profile, exacerbation of KS with steroid use, and prohibitive cost in resource-limited settings. Because of its high cost, paclitaxel, like pegylated liposomal doxorubicin, is generally not affordable or accessible to public-sector patients in resource-limited settings.

CONCLUSION
The high rates of HIV infection coupled with the high background seroprevalence of HHV-8 across sub-Saharan Africa set the stage for KS to continue to represent a significant public health threat into the foreseeable future. The currently low coverage of ARVs in many settings will only exacerbate the situation. Health-care professionals can play a pivotal role in managing KS through increasing awareness and prevention, as well as through ensuring early diagnosis, therapy, and palliation of late-stage disease.
Plate 1. Violaceous plaque in a linear distribution on the trunk in early KS

Plate 2. Nodules of KS with secondary verrucous change on the lower limbs

Plate 3. Violaceous plaques and nodules with surrounding lymphedema

Plate 4. Fungating tumor of lip indicating aggressive late-stage KS

Color Plates: Conditions Associated with Kaposi’s Sarcoma
Plate 5. Fungating nodules and tumors with secondary infection seen in late-stage KS

Plate 6. Nodular lesions of the hard palate

Plate 7. Hyperpigmented plaques of KS with swelling of the hand due to lymphedema

Plate 8. Profuse nodular lesions with secondary lymphedema and elephantiasis seen in late KS
REFERENCE LIST


ANY PEOPLE LIVING WITH HIV ARE confronted with gastrointestinal problems at some point during the course of their infection. Such problems include oral lesions, esophageal problems, nausea/vomiting, chronic diarrhea, and abdominal pain. Gastrointestinal infections in the immunocompromised host continue to have significant morbidity and mortality throughout the world. Gastrointestinal syndromes are of critical importance in HIV care because they interfere with the patient’s nutritional status and can considerably decrease quality of life. Gastrointestinal symptoms are also challenging for the clinician, as they can occur as side effects of HIV therapy as well as due to conditions related and unrelated to HIV.

This chapter is a syndrome-based guide to the management of gastrointestinal problems. A syndromic approach is recommended given that multiple enteric complications may coexist and one organism may produce several different clinical syndromes. A syndromic approach provides caregivers in resource-limited settings with the essential tools to identify and treat the most common problems based on clinical signs and/or simple laboratory findings. For each clinical syndrome, a flowchart algorithm for diagnosis and treatment is provided. These algorithms are not exhaustive and should be adapted for use in a particular setting based on local HIV prevalence and diagnostic capabilities. Further information regarding differential diagnosis is presented separately as a table. At the end of each section, practical tips on symptom relief and information for patients on preventive measures are given. All recommendations in this chapter are for the immunocompromised, and as such, non-HIV-related diseases are not discussed.

ORAL LESIONS

Incidence and Significance of Symptoms
Oral problems occur frequently in people with HIV disease. In the pre-antiretroviral therapy (ART) era, approximately 40% to 50% of patients developed oral fungal, bacterial, or viral infections over the course of their disease, and oral manifestations still are one of the earliest manifestations of immune deficiency in people living with HIV. Although there are considerable regional variations in the prevalence of the various oral manifestations of HIV infection, it is clear that oral candidiasis is one of the most frequent infections occurring during the course of HIV disease on all continents. Prevalence of oral candidiasis among people living with HIV ranges from 11%
Figure 1. Algorithm for the diagnosis and management of oral lesions

1. **oral lesions/discomfort**
   - **Yes** oral hairy leukoplakia
   - **No**
     - **Yes** bluish nodules? Kaposi’s sarcoma
     - **No** (bleeding) gum destruction?
       - **Yes** necrotizing ulcerative gingivitis
       - **No**
         - **Yes** white/erythematous lesions?
           - Presumptive candida: nystatin/gentian blue/miconazole gum 1 week
             - Improvement continue until symptoms gone
             - No improvement fluconazole 200 mg daily
           - Vesicles/ulcers?
             - Presumptive herpes simplex painkiller topical antiseptic acyclovir 200–400 mg 5 × daily 1 week
               - Improvement continue until symptoms gone
               - No improvement presumptive aphthous ulcers prednisolone 40 mg daily 1 week
to 90%, depending on the study population and the variability of the diagnostic tools used in the various studies. Because oral candidiasis is common and can recur frequently, it is often the first physical manifestation of HIV disease. It may also be a valuable clinical indicator of virological and immunological failure of patients on ART.

Physical examination should include an inspection of the oral cavity, even without the presence of symptoms. Oral lesions can significantly affect quality of life in people living with HIV and can interfere with their ability to chew solid foods, leading to weight loss and malnutrition. Most mouth lesions have a prognostic value and are helpful in determining the stage of HIV disease because they are correlated with the patient’s CD4 count.

Symptomatic Care

*Mouth Care*
- Remove bits of food stuck in the mouth with a soft cloth soaked in salted water.
- Avoid dry mucous membranes—regularly rinse the mouth with warm salty water (one-half teaspoon of salt in a cup of water) or take frequent sips of diluted fruit juices and chew on sugarless gum or candy.
- Patients who have candidiasis under a denture or partial denture should remove the prosthesis before using topical agents. At bedtime, the prosthesis should be placed in a chlorhexidine solution until reinserting it into the mouth.

*Pain Relief*
- Take a nonsteroidal anti-inflammatory drug (NSAID) or apply lidocaine mouth gel.
- Mix two tablets of aspirin in water and rinse the mouth up to four times daily.
- Modify food intake—eat more frequent, smaller meals.
- Avoid foods or liquids that are very hot in temperature or very spicy.

Preventive Measures
- Herpes simplex is easily spread through kissing. If mouth or lips have visual lesions, kissing should be avoided.
- Bleeding gums may transmit HIV during “deep kissing” or oral-genital contact. Advise patients to avoid exposing partners to HIV by taking all necessary precautions, including abstaining from risky activities until their condition has been cured.
- Patients should maintain good oral hygiene by using a soft toothbrush on teeth, gums, and tongue after each meal or at least three times a day. They should rinse their mouth with warm salty water (one-half teaspoon of salt in a cup of water) after eating and between meals.

ESOPHAGEAL PROBLEMS

Esophageal problems in people living with HIV include difficulty swallowing (dysphagia) or midline retrosternal pain when swallowing (odynophagia). Odynophagia and dysphagia cause significant discomfort and, if left untreated, may result in scarring of the esophagus, dehydration, and weight loss. Most esophageal conditions are an indication of severe immunosuppression (World Health Organization stage IV) and are therefore an indication for ART. ART has been shown to reduce esophageal opportunistic infections in HIV patients compared with patients who are not receiving therapy. The exact prevalence of esophageal infections is unknown, and not all patients with esophagitis are symptomatic. However, esophageal complaints are common in HIV-infected patients, occurring in at least one-third of patients at some point during the course of their disease. The majority (50% to 70%) of patients with dysphagia or odynophagia have candidal esophagitis alone or in association with other infectious pathogens.
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Signs and Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>Pseudomembranous white plaques on mucosa or tongue that can easily be scraped off, leaving a red/ bleeding surface (taste disturbances) Erythematous flat red lesions (burning sensation) Angular cheilitis—red fissures in mouth corner</td>
<td>Clinical: KOH (potassium hydroxide) preparation of mouth scraping showing pseudohyphae and yeasts</td>
<td>Nystatin oral tablets 500,000 IU four times daily until two days after resolution of symptoms Gentian violet 1% two times daily for one week Miconazole gum patch once daily for one week If no improvement after one week, fluconazole 200 mg daily until symptoms are gone</td>
</tr>
<tr>
<td>Oral hairy leukoplakia (caused by Epstein-Barr virus)</td>
<td>Unilateral or bilateral painless adherent white or grey patches on lingual lateral margins that cannot be scraped off</td>
<td>Clinical</td>
<td>ART</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Small painful erosions/ ulcerations with history of vesicles on inflamed base on hard palate and gingiva</td>
<td>Clinical</td>
<td>Topical antiseptic acyclovir 200–400 mg five times daily for one week</td>
</tr>
<tr>
<td>Necrotizing ulcerative gingivitis</td>
<td>Inflammation of gums, loss of teeth</td>
<td>Clinical</td>
<td>Oral hygiene, topical antiseptic, metronidazole 500 mg three times daily for one week</td>
</tr>
<tr>
<td>Aphthous ulcers</td>
<td>Painful large ulcers with history of vesicles on mucosa</td>
<td>Clinical</td>
<td>Prednisolone 20–40 mg daily for one week, topical antiseptic, painkillers</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>Bluish nodules on palate and gingiva</td>
<td>Clinical biopsy</td>
<td>ART, chemotherapy</td>
</tr>
<tr>
<td>Salivary gland dysfunction</td>
<td>Dry mouth</td>
<td>Clinical</td>
<td>Sugarless candy, gum</td>
</tr>
<tr>
<td>Oral warts</td>
<td>Papillomatous lesion</td>
<td>Clinical</td>
<td>Excision</td>
</tr>
</tbody>
</table>

Source: Adapted from Lynen.19
Figure 2. Algorithm for the diagnosis and management of esophageal problems

- odyno-/dysphagia

  presumptive candida: fluconazole 200 mg 1 week

  improvement no improvement

  continue 1 week

  endoscopy possible?

  yes

  treat according to diagnosis

  no

  presumptive herpes simplex esophagitis: acyclovir 800 mg 3× daily 1 week

  improvement no improvement

  presumptive aphthous ulcers: prednisolone 20–40 mg daily 1 week*

  improvement no improvement

  stop steroids, symptomatic treatment

- follow up

* If patient is severely ill or suffers from systematic symptoms such as weight loss, night sweats and particularly fever: exclude systematic infection (TB, CMV) before giving steroids.
Diet and Lifestyle

Patients should do the following:

- Test their ability to swallow with a small amount of water before each feeding to avoid aspiration of food.
- Eat slowly in the upright position and do not bend over or lie flat soon after eating.
- Avoid eating too late at night.
- Raise the head of the bed so that the patient is lying in an upright position. (This can be achieved by placing a block under the bed legs at the head of the bed or by placing some pillows between the mattress and the bed frame at the head of the bed.)
- Maintain adequate caloric intake by taking small but frequent meals containing cool and soft foods and avoiding foods and drinks that are known to cause or worsen odyno-/dysphagia (e.g., spicy, fatty, or fried foods; chocolate; caffeinated drinks or alcohol).
- Try to stop smoking.
- Wear clothes that are loose fitting around the stomach.

Medication

- Stepwise analgesia but avoid NSAIDs.
- Magnesium hydroxide—two tablets after each meal and at bedtime to neutralize acid. When patients are on ART or take other medication for opportunistic infections, it is advised to leave at least one hour between taking these medications and the magnesium hydroxide (since many of these drugs require an acid pH to work properly).

Preventive Measures

See recommendations for oral lesions.

NAUSEA AND VOMITING

Nausea, vomiting, or both are very common symptoms in any stage of HIV infection but rarely dominate the clinical picture. Nausea is a common adverse effect of many antiretroviral...
of note, various clinical studies indicate a lower prevalence of *Helicobacter pylori* infection in HIV patients. This is relevant because in the general population, gastritis due to *H. pylori* is the most common cause of nausea.

### Symptomatic Care

#### Diet and Lifestyle

Patients should stay nourished and well hydrated even if they are experiencing nausea and vomiting. Eating small, frequent meals may be best tolerated, while avoiding dairy products, greasy and spicy foods. Seek locally available drinks and foods that the patient likes. Ginger may help.

Patients should avoid smoking and drinking coffee or alcohol.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Signs and Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effect of ARVs or other medications (e.g., anti-TB medications)</td>
<td>Associated abdominal pain caused by lactic acidosis, pancreatitis, hepatitis (due to PIs, zidovudine, anti-TB drugs) Renal insufficiency (due to tenofovir)</td>
<td>See Table 8 Creatinine (clearance)</td>
<td>See Table 8 Switch ARVs</td>
</tr>
<tr>
<td>Mycotic colonization of gastric system</td>
<td>Associated odynophagia/dysphagia</td>
<td>See Table 2</td>
<td>See Table 2</td>
</tr>
<tr>
<td>Central nervous system lesion (e.g., Cryptococcus neoformans, toxoplasmosis, TB, bacterial, viral, lymphoma)</td>
<td>Fever, neck stiffness, headache, photophobia, confusion, behavioral changes</td>
<td>Lumbar puncture</td>
<td>Based on found etiology</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>See section on diarrhea</td>
<td>See section on diarrhea</td>
<td>See section on diarrhea</td>
</tr>
<tr>
<td>Bowel obstruction (Kaposi’s sarcoma, non-Hodgkin lymphoma)</td>
<td>No flatus/stools, clangor, bloating</td>
<td>X-ray standing: proximal dilation of bowel, air-fluid levels Ultrasound: air-fluid levels</td>
<td>Surgery Chemotherapy ART</td>
</tr>
</tbody>
</table>

*Source: Adapted from Lynen.*

Of note, various clinical studies indicate a lower prevalence of *Helicobacter pylori* infection in HIV patients. This is relevant because in the general population, gastritis due to *H. pylori* is the most common cause of nausea.

### Differential Diagnosis and Disease-Specific Management of HIV-Related Nausea and/or Vomiting

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Signs and Symptoms</th>
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</tr>
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<td>Surgery Chemotherapy ART</td>
</tr>
</tbody>
</table>

*Source: Adapted from Lynen.*
Medication
It is important to stress to patients that they cannot stop taking any of their medications because of vomiting. If vomiting occurs within one hour of taking ARVs, another dose should be taken.

Patients may take metoclopramide (10 mg every eight hours) to relieve symptoms.

CHRONIC DIARRHEA
Chronic diarrhea is defined as more than three loose stools a day for more than one month. Despite the decreased incidence of this condition since the advent of effective antiretroviral drugs, it remains a very common clinical presentation in HIV-infected people and may have a variety of causes. Before the widespread availability of combination ART, chronic diarrhea was reported to occur in 40% to 90% of HIV-infected patients, with large variations in pathogens and among studies. Prevalence of diarrhea tended to be particularly high in communities with overcrowding and/or poor sanitation and limited access to clean water. Diarrhea may cause deterioration of appetite and therefore malnutrition as well as malabsorption, with subsequent dehydration and weight loss. Persistent diarrhea may also have a significant impact on patients' quality of life and may interfere with adherence to and efficacy of ART. In areas where both financial and human resources are limited in providing adequate care, it is associated with significant morbidity and mortality rates.

Chronic diarrhea is more common in patients with low CD4 counts, signaling advanced immunosuppression. Some organisms, such as microsporidia, usually cause diarrhea only in the immunosuppressed; others, such as Cryptosporidium, Salmonella, Shigella, and Campylobacter, which can cause diarrhea in the immunocompetent population, produce more severe or prolonged infections in people living with HIV. Because treatment options vary widely depending on the infectious agent, microbiologic evaluation is warranted. However, the isolation of the underlying causative agent is possible in only 40% to 60% of patients who present with chronic diarrhea in sub-Saharan Africa and Asia. Therefore, familiarity with the most common pathogens in the clinician’s region will help with diagnosis and treatment. For patients taking ARVs (especially PIs) in whom no infectious agent can be found, diarrhea may be due to the medication.

Some of the infectious agents can also cause acute self-limiting diarrhea (e.g., bacterial enteritis). Cases of principally acute diarrhea in HIV-infected people do not require a different approach than those in uninfected people. However, monitor closely and ensure adequate fluid intake and continuation of ARVs.

It should be noted that cases of principally acute diarrhea in HIV-positive individuals can be managed in the same way as chronic diarrhea. However, such patients should be monitored closely to ensure adequate fluid intake and continuation of ART.

Symptomatic Care

Diet and Lifestyle
- Patients with severe diarrhea must maintain adequate hydration. Encourage drinking frequent small amounts of (rice) soup, porridge, water, or oral rehydration solution. Patients should avoid high-sugar drinks, caffeinated beverages, and alcohol and should drink at least 200 mL extra on top of normal fluid intake after each unformed stool.
- Encourage frequent intake of easily digested foods such as bananas (rich in potassium), rice and potatoes (reduce diarrhea), boiled vegetables, crackers, and carrot soup (replaces minerals and vitamins). Patients should avoid high-fiber foods, greasy, spicy, or raw foods, and dairy products. Nutritional support is very important to avoid wasting. At least 2,500 kcal daily are needed.
- In case of cramps, avoid beans, cabbage, cauliflower, spices, and carbonated drinks.
Figure 3. Algorithm for the diagnosis and management of chronic diarrhea
Table 4. Assessment of Dehydration

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Mild Dehydration</th>
<th>Moderate Dehydration (two signs present)</th>
<th>Severe Dehydration (more than two signs present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance</td>
<td>Thirsty, alert</td>
<td>Thirsty, alert</td>
<td>Anxious, cold extremities, clammy, muscle cramps, dizzy if standing, wrinkled skin of fingers</td>
</tr>
<tr>
<td>Pulse</td>
<td>Normal</td>
<td>Rapid</td>
<td>Rapid or absent</td>
</tr>
<tr>
<td>Respiration</td>
<td>Normal</td>
<td>Deep, sometimes rapid</td>
<td>Deep, rapid</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Low, immeasurable</td>
</tr>
<tr>
<td>Eyes</td>
<td>Normal</td>
<td>Sunken</td>
<td>Severely sunken</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Moist</td>
<td>Dry</td>
<td>Very dry</td>
</tr>
<tr>
<td>Urine output</td>
<td>Normal</td>
<td>Reduced, dark</td>
<td>Anuria</td>
</tr>
<tr>
<td>Percentage of body weight loss</td>
<td>1–5%</td>
<td>6–9%</td>
<td>10% or more</td>
</tr>
</tbody>
</table>

*Source: Adapted from World Health Organization.*

Table 5. Management of Dehydration

<table>
<thead>
<tr>
<th>Mild Dehydration</th>
<th>Moderate Dehydration</th>
<th>Severe Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management</td>
<td>Continue drinking extra fluid or oral rehydration solution (ORS) until diarrhea stops</td>
<td>2,200–4,000 mL ORS in four hours, then continue drinking extra fluid (or ORS) until diarrhea stops</td>
</tr>
<tr>
<td></td>
<td>At least 200–300 mL extra after each loose stool</td>
<td>At least 200–300 mL extra after each loose stool</td>
</tr>
</tbody>
</table>

*Source: Adapted from World Health Organization.*

Table 6. Differential Diagnosis and Disease-Specific Management of HIV-Related Diarrhea

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidia</td>
<td>Profuse watery diarrhea with malabsorption and wasting, CD4 &lt; 100 cells/mm³, usually no fever, cramping pain</td>
<td>Stool microscopy: modified acid-fast stain</td>
<td>ART and symptomatic treatment</td>
</tr>
<tr>
<td>Microsporidia</td>
<td>Profuse watery diarrhea, weight loss, CD4 &lt; 100 cells/mm³, no fever, cramping pain</td>
<td>Modified trichrome stain</td>
<td>ART</td>
</tr>
<tr>
<td>Cyclospora</td>
<td>Watery diarrhea, CD4 &lt; 100 cells/mm³</td>
<td>Stool microscopy: modified acid-fast stain</td>
<td>Cotrimoxazole 1 double strength (DS) (sulfamethoxazole 800 mg + trimethoprim 160 mg) four times daily for 10 days Secondary cotrimoxazole prophylaxis (1 DS daily)</td>
</tr>
<tr>
<td>Etiology</td>
<td>Symptoms</td>
<td>Diagnosis</td>
<td>Treatment</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><em>Isospora belli</em></td>
<td>Watery stools, no fever, CD4 &lt; 100 cells/mm³, abdominal pain, wasting⁴⁹</td>
<td>Stool microscopy: modified acid-fast stain</td>
<td>Cotrimoxazole 1 DS four times daily for 10 days, then 1 DS two times daily for three weeks Secondary cotrimoxazole prophylaxis (1 DS daily)</td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
<td>Watery diarrhea, flatulence, bloating</td>
<td>Antigen detection Stool microscopy</td>
<td>Metronidazole 250 mg three times daily for 10 days</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>Bloody stools, cramps</td>
<td>Stool exam</td>
<td>Metronidazole 750 mg three times daily for 10 days, then paromomycin 500 mg four times daily for one week</td>
</tr>
<tr>
<td><em>Disseminated Mycobacterium avium complex disease</em></td>
<td>Watery diarrhea, CD4 &lt; 100 cells/mm³, prolonged fever, wasting</td>
<td>Exclusion diagnosis Severe anemia Blood culture Intestinal biopsy</td>
<td>Clarithromycin 500 mg two times daily or azithromycin 500 mg daily + ethambutol 15 mg/kg daily (+ rifabutin 300 mg daily) for 24 weeks ART after one month Lifelong secondary prevention Azithromycin 1,200 mg one time weekly or clarithromycin 500 mg two times daily</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>After antibiotics/ hospitalization: watery stools, fever, any CD4</td>
<td><em>C. difficile</em> toxin assay on stool Leucocytes in stool</td>
<td>Metronidazole 500 mg three times daily for one week Stop antibiotics</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Fever, malaise, any CD4</td>
<td>Stool culture</td>
<td>Ciprofloxacin 500 mg two times daily for one week</td>
</tr>
<tr>
<td><em>Shigelloïdes stercoralis</em></td>
<td>Stool with blood/mucus, high fever, abdominal pain, tenesmus</td>
<td>Stool culture</td>
<td>Cotrimoxazole 1 DS two times daily for five days⁵⁴ or ciprofloxacin 500 mg two times daily for one week⁵⁴</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>Fever, stool with blood, abdominal pain, tenesmus</td>
<td>Stool culture</td>
<td>Erythromycin 500 mg two times daily for five days</td>
</tr>
<tr>
<td><em>Strongyloïdes stercoralis</em></td>
<td>Larva currens, cough (ARDS), abdominal pain, more likely after taking high-dose steroids</td>
<td>Larvae in stool/ sputum Eosinophilia</td>
<td>Ivermectin 12 mg daily for three days or albendazole 400 mg two times daily for five days</td>
</tr>
<tr>
<td><em>Cytomegalovirus</em></td>
<td>Watery diarrhea +/- blood, can cause perforation/hemorrhage, toxic megacolon, CD4 &gt; 50 cells/mm³, fever, pain</td>
<td>Endoscopic biopsy</td>
<td>Ganciclovir 5 mg/kg IV two times daily for two weeks or valganciclovir 900 mg two times daily for three weeks, then 900 mg daily ART</td>
</tr>
<tr>
<td>ARVs (nelfinavir, ritonavir, lopinavir, zidovudine, didanosine)</td>
<td>Watery diarrhea, no fever</td>
<td>No diagnostic test available; diagnosis made by ruling out other options</td>
<td>Oat bran Calcium carbonate Consider switching ART regimen</td>
</tr>
</tbody>
</table>

*Source: Adapted from Lynen.¹⁹*

*Studies in Lima, Peru, and Nairobi, Kenya, have reported high resistance rates of bacterial pathogens to cotrimoxazole.⁵⁰⁻⁵¹*
Abdominal pain is frequent in people living with HIV; one study in South Africa reported a 45% prevalence of abdominal pain among HIV-positive outpatients. In that study, abdominal pain was associated with poor survival. Abdominal pain can occur at any stage of HIV infection, but etiology will differ according to immune status and geographic location. It is a challenging problem for the clinician because it can be caused by very benign as well as very serious etiologies. Abdominal pain in HIV patients is often a marker of an underlying opportunistic pathologic condition. In areas of high TB prevalence, abdominal pain should be highly suspected as a sign of disseminated TB infection. Patients on ART can also suffer from various side effects that provoke abdominal pain.

**Symptomatic Care**

*Diet and Lifestyle*

In case of cramps, avoid beans, cabbage, cauliflower, spices, and carbonated drinks.

**Medication**

Pain relief:

- Step 1: nonopioid (e.g., aspirin, paracetamol, NSAID)
- Step 2: weak opioid (e.g., codeine) +/− step 1
- Step 3: strong opioid (e.g., morphine/tramadol) +/− step 1

The following adjuvants may be added:

- For cramps: codeine 30 mg every four hours or hyoscine 10 mg three times daily or loperamide 2 to 4 mg four times daily
- For visceral pain: prednisone 10 to 80 mg daily for one week

**Preventive Measures**

See section on diarrhea.

---

**Preventive Measures**

Provide devices for incontinence (e.g., protective bed coverings, sheets, etc.) to prevent soiling.

Ensure good anal care. Clean anal area with soft tissue after passing stool, wash with water and soap if necessary, and apply petroleum jelly or sit in a basin of water with a pinch of salt twice daily.
Figure 4. Algorithm for the management of abdominal pain

abdominal pain

danger signs? see Table 6

no

Rx abdomen/ultrasound possible?

yes

treat according to diagnosis

no

localized pain

no

generalized pain

patient on ART?

yes

no

colicky flank pain?

yes

consider renal lithiasis

no

colicky right upper quadrant pain?

yes

consider cholecystitis, sclerosing cholangitis

no

upper abdominal pain?

yes

consider pancreatitis, hepatitis

no

consider visceral leishmaniasis

left upper quadrant pain/fever?

no

right upper quadrant pain/fever?

yes

consider liver abscess (entamoeba histolytica, bacterial)

no

diarrhea?

yes

see section on diarrhea

no

consider lactic acidosis

no

patient on ART?

no

consider TB/MAC Crypto CMV

fever/wasting?
### Table 7. Assessment of Danger Signs in Cases of HIV-Related Abdominal Pain

<table>
<thead>
<tr>
<th>Danger Sign</th>
<th>Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction</td>
<td>No flatus/stools, clangor, bloating, nausea, vomiting</td>
<td>X-ray standing: proximal dilatation of bowel, air-fluid levels Ultrasound: fluid levels</td>
<td>Nasogastric tube surgery</td>
</tr>
<tr>
<td>Peritonitis/Perforation</td>
<td>Patient lies still, toxic, fever, shock, no bowel sounds, rebound tenderness</td>
<td>Rx standing: free air under diaphragm</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

### Table 8. Differential Diagnosis and Disease-Specific Management of HIV-Related Abdominal Pain

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Signs and Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized Abdominal Pain</td>
<td>Left upper quadrant pain, splenomegaly, fever</td>
<td>Amastigotes in blood / bone marrow / lymph node smear</td>
<td>Pentavalent antimonium 20 mg/kg/day for one month or amphotericin B 0.7 mg/kg/day for 28 days</td>
</tr>
<tr>
<td>Visceral Leishmaniasis</td>
<td>Right upper quadrant pain due to liver abscess, fever</td>
<td>Ultrasound</td>
<td>Metronidazole 750 mg three times daily for 10 days, then diloxanide furoate 500 mg three times daily for 10 days</td>
</tr>
<tr>
<td>Entamoeba histolitica</td>
<td>Upper abdominal pain, rapid onset with band-like irradiation to back, relieved by leaning forward, fever, malaise, nausea, anorexia</td>
<td>Elevated amylase/lipase</td>
<td>Stop didanosine Stop stavudine (restart at lower dose after lab and symptoms normal) Nasogastric suction, IV fluids, no enteral feeding</td>
</tr>
<tr>
<td>Pancreatitis (didanosine, stavudine, pentamidine, sulphonamides)</td>
<td>Colicky flank pain irradiating to groin Dysuria/hematuria</td>
<td>Clinical Urine analysis</td>
<td>IV fluid Pain relief If patient on indinavir, consider changing to other PI or non-nucleoside reverse transcriptase inhibitor50</td>
</tr>
<tr>
<td>Hepatitis (all ARVs including nevirapine, ritonavir, isoniazid, fluconazol)</td>
<td>Right upper quadrant pain, jaundice, malaise, anorexia, nausea/vomiting, weight loss</td>
<td>Elevated AST/ALT</td>
<td>Stop ART/isoniazid if AST and/or ALT elevations more than five times normal</td>
</tr>
<tr>
<td>Renal colics/nephrolithiasis (indinavir, sulfadiazine)</td>
<td>Colicky flank pain irradiating to groin Dysuria/hematuria</td>
<td>Clinical Urine analysis</td>
<td>IV fluid Pain relief If patient on indinavir, consider changing to other PI or non-nucleoside reverse transcriptase inhibitor50</td>
</tr>
</tbody>
</table>
Table 8. Differential Diagnosis and Disease-Specific Management of HIV-Related Abdominal Pain (cont.)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Signs and Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized Abdominal Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated TB</td>
<td>Prolonged high fever, chills, night sweats, anorexia, weight loss, abdominal swelling, peripheral lymphadenopathy</td>
<td>Ultrasound: lymph nodes &gt; 1.5 cm (with central necrosis), splenic microabscesses, lymphocytic transudate (protein &gt; 2.5 g/dL) after peritoneal puncture Chest X-ray AFB smear other sites</td>
<td>Based on national TB treatment guidelines</td>
</tr>
<tr>
<td>Mycobacterium avium complex (MAC)</td>
<td>CD4 &lt; 50 cells/mm³; prolonged fever, gradual wasting, hepatosplenomegaly</td>
<td>Severe anemia, neutropenia, alkaline phosphatase × 2 Blood culture, exclusion diagnosis after failing TB treatment</td>
<td>See Table 6</td>
</tr>
<tr>
<td>Bacteria (Salmonella typhi and non-typhi, Shigella, Campylobacter, Clostridium difficile)</td>
<td>Acute onset, high fever, toxic, acute diarrhea</td>
<td>See section on diarrhea</td>
<td>See Table 6</td>
</tr>
<tr>
<td>Parasites and protozoa (microsporidia, cryptosporidia, Isospora belli, Strongyloides stercoralis)</td>
<td>Cramping abdominal pain, diarrhea, malabsorption, wasting Right upper quadrant pain: sclerosing cholangitis, (acalculous) cholecystitis</td>
<td>See section on diarrhea</td>
<td>See Table 6</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Bulky lymphadenopathy, fever, CD4 &lt; 50 cells/mm³</td>
<td>Ultrasound Serum Ag test Pathogen isolation Lymph node / sputum / cerebrospinal fluid</td>
<td>Amphotericin B IV 0.7 mg/kg daily for two weeks, followed by fluconazole 400 mg daily for two months Secondary prophylaxis: fluconazole 200 mg daily</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>CD4 &lt; 50 cells/mm³; fever, bloody diarrhea, mucosal ulcers, CMV retinitis</td>
<td>Exclusion diagnosis after failure Antibacterial and antifungal therapy</td>
<td>See Table 6</td>
</tr>
<tr>
<td>Lactic acidosis⁵⁰</td>
<td>Patient on ART, fatigue, shortness of breath, nausea, vomiting, anorexia, muscle pain, numbness</td>
<td>Anion gap &gt; 13 mmol/L Venous lactate &gt; 5 mmol/L</td>
<td>Stop ARVs; IV fluids Oxygen Sodium bicarbonate Resume ART after symptoms/ lab okay, switch to other nucleoside reverse transcriptase inhibitor</td>
</tr>
</tbody>
</table>

Source: Adapted from Lynen.²³
CONCLUSION
Because the majority of people living with HIV are confronted with gastrointestinal problems at some point during the course of disease, and because those conditions are a significant cause of morbidity and mortality throughout the world, dealing with them properly is of critical importance in comprehensive HIV care. With the advent and increasing availability of combination ART, HIV is gradually becoming a manageable chronic disease. Gastrointestinal symptoms can interfere with the patient’s nutritional status and can considerably decrease the quality of life. As such, neglecting such symptoms, whether they are due to medication side effects or disease progression, will decrease the overall quality of HIV care.

Although gastrointestinal symptoms may be challenging to diagnose and manage due to multiple etiologies, it is highly important to follow them closely and to consider any and all causes of gastrointestinal discomfort. Additionally, any clinical feature related to the gastrointestinal tract is an important opportunity for the clinician to discuss nutritional status, fluid intake, feeding habits, hygiene, and adherence to ARVs with the patient.

ACKNOWLEDGMENTS
The recommendations in this chapter are largely adapted from the guidebook Clinical HIV/AIDS Care Guidelines for Resource-Poor Settings, 2nd ed., by Lut Lynen (Brussels, Belgium: Médecins Sans Frontières; 2006).
REFERENCE LIST


18. Van Roey J, Haxaire M, Kamya M, Lwanga I, Katabira E. Comparative efficacy of topical therapy with a slow-release mucoadhesive buccal tablet containing miconazole nitrate


DISEASES AFFECTING THE SKIN AND oral mucosa affect approximately nine of ten people living with HIV. Cutaneous manifestations may be the initial indication of a diagnosis of HIV infection, especially in cases when the host immunity is still relatively robust (as is often the case with herpes zoster). These manifestations may also occur further along in the course of HIV infection as immunity begins to decline (as with seborrheic eczema) or as a manifestation of full-blown AIDS. These conditions can also serve as markers of severe immunodeficiency, which if left untreated can be fatal (as in histoplasmosis).

As with other systems, several signs of immune deficiency can manifest in the skin. As CD4 counts decline and patients suffer with more severe immune deficiency, multiple skin pathologies will present. These may require longer periods of therapy and can relapse more frequently than pathologies occurring in HIV-negative individuals.

Thus, the importance of having a thorough working knowledge of the cutaneous manifestations of HIV/AIDS cannot be overemphasized for those working with HIV-infected individuals. Skin disease, although not a common cause of mortality, is a significant cause of morbidity and thus requires timely recognition and appropriate therapy to significantly improve quality of life for the affected person. Appropriate and timely diagnosis and treatment is even more critical in resource-limited settings, where patients often have limited access to antiretroviral therapy and therefore may suffer from the manifestations of immune deficiency for prolonged periods.

**CUTANEOUS MANIFESTATIONS OF HIV INFECTION**

The most common cutaneous manifestations of HIV infection are described here and summarized in Table 1, while cutaneous AIDS-defining conditions are described in Box 2.

**Infections and Infestations**

Infections and infestations form the largest group of cutaneous manifestations of HIV. This group comprises fungal, viral, bacterial, and parasitic infestations. Infections occurring in HIV-infected individuals are usually common in the general population but in the immunocompromised individual tend to be more severe and more resistant to conventional therapy, may be prone to more frequent relapses, and may require recurrent courses of therapy (e.g., oral candidiasis). Some conditions, such as cutaneous...
cryptococcosis, are peculiar to immunosuppression, and their presence necessitates further investigation.

**Inflammatory Conditions**

The most common conditions in this group are the seborrheic eczemas, pruritus, xerosis, and papular eruptions. Although not associated with mortality, these conditions are extremely debilitating to the individual, and simple measures can be taken to significantly improve quality of life.

**Tumors**

Kaposi’s sarcoma, as well as Hodgkin’s and non-Hodgkin’s lymphomas, can present on the skin and can be diagnosed based on characteristic presentations, aided by histopathology. These are described elsewhere in this text and will therefore not be discussed here.

### An Algorithmic Approach to Skin Manifestations of HIV

The cutaneous manifestations of HIV have always been classified etiologically. In contrast, this chapter classifies them according to lesion type (i.e., morphologically) as an aid to readers who have no specific training in diagnosing skin conditions.

The sections that follow cover six categories of cutaneous lesions: plaques, nodules, oral mucosal lesions, papules, blisters, and ulcers. Each section begins with an algorithm to assist in diagnosing the more common morphologically related skin conditions, followed by brief descriptions of possible etiologies and recommended therapy. Color plates featuring photographs of these various conditions are included at the end of this chapter. The categories of lesions described are defined as follows:

---

**Box 1. Skin Rash Terminology**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>partial or complete loss of hair</td>
</tr>
<tr>
<td>Bulla</td>
<td>a fluid-filled lesion with a diameter greater than 0.5 cm</td>
</tr>
<tr>
<td>Crusts</td>
<td>dried serum, pus, or blood usually mixed with epithelial and sometimes bacterial debris</td>
</tr>
<tr>
<td>Erosion</td>
<td>complete loss of the epidermis alone; heals with no scarring</td>
</tr>
<tr>
<td>Erythema</td>
<td>redness of the skin</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>diffuse redness of the entire skin, usually associated with scaling</td>
</tr>
<tr>
<td>Excoriation</td>
<td>linear breech of the epidermis, usually secondary to scratching</td>
</tr>
<tr>
<td>Fissure</td>
<td>linear breech of the epidermis plus a portion of the dermis</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>overgrowth of the cornified layer of the skin clinically manifesting as scaling or thickening of the epidermis</td>
</tr>
<tr>
<td>Macule</td>
<td>lesion characterized by alteration in skin color (not palpable)</td>
</tr>
<tr>
<td>Maculopapular</td>
<td>combining the characteristics of a macular and papular lesion, synonymous with morbilliform or exanthematous</td>
</tr>
<tr>
<td>Nodule</td>
<td>solid elevated lesion with a diameter greater than 0.5 cm with substantial depth</td>
</tr>
<tr>
<td>Papule</td>
<td>solid elevated lesion with a diameter less than 0.5 cm</td>
</tr>
<tr>
<td>Papulosquamous</td>
<td>characterized by discrete raised dry scaling lesions</td>
</tr>
<tr>
<td>Plaque</td>
<td>slightly elevated lesion with a diameter greater than 0.5 cm without substantial depth</td>
</tr>
<tr>
<td>Pruritus (itch)</td>
<td>unpleasant sensation that provokes the desire to scratch the skin</td>
</tr>
<tr>
<td>Pustule</td>
<td>lesion filled with pus with a diameter less than 0.5 cm</td>
</tr>
<tr>
<td>Scale</td>
<td>visible aggregate of corneocytes varying in size and color</td>
</tr>
<tr>
<td>Ulcer</td>
<td>rounded or irregularly shaped excavation that results from complete loss of the epidermis plus a portion of the dermis</td>
</tr>
<tr>
<td>Umbilicated lesion</td>
<td>an elevated lesion with a depressed central area</td>
</tr>
<tr>
<td>Urticaria</td>
<td>transient papules or plaques caused by dermal edema</td>
</tr>
<tr>
<td>Vesicle</td>
<td>fluid-filled lesion with a diameter less than 0.5 cm</td>
</tr>
<tr>
<td>Xerosis</td>
<td>dryness of the skin</td>
</tr>
</tbody>
</table>

---
• Plaques: solid, flat lesions more than 2 cm in diameter (e.g., psoriasis)
• Nodules: solid, rounded lesions more than 0.5 cm in diameter (e.g., Kaposi’s sarcoma)
• Oral mucosal lesions: plaques on tongue or buccal mucosa
• Papules: solid lesions less than 0.5 cm in diameter (e.g., molluscum contagiosum)
• Blisters: clear, fluid-filled lesions (e.g., herpes zoster)
• Ulcers: breaches in the epidermis of the skin (e.g., aphthous ulcers)

**PLAQUES**

*Seborrheic Eczema*[^16]

Seborrheic eczema (Plates 1a–1d) is one of the conditions most commonly associated with HIV. Although it can occur at any CD4 count, it tends to become more severe and recalcitrant to therapy as the CD4 count declines.[^3] It begins insidiously with plaques, weeping, and pruritus involving the scalp and flexures (i.e., axilla, inframammary, groin, and retroauricular folds). The scalp has yellow, greasy scales, and the flexures are erythematous and often secondarily infected. It may be difficult to distinguish from flexural psoriasis, and the clinician should look for the distinguishing features of psoriasis. In infants, it may present as erythroderma (i.e., redness and scaling of more than 90% of the body) or napkin dermatitis. As the child grows, it presents in the adult form but heals with hypopigmentation.

*Therapy*[^4]

If infected (i.e., weepy and malodorous), treatment begins with a systemic broad-spectrum antibiotic, such as erythromycin 500 mg four times a day for seven days, and potassium permanganate ($\text{KMnO}_4$) soaks. That is followed with specific therapy such as topical corticosteroids (1%...)

### Table 1. Common Cutaneous Manifestations of HIV/AIDS

<table>
<thead>
<tr>
<th>Type</th>
<th>Specific Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungal</strong></td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td></td>
<td>Tinea capitis, corporis, cruris, and unguium</td>
</tr>
<tr>
<td></td>
<td>Cryptococcosis</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Sporotrichosis</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td>Herpes labialis and genitalis</td>
</tr>
<tr>
<td></td>
<td>Herpes zoster</td>
</tr>
<tr>
<td></td>
<td>Chicken pox</td>
</tr>
<tr>
<td></td>
<td>Warts</td>
</tr>
<tr>
<td></td>
<td>Molluscum contagiosum</td>
</tr>
<tr>
<td></td>
<td>Oral hairy leukoplaik</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td>Impetigo</td>
</tr>
<tr>
<td></td>
<td>Ecthyma</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Atypical mycobacteria</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>Bacillary angiomatosis</td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
<td>Scabies</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td>Seborrheic eczema</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Papular eruptions</td>
</tr>
<tr>
<td></td>
<td>Xerosis</td>
</tr>
<tr>
<td></td>
<td>Drug eruptions</td>
</tr>
<tr>
<td></td>
<td>Photodermatitis</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td>Nutritional disorders</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td></td>
<td>Immune reconstitution inflammatory syndrome</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Hodgkin’s lymphoma</td>
</tr>
</tbody>
</table>

### Box 2. AIDS-Defining Skin Conditions

- Kaposi’s sarcoma
- Histoplasmosis
- Cryptococcosis
- Herpes simplex ulcers for more than one month
Figure 1. Algorithm for the diagnosis of patients presenting with plaques
Psoriasis

Psoriasis (Plates 2a–2c) can occur in the severely immunocompromised patient. It may present as psoriasis vulgaris (i.e., well-defined erythematous plaques with silvery scales involving the extensors) or as flexural lesions, which can overlap with seborrheic eczema or as erythroderma. Clues to psoriasis include silvery scaling, scalp involvement, nail changes (e.g., pitting and onycholysis), and joint pain. Psoriasis in HIV-infected individuals tends to be hyperkeratotic or rupioid and unstable (i.e., tending toward erythroderma), and the affected individuals are more likely to develop arthritis.10,11

Therapy

If localized, topical therapy can be used as follows:

- **For face, flexures, hands, and feet:** topical corticosteroids, such as 1% hydrocortisone for the face, methylprednisolone aceponate cream or betamethasone valerate [one-third strength] for face and body, ketoconazole shampoo, antihistamines (e.g., chlorpheniramine maleate 4 mg via transdermal delivery system [TDS], hydroxyzine 25 mg TDS, or promethazine 25 mg nightly).

Ichthyosis

Ichthyosis is common in the presence of any chronic disease or malnutrition and as such is also commonly found in people living with HIV. It presents with “fishlike” scales on the extensors of the lower limbs but may progress to involve the upper limbs and trunk. It may be associated with pruritus and xerosis. Xerosis is common in HIV, seen in approximately 30% of patients, whereas pruritus is seen in advanced disease and is a marker of disease progression because it commonly occurs in patients with CD4 counts less than 50 cells/mm³.1,3

Pruritus in the HIV-infected individual may have various cutaneous and systemic causes, including cutaneous infestations with scabies or insect bites, inflammatory conditions like drug reactions and papular eruptions, iron deficiency, or more sinister malignancies like Hodgkin’s or non-Hodgkin’s lymphoma. In addition to searching for an underlying cause, therapy should aim at relieving the pruritus.7,9

**Therapy**

Therapy is aimed at moisturizing the skin with emollients. A combination of white soft paraffin and liquid paraffin in a 50:50 mixture or 2% salicylic acid should be applied twice a day. Antihistamines, such as chlorpheniramine maleate 4 mg TDS, hydroxyzine 25 mg TDS, or promethazine 25 mg nightly, can also be used.

If the patient is still symptomatic, amitriptyline 25–75 mg nightly can be added.

Photodermatitis

Individuals whose immunity is declining are prone to photosensitivity that may be worsened by certain drugs (e.g., tetracyclines, antituberculosis therapy). People with this condition complain of burning or pruritus of the sun-exposed areas (i.e., the face, “V” and nape of the neck, extensors of the arms, and in females, extensors of the lower legs). Areas of sparing include the upper eyelids, retroauricular area, and under the chin. If left untreated, the condition may progress to a chronic lichenified eczema (i.e., thickening, hardening, and darkening of the skin) involving the affected areas. With constant scratching, secondary infection may occur, leading
to depigmentation caused by the inflammation (Plates 3a–3b).

**Therapy**

Topical corticosteroids, such as 1% hydrocortisone, are effective for the face; methylprednisolone acetate or betamethasone valerate can be used at one-third strength for the face and body.

Antihistamines (e.g., chlorpheniramine maleate 4 mg TDS, hydroxyzine 25 mg TDS, or promethazine 25 mg nightly) can also be used.

Sun avoidance and regular use of sunscreen are mandatory.

**Tinea Infections**

Dermatophyte (fungus parasitic on the skin or skin derivatives) infection, which presents as “ringworm,” occurs more frequently in HIV-infected individuals. Infection presents in both children and adults as tinea corporis or ringworm of the glabrous (hairless) skin (Plates 4a–4b). The lesions are annular plaques that clear centrally and have an active border consisting of papules, vesicles, or excoriations. Lesions in HIV-infected individuals may be more extensive, atypical, nodular, and recalcitrant to therapy. Similar lesions occur on other sites of the body, such as the groin (tinea cruris), hands (tinea manum), feet (tinea pedis), and scalp (tinea capitis). On the hands and feet, scaling may occur, and the nails may also be affected. The nails are usually discolored, crumbly, and hyperkeratotic. Scalp involvement, or tinea capitis, typically presents as scaling, broken-off hairs, and cervical adenopathy. However, there may be secondary infection, pustules, and boggy plaques. Diagnosis can be confirmed under a microscope with the addition of potassium hydroxide (KOH 20%). Visualization of the hyphae in the keratin of the skin, hair, or nails will confirm the diagnosis. Scales, hair, or nail clippings can also be sent to the laboratory for direct microscopy and culture.

**Therapy**

Therapy for tinea corporis, cruris, manum, and pedis depends on the extent of the fungal infection.

If localized, topical antifungal creams (e.g., econazole, miconazole, clotrimazole, or terbinafine cream) can be given twice daily for 14 days.

If there is extensive skin, hair, or nail involvement, systemic antifungal therapy is required:
- Griseofulvin 1 g/day for 28 days and 20 mg/kg in children, or
- Itraconazole 200 mg/day for 5 days or 5 mg/kg in children, or
- Terbinafine 250 mg/day for 14 days for extensive tinea corporis. In children, 250 mg if child weighs more than 40 kg, 125 mg if 20–40 kg, and 62.5 mg if less than 20 kg; administer for 14 days for tinea corporis or 28 days for tinea capitis.

For tinea unguium (nail infection), the duration is much longer:
- Griseofulvin for 6 months for fingernails, 12 months for toenails, or
- Itraconazole 400 mg/day for 1 week every month and continued for 2 months for fingernails, 4 months for toenails, or
- Terbinafine 250 mg/day continuously for 6 weeks for fingernails and 12 weeks for toenails

If patients are on antiretroviral drugs (ARVs), especially non-nucleoside reverse transcriptase inhibitors (NNRTIs), the azole antifungals should be avoided. The least interaction is expected with terbinafine. However, if a few nails are affected (less than three), it is cost-effective to use topical therapy because it avoids the problem of drug interactions. A combination of 2% clotrimazole in 40% urea or amorolfine nail lacquer can be used.

**Drug Eruptions**

Drug eruptions (Plates 5a–5b) occur 100 times more frequently in HIV-infected individuals, with the probability of drug reactions increasing with advancing immunodeficiency. The most
Secondary Syphilis

Syphilis (Plates 6a–6e) can present as a variety of cutaneous lesions. The classical lesions of secondary syphilis are an asymptomatic papulosquamous truncal eruption, annular plaques (especially of the “muzzle” area of the face), split papules involving the angles of the mouth, snail track ulcers of the tongue, and hyperpigmented papules of the palms and soles. There may also be alopecia and/or lymphadenopathy. The rash of secondary syphilis in HIV-infected individuals may present as it does in the immunocompetent individual. However, there are some differences: more than one primary lesion, or primary and secondary lesions may coexist. Secondary lesions may be more aggressive, profuse, and ulcerated (i.e., lues maligna, a form of secondary syphilis) and there is a more rapid conversion from secondary to tertiary syphilis.

Diagnosis can be confirmed with nontreponemal tests (e.g., Wasserman reaction, rapid plasma reagin, and Venereal Disease Research Laboratory [VDRL]), but therapy should only be considered with titers greater than 1:8. The rate of false-negative serologies is higher when syphilis is strongly clinically suspected, and the treponemal tests are more sensitive. Lumbar puncture should be done for serology of the cerebrospinal fluid (CSF) because a positive CSF serology would require intravenous penicillin therapy.

Therapy

Therapy is aimed at identifying the causative drug and withdrawing it from use. For mild reactions, therapy with antihistamines and topical steroids is recommended.

When SJS or TEN is suspected, withdraw the most likely offending drug, monitor for sepsis, maintain fluid and electrolyte balance, dress denuded skin, and prescribe adequate analgesia.
NODULES

Papulopruritic Eruptions and Prurigo
Papulopruritic eruptions and prurigo (Plates 7a–7b) are itchy papules and nodules on the extensors of the limbs and the face. They are distressing to the patient, and repeated scratching leads to hyperpigmented nodules on a background of lichenification. Scratching and secondary infection may cause postinflammatory depigmentation. See the discussion of papular eruptions under “Papules” for a complete description.

Therapy
Therapy is aimed at relieving the pruritus:
- Hydration of the skin with emollients (e.g., 50:50 white soft paraffin and liquid paraffin)
- Topical corticosteroids
- Oral antihistamines

Scabies
Scabies are itchy papules and nodules involving the axillae, groin, or trunk with crusting and burrows of the web spaces of the hands and feet. These may be secondarily infected with purulent discharge. Patients presenting with itchy nodules should be given a therapeutic trial of antiscabies therapy (see “Papules”).

Cryptococcosis
Cryptococcosis (Plates 8a–8d) presents as non-itchy nodules of the skin and indicates an underlying systemic disease. In patients with advanced immunosuppression, disseminated, invasive fungal infection (most commonly, cryptococcosis) should be excluded because it can result in high mortality in HIV-infected individuals with CD4 counts less than 100 cells/mm³. Cutaneous involvement occurs in 10%–20% of individuals and usually represents hematogenous dissemination. The nodules typically appear on the face and scalp and are umbilicated or have central hemorrhagic crusts. In addition to the nodules, there may be papules, ulcers, pustules, plaques, and cellulitis. Any of the skin lesions in an ill patient should be biopsied and sent for histopathology and culture. The patient should be assessed for neck stiffness and should have a lumbar puncture to exclude cryptococcal meningitis.

Therapy
- Intravenous amphotericin B 1 mg/kg for 14 days followed by oral fluconazole 200 mg two times daily for 10 weeks, or
- Itraconazole 200 mg two times daily for 10 weeks

Secondary prophylaxis once the lesions are cured includes the following:
- Fluconazole (200 mg/day) or itraconazole (200–400 mg/day) until immunity has been restored (defined as CD4 count greater than 100–150 cells/mm³ for at least six months)¹⁹
If patients are on concomitant NNRTI therapy, itraconazole may reduce therapeutic levels, so fluconazole is preferred.

Histoplasmosis
Histoplasmosis (Plates 9a–9d) is an AIDS-defining, disseminated fungal infection associated with high mortality. It occurs with advanced immunosuppression, usually at CD4 counts less than 150 cells/mm³. Diagnosis is difficult because the condition can masquerade as tuberculosis. Patients are ill, pyrexial (feverish), have chest infiltrates, lymphadenopathy, hepatosplenomegaly, and hematologic abnormalities. The skin manifestations can be protean (i.e., papules, nodules, plaques, ulcers) but have a predilection for the oral and nasal mucosa. Condition should be suspected in patients who have not responded to treatment with antibiotics and antituberculous therapy. Biopsy and culture is mandatory for diagnosis.
Opportunistic Infections, Cancers, and Coinfections

It is a systemic illness that occurs with advanced immunosuppression (CD4 count less than 100 cells/mm³). The cutaneous lesions are angiomatic papules and nodules that are friable, exophytic, and surrounded by a collarette. Lesions vary in number and can present as abscesses and cellulitic plaques. Systemically infected patients present with fever, constitutional illness, hepatic and splenic peliosis, and even endocarditis. Biopsy and culture and blood culture are necessary for diagnosis.

Therapy
Administer amphotericin B intravenously at 3 mg/kg for 14 days. Follow with itraconazole 200 mg twice daily for 10 weeks, and then give 200 mg daily for patients in endemic areas or with CD4 counts less than 150 cells/mm³.

Bacillary Angiomatosis
Bacillary angiomatosis (Plates 10a–10b) is a spirochetal infection caused by Bartonella henselae.

Figure 2. Algorithm for the diagnosis of patients presenting with nodules

CXR = chest X-ray; LP = lumbar puncture; PPE = papulopruritic eruptions
Culture, however, is difficult and a therapeutic trial of antibiotic can be used (if diagnosis is in doubt) to differentiate from Kaposi’s sarcoma.

**Therapy**

- Erythromycin 500 mg four times daily for 8 to 12 weeks, or
- Doxycycline 100 mg twice daily for 8 to 12 weeks

**ERYTHEMA NODOSUM/INDURATUM**

Erythema nodosum (Plate 11) is characterized by painful nodules occurring most commonly on the shins of the lower limbs. Presence of nodules should prompt a search for underlying tuberculosis or disseminated fungal infection, which may cause ulcerating nodules on the calves (i.e., erythema induratum).

Management is aimed at searching for underlying causes, especially tuberculosis. A chest radiograph and Mantoux test are warranted. If no underlying cause is found, treatment with anti-inflammatories is recommended.

**ATYPICAL MYCOBACTERIA INFECTION**

Atypical mycobacteria infection (Plate 12) presents as tender subcutaneous nodules and abscesses with erythematous, pustular centers. The nodules and abscesses tend to ulcerate. Infection occurs in severely immunocompromised patients. A biopsy and culture is required for diagnosis. Often these patients have been prescribed antibiotics and antituberculous therapy without improvement. Therapy with antibiotics (e.g., minocycline, macrolides) is recommended.

**KAPOSI’S SARCOMA**

Kaposi’s sarcoma (Plate 13) is a constellation of violet-colored asymptomatic macules, plaques, nodules, and tumors. They may present insidiously, and early lesions may be difficult to diagnose in dark-skinned patients. However, they are usually symmetrical, have a predilection for the lower limbs, follow the skin creases on the trunk, involve the hard palate, and present commonly with gastrointestinal tract and chest involvement. It is important to recognize and confirm lesions on biopsy because they are AIDS-defining and thus patients are eligible for antiretroviral therapy. Kaposi’s sarcoma is discussed in more detail elsewhere in this text.

**LYMPHOMA**

Patients living with HIV who have generalized lymphadenopathy and nontender, nonpruritic nodular lesions that have a tendency to ulcerate should have a biopsy to exclude lymphoma (Plates 14a–14c).

**MUCOSAL LESIONS**

**Candidiasis**

Candidiasis (Plate 15) is one of the most common mucocutaneous manifestations of HIV infection and is a marker of progression to AIDS. In children under six months, it should be taken into consideration with other signs of immunodeficiency. In addition, mucocutaneous candidiasis in children can present as diaper and flexural lesions and paronychia. The spectrum of cutaneous lesions is onychodystrophy, paronychia, urethritis, and intertriginous lesions. Disseminated skin lesions may occur in severely immunosuppressed patients and present as pustules or nodules on an erythematous base with or without central necrosis.

Among the several types of oral candidiasis, the most common is the pseudomembranous type, which presents as painful, whitish plaques of the
Attention to xerostomia (dry mouth) is important in all oral conditions; thus, using a fluoride or chlorhexidine mouthwash is important to ensure good oral hygiene and to prevent recurrences.

**Therapy**

Therapy with topical antifungals is recommended unless there is esophageal involvement or recurrent poor response to topicals.

- Gentian violet 0.5% TDS (although messy) is effective
- Oral nystatin suspension (“swish ‘n’ swallow”), lozenges, or troches for 10 to 14 days
- Fluconazole or itraconazole 200 mg daily for five to seven days

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**Figure 3. Algorithm for the diagnosis of patients presenting with mucosal lesions**

- **Plaques on tongue or buccal mucosa**
  - Pseudomembranous candidiasis: whitish, painful, adherent, cottage cheese–like, erythematous base
  - Hyperplastic candidiasis: whitish-yellowish on either side of tongue or buccal mucosa
  - Kaposi’s sarcoma: violet-colored plaques, nodules on tongue, palate, gingiva
  - Oral hairy leukoplakia: corrugated, whitish ridges on sides of tongue, adherent

- **Painful ulcers**
  - Herpes simplex: shallow, irregular border, yellowish base on lips, tongue, hard palate
  - Aphthous ulcers: well defined, deep, whitish base, erythematous halo on soft palate, buccal mucosa, tongue, tonsils

- **Tongue, uvula, and buccal mucosa (resembling cottage cheese).** Removal of the plaques with a gauze or spatula will reveal an underlying erythematous base. The erythematous type of candidiasis presents as erythematous macular lesions on the dorsum of the tongue, without plaques. Hyperplastic candidiasis presents as yellowish plaques on the lateral borders of the tongue, while candidiasis can also present as angular cheilitis or fissuring at the angles of the mouth, which is painful. In general, oral candidiasis is asymptomatic, but patients may complain of pain, burning, and dysphagia. Pain on swallowing signals the possibility of esophageal involvement. Vulval candidiasis presents with pruritus, burning, and a whitish discharge.
If there is no response to fluconazole, resistance should be suspected. In cases of fluconazole resistance, amphotericin B may be effective.¹²

**Oral Hairy Leukoplakia**

This is an asymptomatic condition that presents as white corrugated ridges along the lateral surface of the mouth. It is caused by the Epstein-Barr virus and is associated with advanced HIV disease.¹⁸

**Therapy**

Therapy is generally not indicated, but if symptomatic, one of the following can be used:
- Topical podophyllin or tretinoin gel
- Oral acyclovir 800 mg TDS for 10 days

**Aphthous Ulcers**

Aphthous ulcers (canker sores) can present in persons infected with HIV, but their presence should not be taken as a sign of immunosuppression because the ulcers are common in the general population. Presenting as painful and recurrent, the ulcers can be very difficult to distinguish from herpes simplex infection. They can be single or multiple and are well defined with a whitish base and surrounding erythema. Aphthous ulcers are usually deeper than herpes simplex ulcers and typically occur on the soft palate, tongue, buccal mucosa, and tonsils.

**Therapy**

Therapy is symptomatic and aimed at keeping the mouth clean and analgesic to allow the ulcers to heal. If the ulcers are large and/or persistent, or if herpes simplex is suspected as a cause, therapy with acyclovir 400 mg TDS may be given. Other recommended therapy includes the following:
- Analgesics (e.g., paracetamol or combination preparations)
- Topical lignocaine (lidocaine) gel
- Oral antihistamines alleviate the pruritus.
- All household contacts should be treated.
- Secondary bacterial infections, if present, should be treated first with appropriate antibiotics.
Figure 4. Algorithm for the diagnosis of patients presenting with papules

In HIV-infected persons, scabies may be resistant to treatment and require repeated courses of the scabicide.

Topical scabicides include the following:
- Benzoyl benzoate (25%) lotion should be applied twice, from neck to toes, after a bath on the first day. On the second day, two applications are reapplied from neck to toes, but the patient should not bathe. On the third day, a bath should be taken and all clothes and bed linen should be washed and dried in the sun.
- Sulfur (5%) ointment recommended for children under the age of two. Ointment should be applied daily for five days.
- Permethrin (5%) lotion is applied and left overnight; repeated applications may be required, usually one week after the initial application. Permethrin should not be used in infants younger than two months of age or in pregnant or nursing women.
- Lindane 1% (gamma benzene hexachloride) is effective but may cause neurotoxicity. An application of lindane is left on the patient for eight hours and then washed off. Repeated applications after seven days may be required in some patients. Lindane should not be used in children, pregnant females, lactating mothers, and patients with neurological disorders.20

Management of Norwegian (Crusted) Scabies
Pretreatment with keratolytic creams, such as creams or ointments containing salicylic acid, may be helpful. The scabicide should be applied on the scalp and face (avoid the eyes, nose, and mouth). Patients with crusted scabies should first be treated with a preparation of 5% sulphur and 5% salicylic
acid in emulsifying ointment to treat any secondary infection and debride the lesions. After the lesions have been debrided (usually 10–14 days), benzyl benzoate lotion can be used. Oral ivermectin is the drug of choice for crusted scabies and is administered at 200 µg/kg as a single dose.20

**Papulopruritic Eruptions of HIV**

Papulopruritic eruptions (Plates 17a–17b) and eosinophilic folliculitis are distinct clinicopathological entities seen in HIV-infected patients. This chapter refers to both as papulopruritic eruptions (PPE) of HIV. Clinically, the patients present with excoriated widespread pruritic papular lesions. The papules are symmetrical, involving the limbs, trunk, face, and neck; the web spaces, mucous membranes, palms, and soles are spared. More than 50% of HIV-infected patients report PPE as the first presenting feature of HIV infection.24

**Therapy**

Sedating oral antihistamines, such as hydroxyzine or chlorpheniramine, alleviate the pruritus. Potent topical steroids, such as methyl prednisolone aceponate or dilute betamethasone cream, used alone or together with oral antibiotics (e.g., metronidazole or tetracyclines) are usually effective. Short courses of systemic steroids, such as prednisone given at 70 mg and gradually reduced by 5 to 10 mg over a period of 7 to 14 days, have been reported to be effective. However, systemic steroids should be used with caution in immunosuppressed patients. Phototherapy, if available, is useful for resistant cases.25

**Papular Urticaria**

Papular urticaria (Plates 18a–18b) presents with pruritic, excoriated papules, usually on exposed sites. This exaggerated insect bite reaction may be indistinguishable from PPE. A history of insect bites will favor the diagnosis of papular urticaria. In addition, the lesions tend to be in groups or in a linear pattern.

**Therapy**

- Protective measures against insects (e.g., insect repellents, bed nets)
- Topical steroids and oral antihistamines
- Systemic steroids in severe recalcitrant cases, but long-term use of systemic steroids by HIV-infected patients may result in serious complications.26

**NON-ITCHY PAPULES**

**Human Papillomavirus Infection**1,2

Human papillomavirus (HPV) can cause numerous manifestations in the HIV-infected individual (Plates 19a–19b). These include verruca vulgaris (common warts), widespread plane warts, and condyloma acuminata. The warts can be single but are usually multiple, large, and disfiguring in patients with HIV infection.27

HPV infection has been associated with anogenital cancer. Cervical cancer is the most common malignancy in women in the developing world and there is a higher incidence of cervical intraepithelial neoplasia in HIV-infected women. Thus, appropriate screening for cervical cancer is important in HIV-infected patients.

The spread of HPV infection is associated with higher numbers of sexual partners and lack of condom use; preventive measures should focus on addressing those issues.28

**Therapy**

Treatment is usually less effective in HIV-infected patients, and repeated treatment courses are often required. Several modalities of treatment are available for warts. Treatments are classified as either patient or clinician administered.
Molluscum Contagiosum Infection

Molluscum contagiosum (Plate 20) is a viral infection of the skin or occasionally of the mucous membranes. The typical lesion is a dome-shaped, pearly, umbilicated papule with a central curdlike core. In HIV infection, the lesions of molluscum can be large, multiple, and confluent and are often very difficult to treat. The important differentials to consider in HIV-infected patients include cryptococcosis, histoplasmosis, and penicilliosis. Toluidine blue or Giemsa staining of the white, curdlike material expressed from the lesions reveals eosinophilic molluscum bodies.

Therapy

Treatment of molluscum contagiosum can be subdivided into physician-administered and patient-administered treatments.

Patient-administered treatments include the following:
- Salicylic acid/lactic acid combination in flexible collodion (Duofilm). Duofilm provides good results, particularly in children with extensive lesions. It is applied daily to the lesions and may cause irritation.
- Salicylic acid
- Podophyllotoxin gel
- Imiquimod
- Tretinoin (0.05%) cream (to treat plane warts)

Clinician-administered treatments include the following:
- Cryotherapy
- Electrocautery
- Podophyllotoxin solution or resin
- 80% trichloroacetic acid
- Laser
- Surgical debulking of giant warts followed by topical therapy
Physician-administered treatments include the following:
- Manual extrusion of the molluscum body with gloved fingers
- Removal of the molluscum body using an orange stick
- Curettage
- Cryotherapy
- Electrocautery

Patient-administered treatments include the following:
- Benzoyl peroxide cream applied daily
- Tretinoin (0.05%) cream applied daily
- Lactic acid or salicylic acid in flexible collodion (Duofilm). Duofilm provides good results in children with molluscum contagiosum. It is applied daily to the lesions. Irritation may occur in some patients.
- Imiquimod
- Potassium hydroxide (10%) applied twice daily until either lesions undergo inflammation or ulceration results in resolution of the lesions.
- Silver nitrate
- Duct tape occlusion of the lesions has also been reported to be helpful.

**Papulonecrotic Tuberculid**

Tuberculids are skin eruptions associated with an underlying or silent form of tuberculosis. Papulonecrotic tuberculids (PNTs) present with asymptomatic papular lesions that can become pustular or necrotic (Plate 21). Lesions tend to be distributed on the extensors of the limbs. The face and earlobes may be involved. Typically, the lesions are recurrent, resolve spontaneously, and heal with scarring, only to reemerge later with lesions appearing in crops. Papulopustular secondary syphilis should be considered if the presentation is atypical. The condition can be confused with PPE; however, pruritus is not a predominant feature in PNT. A Mantoux test should be done because it is strongly positive in most patients with PNT. A skin biopsy should be also done to confirm the diagnosis of PNT. A chest X-ray is necessary to rule out the presence of pulmonary tuberculosis.

**Therapy**

The decision to treat is based on the characteristic skin lesions, a strongly positive Mantoux test, and histological confirmation of PNT. Chest X-ray is a noninvasive test that should be done in all patients with suspected PNT. Using invasive investigations of other systems to search for the mycobacterium should not be done routinely; the decision to investigate further should be guided by findings on history and physical examination.

Standard tuberculosis treatment for six to nine months should result in resolution of the lesions.

*Note: Several other dermatoses can present as papules, and a detailed discussion of them is beyond the scope of this chapter. When in doubt, a skin biopsy aids diagnosis.*

**BLISTERS**

Blisters can present as vesicles or bullae. A vesicle is a clear, fluid-filled, elevated lesion with a diameter of less than 0.5 cm. A bulla is a clear, fluid-filled lesion with a diameter of more than 0.5 cm. In HIV infection, vesicles and bullae may be the presenting cutaneous manifestation of several pathological processes, as outlined in the following algorithm.

**Varicella Zoster Infection**

Varicella zoster viral infections occur frequently in the setting of HIV infection. The patterns of presentation are usually typical, but atypical presentations can occur in HIV-infected patients. In these circumstances, diagnosis may be difficult.

Primary infection with the varicella zoster virus (VZV) presents as chicken pox (varicella; Plate
The initial lesions are vesicles associated with fever. The vesicular eruption begins on the face and extends to the trunk and extremities. In children living with HIV, primary zoster infection can be severe, with internal organ involvement causing encephalitis, pneumonitis, or pancreatitis. Other uncommon presentations of chickenpox in HIV infection include recurrent varicella (defined as recurrence of lesions at least one month after a previous episode of chickenpox) and chronic varicella (lesions that persist for more than one month). Reactivation of the latent varicella zoster virus from the dorsal root ganglia manifests as herpes zoster (shingles). The lesions present as painful vesicles and bullae in a dermatomal distribution (Plate 22b). Reactivations frequently involve the thoracic or cervical root ganglia and the ophthalmic branch of the trigeminal ganglion. Herpes zoster is common in HIV-infected patients and may present at any stage of the infection, irrespective of CD4 count.

HIV-infected patients with herpes zoster involving the ophthalmic branch of the trigeminal nerve, with or without conjunctivitis, need to be assessed by an ophthalmologist to exclude ocular involvement. Disseminated zoster is defined as lesions extending over three contiguous dermatomes or more than 20 lesions outside the initial dermatome (Plate 22c). Disseminated zoster can occur in a setting of HIV infection. Visceral dissemination, though uncommon, needs to be carefully excluded. Postherpetic neuralgia, defined as zoster pain that lasts more than one month, can occur as a complication in HIV-infected patients.

Diagnoses of varicella and zoster are made clinically, but a Tzanck smear may be useful in atypical cases.

Zoster can present as part of immune reconstitution in adult and child patients who have been initiated on antiretroviral therapy.

**Therapy**
- Acyclovir 800 mg five times a day for seven days
- Calamine lotion
- Treatment of secondary infection with appropriate antibiotics (e.g., topical mupirocin ointment applied twice daily to infected lesions)
- Pain management with analgesics

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**Figure 6. Algorithm for the diagnosis of patients presenting with painful blisters**

- **Generalized**
  - Chickenpox (varicella zoster)
  - Drug reactions

- **Localized**
  - Oral or genital involvement
  - Dermatomal in distribution
  - Herpes simplex viral infection
  - Herpes zoster
Treatment of postherpetic neuralgia:
- Analgesics
- Amitriptyline 25 mg at night
- Neuroleptics, such as carbamazepine and lamotrigine, are useful alternatives to amitriptyline.

HIV-infected patients exposed to varicella zoster for the first time should receive VZV immunoglobulin within 96 hours of exposure.38,39

The Centers for Disease Control and Prevention (CDC) recommend VZV (live attenuated Oka strain) as a routine immunization for HIV-infected children who have no stigmata of immunosuppression.41

ULCERS

Herpes Simplex Infection1,2
In the early stages of HIV infection, the clinical presentation of herpes simplex virus (HSV) infection is similar to that seen in immunocompetent patients and is characterized by recurrent painful ulcers involving the genitalia and the perioral and perianal regions (Plates 23a–23b). Ulcers typically present as groups of vesicles that erode and heal in about two weeks.

In advanced HIV disease, the ulcers can be larger; disseminated disease is rare. Herpetic ulcers that fail to heal for longer than one month are a marker of severe immunosuppression and are considered by the CDC to be an AIDS-defining condition. It is therefore important to differentiate between these chronic herpetic ulcers and recurrent HSV infection.21,31,42 A Tzanck smear may be helpful to confirm the diagnosis of HSV.

Therapy
- Primary infection is treated with acyclovir 200 mg five times a day or 400 mg three times a day for 10 days.
- Treatment of recurrent episodes is acyclovir at a similar dosage but for 5 days.
- Valacyclovir and famciclovir can also be used when available.
- Suppressive therapy should be administered when recurrences are frequent, usually with acyclovir 400 mg twice daily.
- If lesions do not respond to acyclovir, consider using higher doses. If acyclovir resistance is suspected, intravenous foscarnet can be used.
- For alternative diagnoses, a skin biopsy for routine histology and bacterial, fungal, and mycobacterial cultures are helpful.

Cutaneous Bacterial Infection

Staphylococcus aureus1,2
S. aureus skin infections are significantly more common in the HIV-infected patient than in the immunocompetent patient. HIV-infected individuals do not have significantly different presentations, yet they tend to have more severe recurrent and atypical infections. Higher rates of chronic nasal staphylococcal carriage seen in HIV-infected patients account for the increased frequency of staphylococcal infections.43

Staphylococcal infections can present as cellulitis, furuncles (Plate 24a), ecthyma (Plate 24b), persistent and recurrent folliculitis, and impetigo. A case of staphylococcal scalded-skin syndrome in a child with AIDS has also been reported.44

Unusual infections, such as botryomycosis, can also be the presenting feature in HIV infection.18 Botryomycosis is a chronic granulomatous staphylococcal infection that presents with subcutaneous nodules, plaques, ulcers, and fistulae with purulent exudates.

Therapy
A pus swab should be sent for microscopy (Gram stain), culture, and sensitivities.
The following can be used as first-line empirical treatment:
OPPORTUNISTIC INFECTIONS, CANCERS, AND COINFECTIONS

Semisynthetic penicillins (such as cloxacillin or cephalosporins)
- In patients with methicillin-resistant *S. aureus* or patients who have penicillin allergy, oral erythromycin, clindamycin, and trimethoprim/sulfamethoxazole are useful alternatives.
- If the patient is clinically well, oral antibiotics are usually sufficient. However, if the patient is clinically toxic, intravenous antibiotics must be administered.
- The duration of treatment should be longer than normal.
- Nasal mupirocin applied three to five times a day to the nares (nostrils) should be considered in patients with recurrent staph infections.21

**Gram-Negative Bacterial Infections**

Gram-negative infections in HIV-infected patients can be problematic. *Pseudomonas* bacteremia can produce cutaneous manifestations such as ecthyma gangrenosum and otitis externa.22 A severe peri-orbital Gram-negative infection in a child with AIDS has been reported.22 This form of infection requires intravenous antibiotics to prevent septicemia and meningitis.

**CUTANEOUS MANIFESTATIONS ASSOCIATED WITH ANTIRETROVIRAL THERAPY**

Antiretroviral therapy (ART) improves the quality of life and life expectancy of HIV-infected individuals by suppressing viral replication and allowing an increase in CD4 count (i.e., immune reconstitution). Health-care providers should be on the lookout for various skin conditions that may present as a result of patient initiation on ART. Although most of these conditions are not serious, they should be promptly diagnosed and treated to ensure the patient’s comfort and continued adherence to ART.

**Immune Reconstitution Inflammatory Syndrome**

Immune reconstitution inflammatory syndrome (IRIS) is a pathologic inflammatory response to preexisting microbial, host, or other antigens that result in clinical deterioration in HIV-infected individuals after initiating ART. The following criteria for the diagnosis of IRIS have been proposed45-47:
A patient must
- be HIV-positive and receiving ART;
- have a decreasing viral load with or without an increase in CD4 count from baseline; and
- have clinical symptoms consistent with an inflammatory process in which the clinical course is not consistent with the expected course of a previously diagnosed opportunistic infection, expected course of newly diagnosed opportunistic infection, or drug toxicity.

The cutaneous manifestations of IRIS usually respond to appropriate conventional therapies. Clinicians should be familiar with the range of skin conditions associated with IRIS to avoid incorrectly diagnosing patients as having adverse cutaneous drug reactions to ART (which could lead to unnecessary discontinuation of ART). The specific features of IRIS are discussed elsewhere in this text (see chapter entitled “Immune Reconstitution Inflammatory Syndrome”).

**Nucleoside Reverse Transcriptase Inhibitors**

**Zidovudine**
Zidovudine (AZT) was one of the first antiviral agents used in the management of HIV infection. The cutaneous side effects are well documented and relate mainly to nail and mucosal hyperpigmentation. Pigmentation of the nail usually starts proximally and may manifest as complete nail pigmentation or as transverse or longitudinal bands. Pigmentation may occur on select nails or may be universal. Pigmentation also varies from blue to gray to brown, and onset is usually within one month of initiation on AZT. Discontinuation or dose reduction will result in gradual fading. Hypertrichosis (excessive growth) of body hair and eyelashes have been reported. Rare cutaneous side effects include vasculitis, exaggerated response to mosquito bites, hypersensitivity reaction, and paronychia.

**Didanosine**
Cutaneous side effects to didanosine (ddI) are uncommon. However, vasculitis and SJS have been reported. Discontinuation of ddI leads to prompt resolution and is especially important if a severe allergic drug reaction is suspected.

**Non-nucleoside Reverse Transcriptase Inhibitors**

**Lamivudine**
Lamivudine (3TC) is a relatively safe drug with few adverse cutaneous reactions. However, there have been reports of paronychia, pyogenic granuloma, alopecia, and allergic contact dermatitis caused by prolonged contact with the 3TC tablets. These are rare occurrences and do not necessitate discontinuation of the drug.

**Zalcitabine**
Ulcers of the esophagus and buccal mucosa are the most common cutaneous manifestations associated with the use of zalcitabine. Ulcers are self-limiting and resolve within a week. A transient maculopapular eruption occurs in approximately 2% of individuals, also resolving within a week. Hypersensitivity, known as DRESS (drug rash, eosinophilia, and systemic symptoms with fever and multiorgan involvement), has also been reported in isolated cases and develops within two to six weeks of therapy initiation.

**Abacavir**
Abacavir (ABC) is notorious for causing a fatal hypersensitivity syndrome that presents with fever, exfoliation, hepatitis, and eosinophilia. As soon as hypersensitivity is suspected, ABC should be discontinued, and patients should not be rechallenged; several deaths have occurred among patients rechallenged with ABC.
**Nevirapine**

The most notorious toxicities of nevirapine (NVP) are rash and hepatitis. Nevirapine-induced rash usually presents within four to six weeks of initiation as a morbilliform eruption and urticaria. The incidence of these reactions varies from 9% to 32%. However, in the absence of blisters, erythroderma, mucosal involvement, and hepatitis, therapy can be continued and the reaction treated symptomatically with antihistamines and corticosteroids. The proportion of patients requiring discontinuation is 6%–7%. SJS and TEN occur in approximately 1% of treated patients and require prompt recognition and permanent discontinuation of the drug. In these patients, reintroduction is contraindicated. The NVP lead-in period of 100 mg daily for the first two weeks and escalation to 200 mg daily thereafter aims to decrease the incidence of rash. Those at higher risk of developing NVP rash and hepatitis are females with CD4 counts greater than 250 cells/mm³ (or males with CD4 counts greater than 400 cells/mm³) and individuals with low body mass indexes. In nonpregnant females who have high CD4 counts and use reliable contraception, efavirenz is recommended as an alternative to NVP. NVP has also been implicated in the DRESS syndrome, with a 10% mortality rate from liver failure. Thus, close monitoring of patients on NVP is essential in the first eight weeks after initiation. A patient who develops a rash should always be assessed for hepatotoxicity.

**Efavirenz**

Cutaneous adverse reactions to efavirenz (EFZ) are uncommon, but patients who have reacted to NVP also have an increased risk of cutaneous drug reactions to EFZ.

**Protease Inhibitors**

Protease inhibitors (PIs) are potent agents that suppress viral load and aid in CD4 restoration. The most common cutaneous adverse reaction is lipodystrophy (LDS). Symmetrical loss of subcutaneous fat is the primary characteristic of LDS and may occur in three forms: congenital total, partial (affecting the face and lower body), and acquired total. LDS typically occurs 2 to 12 months after initiation of therapy.

Central adiposity is often associated with LDS and occurs in 6% to 64% of individuals with onset 6 to 12 months after initiating treatment with PIs, but onset may be more rapid in those taking saquinavir or ritonavir. Besides central adiposity (“crix belly” or “protease paunch”), supraclavicular deposition and buffalo hump can occur. In addition, hypertriglyceridemia, hypercholesterolemia, hyperglycemia, and insulin resistance have been reported. LDS syndromes have also been reported in those on non-PI regimens and may be related to immune restoration and HIV suppression; however, the exact mechanism is still unknown. Therapy for LDS includes surgical removal, liposuction, ketoconazole, and growth hormone. Nucleoside reverse transcriptase inhibitors, especially stavudine, have also been implicated in lipoatrophy.

Drug reactions also occur and commonly manifest as maculopapular eruptions and urticaria. Uncommonly, acute generalized exanthematous pustulosis (AGEP) can occur and presents with high fever, erythroderma, pustules, and a morbilliform eruption. AGEP should resolve without specific therapy after treatment discontinuation.

**Indinavir**

Indinavir has been implicated in a multitude of cutaneous reactions. Most commonly reported are alopecia, xerosis, lip fissuring, and paronychia. These changes are related to alterations in retinoid metabolism. Hair loss is similar to alopecia areata and occurs in the first six months of therapy. Other reactions include acute porphyria, hypersensitivity syndrome, SJS, and gynecomastia (male breast development).
**Ritonavir**
In addition to drug eruptions and hypersensitivity reactions, spontaneous bleeding is peculiar to ritonavir therapy. Increased bleeding in hemophiliacs has been reported with all PIs.

**Nelfinavir**
Nelfinavir is prescribed for children more frequently than for adults. Cutaneous side effects include maculopapular eruption and urticaria, which usually manifest 5 to 10 days after therapy initiation.

**Saquinavir**
Saquinavir is not commonly prescribed and plays a limited role in multidrug therapy. It has been reported to cause fixed drug eruptions (adverse drug reactions that recur at the same site with each administration) and gynecomastia.

**CONCLUSION**
Skin disease affects approximately 90% of individuals living with HIV.1,3,4 As immunity declines with advancing HIV infection, dermatoses become more prominent and several conditions can coexist. A thorough working knowledge of skin conditions is essential for practitioners working to effectively treat people living with HIV, thereby enhancing their quality of life.
Color Plates: Cutaneous Manifestations of HIV

Plate 1a. A case of seborrheic eczema showing weepy eczematous lesions involving the axilla.

Plate 1b. Erythematous eczematous lesions in the axilla of a child with seborrheic eczema.

Plate 1c. A child with seborrheic eczema showing greasy and yellow scales in the scalp; erythematous eczematous lesions are also present on the forehead.

Plate 1d. A case of seborrheic dermatitis showing involvement of the napkin area.
Plate 2a. A case of psoriasis demonstrating well-defined plaques with silvery white scaling

Plate 2b. Salmon pink plaques with silvery white scale on the dorsa of the hands in a patient with psoriasis

Plate 2c. Widespread plaques with silvery white scaling involving the back and buttocks in an HIV-positive patient with psoriasis
Plate 3a. A case of photodermatitis showing chronic eczematous plaques with areas of depigmentation on the scalp and posterior neck.

Plate 3b. A case of photodermatitis showing chronic eczematous plaques with depigmented areas on the extensor aspect of the upper limb in a patient.

Plate 4a. A case of tinea corporis demonstrating annular plaques that clear centrally with an active erythematous border.

Plate 4b. A case of tinea pedis showing scaling areas on the plantar aspect of the foot.
Plate 5a. A case of drug eruption demonstrating erythematous petaloid lesions involving the back.

Plate 5b. A case of erythema multiforme (EM). The individual typical lesions demonstrate the characteristic zones of EM; a central blister surrounded by a dusky erythematous zone and a pale erythematous margin. Some of the blisters have erupted leaving behind denuded skin areas, and the skin is re-epithelializing in other areas.

Plate 6a. A case of secondary syphilis demonstrating an annular plaque involving the upper limb.

Plate 6b. Papulosquamous lesions on the thigh of a patient with secondary syphilis.
Plate 6c. Annular plaques involving the “muzzle” area of the face and split papules on the angles of the mouth in patient with secondary syphilis.

Plate 6d. A case of secondary syphilis demonstrating erythematous and hyperpigmented papules on the palms of patient with secondary syphilis.

Plate 6e. Erythematous plaques on the foot of a patient with secondary syphilis.

Plate 7a. A case of prurigo showing hyperpigmented nodules on a lichenified background involving the posterior neck and upper back.
Plate 7b. A case of prurigo showing pruritic nodules on a background of lichenification involving the extensor aspect of the upper limb; the central area of the nodules is hypopigmented as a result of scratching the lesions.

Plate 8a. A case of cryptococcosis showing a large nodule on the angle of the mouth and an ulcerated nodule on lower jaw area.

Plate 8b. Ulcerative lesions in a patient with cryptococcosis.
Plate 8c. A case of cryptococcosis demonstrating multiple umbilicated papules and nodules involving the face; some of the lesions are hemorrhagic.

Plate 8d. Ulcerated nodules in a patient with cryptococcosis.

Plate 9a. A case of histoplasmosis showing gross swelling of the lips with hemorrhagic crusting and ulceration; there are crusted plaques involving the face.
Plate 9b. A case of histoplasmosis demonstrating crusted plaques involving the forearms

Plate 9c. A case of histoplasmosis demonstrating an admixture of papules and plaques involving the lower limbs

Plate 9d. Plaques and papules involving the upper limb in a patient with histoplasmosis

Plate 10a. A case of bacillary angiomatosis showing angiomatous nodules involving the posterior arm and upper back; angiomatous nodule in the center of the photograph is ulcerated

Plate 10b. A case of bacillary angiomatosis showing an angiomatous nodule
Plate 11. A blistering strongly positive Mantoux test in a patient who had erythema nodosum.

Plate 12. A case of an atypical mycobacterial infection showing crusted plaques involving the upper limb.

Plate 13. A case of Kaposi’s sarcoma showing a violaceous plaque and a nodule.

Plate 14a. A case of lymphoma showing erythematous crusted plaques involving the upper limb.

Plate 14b. A case of lymphoma showing plaques on the upper limb; there is an ulcerated crusted plaque on the lateral aspect of the forearm.
Plate 14c. Multiple nodules in a patient with lymphoma; the underlying skin is indurated and edematous giving a peau de orange appearance

Plate 16a. A case of scabies showing pruritic papules and scabetic burrows involving the toe web spaces

Plate 16b. A case of Norwegian (crusted) scabies demonstrating crusted plaques on the wrist and dorsa of hand; note the involvement of the web space

Plate 15. Whitish plaques on the tongue of a patient with oral candidiasis
Plate 17a. Erythematous pruritic papules involving the face, with ear lobe involvement in a patient with papulopruritic eruption of HIV

Plate 17b. A case of papulopruritic eruption demonstrating erythematous papules involving the face
Plate 18a. A case of papular urticaria demonstrating excoriated erythematosus papules predominantly involving the upper limbs

Plate 18b. A child with papular urticaria showing erythematous pruritic papules on the forearm (exposed site); a linear distribution of the lesions is apparent

Plate 19a. Multiple filiform warts involving the genital area in an immunocompromised child

Plate 19b. A case of extensive plane warts showing multiple plane topped hypopigmented papules involving the chest, abdomen, and upper limbs
Plate 20. Dome-shaped, pearly, umbilicated papules involving the neck and anterior chest in a child with molluscum contagiosum; larger (giant) molluscum lesions are also present.

Plate 21. A case of papulonecrotic tuberculid showing papular lesions with necrotic centers involving an upper limb extensor.

Plate 22a. Vesicular lesions on an erythematous background involving the shoulder region in a patient with varicella zoster (chicken pox).

Plate 22b. A case of herpes zoster showing grouped vesicles and bullae in a dermatomal distribution.
Plate 22c. Involvement of more than one dermatome in an immunocompromised patient with multidermatomal herpes zoster; erythematous vesicles, crusts, and erosions involving the V3, C3, and C4 dermatomes are shown.

Plate 23a. A case of genital herpes demonstrating multiple punched-out ulcers involving both labia.

Plate 23b. A large painful ulcer with an erythematous base involving the angle of the mouth in an immunocompromised child with chronic herpes.
Plate 24a. A case of furunculosis, some of the furuncles have coalesced to form carbuncles

Plate 24b. A case of ecthyma from a staphylococcal infection showing crusted ulcerative lesions involving the leg; the lesions tend to heal with scarring


HEPATITIS B VIRUS (HBV) INFECTION poses a significant global public health threat, especially in vulnerable populations, such as people living with HIV infection. Approximately two billion people worldwide have serological evidence of HBV infection, and more than 350 million have chronic infection, defined as detection of hepatitis B surface antigen (HBsAg) for more than six months following acute infection (Figure 1). In China, home to 75% of the world’s chronic HBsAg carriers, chronic infection with HBV is the leading cause of both cirrhosis and hepatocellular carcinoma (HCC). Transmission of HBV occurs through percutaneous and mucosal exposure (usually sexual) to blood or body fluids contaminated with blood. HBV is present in most bodily fluids, including blood, semen, and saliva. Studies have demonstrated that HBV is infectious via both semen and saliva, and that HBV DNA is present in urine as well.

EPIDEMIOLOGY OF HBV

The epidemiology and natural history of HBV infection vary significantly by world region. The United States and Western Europe typically have lower prevalence rates, estimated at 5% to 7% with serological evidence of prior exposure and less than 1% with chronic infection. In areas with low hepatitis B prevalence rates, such as the United States, sexual transmission accounts for the majority of disease with onset of disease usually in adolescence and young adulthood. In parts of Asia and sub-Saharan Africa, where hepatitis B is endemic, exposure and acquisition typically occur perinatally or in very early childhood; more than 70% of people in these regions have antibody markers indicative of prior infection.

Areas of moderate HBV prevalence include Eastern Europe, parts of the Middle East, northern Africa, and parts of South America. In these regions, the prevalence of chronic HBV infection ranges from 2% to 7%, with evidence of prior exposure in up to 60%. Risk and infection routes vary by subpopulation—infection may spread through perinatal or early childhood exposure, injection drug use, or sexual transmission.

In East Asia, perinatal transmission is common. In China, it has been estimated that 35% to 50% of chronic hepatitis B infection is due to perinatal transmission. In contrast, infection in sub-Saharan Africa is attributable mainly to horizontal early childhood transmission, occurring before the age of five. Exposure is thought to be mediated by medical procedures, close household contact,
traditional scarification, and other unidentified mechanisms.\textsuperscript{6,11-13} Hepatitis B e antigen (HBeAg) prevalence is low in these regions, raising the speculation of a lower risk of vertical transmission.\textsuperscript{14} For example, in Zimbabwe, HBeAg was present in 5% to 15% of HBsAg-positive carriers.\textsuperscript{14}

**GLOBAL EPIDEMIOLOGY OF HIV AND HBV COINFECTION**

HIV-HBV coinfection is common because of shared routes of transmission; both are spread through parenteral and sexual contact. In North America and Europe, prevalence of chronic HBV infection is higher in HIV-positive populations than among those who are HIV-negative, with rates ranging from 4% to 10%.\textsuperscript{15-17} In Africa and Asia, however, most studies suggest that the prevalence of chronic HBV infection does not differ between HIV-positive and negative populations.\textsuperscript{18-22} Notable exceptions come from data in China and Nigeria, where HBV infection was found to be higher in HIV-positive populations.\textsuperscript{23-24} The reasons for these differences are unclear but may be related to other shared risk factors (such as injection drug use in the Chinese study).

**NATURAL HISTORY OF HBV INFECTION**

The risk of chronic HBV infection is highest with earlier age of infection.\textsuperscript{25} Chronic HBV infection occurs in 90% of infants with perinatal infection,\textsuperscript{25} 30% of children who are exposed to HBV before the age of five,\textsuperscript{26} and 2% of immunocompetent adults.\textsuperscript{25} The natural history of chronic HBV infection can be divided into five phases: immune tolerance, HBeAg-positive chronic hepatitis B, the inactive HBSAg carrier state, HBeAg-negative chronic hepatitis B, and recovery (Table 1).\textsuperscript{27} An interpretation of serologic markers is provided in Table 2. These stages are based on immune status, HBV DNA levels, presence of HBeAg, and alanine aminotransferase (ALT) levels.\textsuperscript{28-29}
Table 1. Phases in the Natural History of Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>Liver Histology</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>HBsAg</th>
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<tr>
<td>Immune tolerance</td>
<td>Normal or</td>
<td>Minimal activity, scant fibrosis</td>
<td>High levels (10^9 to 10^11 copies/mL)</td>
<td>Present</td>
<td>Present</td>
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<td>minimally</td>
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<td>elevated</td>
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<tr>
<td>HBeAg +ve chronic hepatitis B</td>
<td>Elevated,</td>
<td>Active with variable amounts of fibrosis</td>
<td>High levels (10^9 to 10^10 copies/mL)</td>
<td>Present</td>
<td>Present</td>
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<tr>
<td>HBeAg –ve chronic hepatitis B</td>
<td>Elevated,</td>
<td>Active with variable amounts of fibrosis</td>
<td>Moderate levels, often fluctuating (10^3 to 10^4 copies/mL)</td>
<td>Absent</td>
<td>Present</td>
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</tr>
<tr>
<td>Inactive carrier state</td>
<td>Normal</td>
<td>Inactive with variable, usually minimal amounts of fibrosis</td>
<td>Low or no detectable levels (&lt;10^4 copies/mL)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Recovery</td>
<td>Normal</td>
<td>Inactive with scant amounts of fibrosis</td>
<td>No detectable levels in serum (low levels may be present in liver)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen

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Source: Hoofnagle et al.27

The immune tolerance phase, which predominates through early adulthood in perinatally acquired disease, is marked by the presence of HBeAg, high levels of HBV DNA, normal ALT levels, and little histological activity on biopsy.29-30 During HBeAg-positive chronic hepatitis B, fluctuating ALT levels (or flares) are common and are thought to represent the immune-mediated destruction of infected hepatocytes. Progression to cirrhosis and HCC are thought to be related to the frequency and severity of flares as well as the duration of the immune clearance phase.31-32 In the majority of patients, chronic HBeAg-positive disease transitions to the inactive carrier state,33 characterized by seroconversion to hepatitis B e antibody (anti-HBe), persistent HBsAg, and low or undetectable serum HBV DNA.34-36 Seroconversion in those with elevated ALT levels occurs at a rate of 8% to 12% per year.31,34-37,38 Reactivation of the inactive carrier state can also occur spontaneously or through immune suppression.33,39-40

In up to one-third of patients, chronic HBeAg-positive disease transitions to chronic HBeAg-negative disease.41 In this variant form of disease, mutations in the core promoter and precore domains result in diminished or absent HBeAg production, but HBV DNA levels remain high and ALT levels fluctuate.42 Individuals with HBeAg-negative disease have higher relapse rates after treatment cessation, and rates of sustained treatment response are poor.43-45

Occult HBV infection, an additional stage and one that may overlap with the recovery stage,46 is defined as low-level HBV DNA in the absence of detectable HBsAg.47-48 With occult HBV infection, anti-HBc (IgG) may be the only marker present. The isolated anti-HBc may represent a false-positive antibody result, a “window” phase of acute
increased levels of HBV DNA, a higher proportion of HBeAg positivity, a lower likelihood of seroconversion to anti-HBe and antibody to HBsAg (anti-HBs), and a higher prevalence of occult HBV in some, but not all, studies. Notably, ALT levels are not always elevated with chronic hepatitis B, despite progression to cirrhosis.

In those with chronic hepatitis B, coinfection with HIV results in an increased rate of progression to death, cirrhosis, and HCC. An analysis of the U.S. Multicenter AIDS Cohort Study found that liver-related mortality was approximately 14 times higher with HBV/HIV coinfection than with either HBV monoinfection or HIV monoinfection. In HIV-positive individuals, progression of acute to chronic HBV infection occurs at a rate five times higher than in HIV-negative individuals. In another French study, HCC was the cause of

<table>
<thead>
<tr>
<th>Table 2. Serologic Markers for Hepatitis B</th>
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<tr>
<td>HBV DNA</td>
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</tr>
<tr>
<td>Acute infection</td>
</tr>
<tr>
<td>Past infection and clearance</td>
</tr>
<tr>
<td>Prior vaccination</td>
</tr>
<tr>
<td>Chronic infection*</td>
</tr>
<tr>
<td>Carrier</td>
</tr>
<tr>
<td>Candidate for vaccination</td>
</tr>
<tr>
<td>Occult infection</td>
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</tbody>
</table>

*Chronic infection with HBeAg (+) and anti-HBe (−) is the pattern with wild-type virus, whereas HBeAg (−) and anti-HBe (+) is the pattern with precore or basal core promoter virus.

Abbreviations: HBV = hepatitis B virus; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; anti-HBs = antibody against HBV surface antigen; anti-HBc = antibody against HBV core antigen; anti-HBe = antibody against HBV e antigen; IgM = immunoglobulin M.


infection (if IgM antibody positive), recovery from acute hepatitis B but without the development of or loss of anti-HBs, or true occult infection. Occult HBV has been associated with HBV reactivation, diminished treatment response to interferon in HCV-coinfected individuals (according to some publications), and development of HCC. Occult HBV infection has also been associated with HBV transmission through blood donation and liver transplantation.

Impact of HIV on the Natural History of HBV Infection
HIV modifies HBV disease in many ways. Most importantly, HIV infection results in an increased incidence of death and cirrhosis in those with hepatitis B infection. HIV infection also results in an increased risk of developing chronic hepatitis B,
liver-related death in 50% of HIV/HBV-coinfected individuals, a proportion higher than in HIV/HCV coinfection or HIV disease alone.\(^6^0\)

In the era prior to antiretroviral therapy (ART), having HIV increased the risk of both contracting HBV\(^6^1-^6^4\) and becoming a chronic HBsAg carrier,\(^5^9\) although chronic carrier likelihood may differ in areas of high versus low HBV prevalence.\(^4^4\) In addition, studies from the United States and Europe demonstrated that HBV viremia was higher in those with HIV coinfection and that the loss of HBeAg occurred at a slower rate.\(^6^3,^6^5-^6^7\)

Similar results were seen in Africa. In Côte D’Ivoire, HIV/HBV-coinfected pregnant women were more likely to have HBV viremia (27%) than those with HBV infection alone (9%).\(^1^9\) In Zambia, HBeAg was more prevalent during HIV infection.\(^5^8\) As the presence of HBeAg and elevated HBV DNA levels are associated with an increased risk of HBV transmission, these results may indicate that HIV- and HBV-coinfected individuals may be at higher risk for HBV transmission.

Occult HBV infection, defined as either the prevalence of anti-HBc alone or HBV DNA in the absence of HBsAg, is greater in HIV-positive individuals than in those who are HIV-negative.\(^6^9-^7^2\) Prevalence estimates in several HIV-positive cohorts vary widely, ranging from 0% to 54%.\(^6^9,^7^3-^7^7\) These differences are likely related to the sensitivity of the assays. Paradoxically, a study from South Africa reported a higher prevalence of the “anti-HBc alone” marker pattern in HIV-negative versus HIV-positive patients.\(^7^8\)

The clinical relevance of occult HBV in HIV disease has yet to be determined. In the Swiss HIV cohort, Hofer et al. detected elevated liver enzymes in pre-ART patients with occult HBV infection regardless of HCV serostatus.\(^6^9\) Another recent prospective study detected a significantly higher rate of liver enzyme elevations in HIV-positive patients with occult HBV than in those without HBV DNA.\(^7^9\) These patients experienced hepatic flares upon immune reconstitution with lamivudine-containing ART. In contrast, French investigators have reported prospective follow-up of HIV-positive patients with anti-HBc alone that included four occult infections with no evidence of liver enzyme elevations.\(^8^0\) In summary, occult HBV is prevalent in HIV infection and, in those without HIV disease, has been implicated in several types of adverse clinical outcomes, but its long-term clinical relevance deserves further study.

Finally, ALT levels are often not significantly elevated in HBV/HIV coinfection. One pre-ART analysis in HIV-positive patients concluded that although HIV-positive patients were more likely to be HBeAg-positive and HBV DNA-positive than those without HIV, liver enzyme elevations were significantly less elevated in those with HIV infection.\(^5^9\) Furthermore, ALT was positively correlated with CD4 count in this study, suggesting that liver inflammation is dependent on immune function preservation even within the setting of HIV.

ART-Associated Hepatotoxicity
Another effect of HBV on HIV is the increased risk of hepatotoxicity during treatment with antiretroviral therapy. Nearly 10% of subjects initiating ART will experience significant aminotransferase flares.\(^8^1\) Coinfection with HBV increases the risk of hepatotoxicity after initiation of ART.\(^8^2-^8^4\) A study in Thailand in which nearly 8% of the 692 HIV-positive patients were HBV coinfected found that the incidence of severe hepatotoxicity for those with HBV was 15.3/1,000 person-years—greater than twice the overall incidence. HBV was a significant predictor of hepatotoxicity with an adjusted relative risk of 3.2.\(^8^5\)

The mechanisms underlying hepatotoxicity remain unclear. ART-associated hepatotoxicity may be mediated through mitochondrial toxicity,\(^8^6\) hypersensitivity reactions (such as with nevirapine
and abacavir), direct liver injury from antiretroviral agents, or HBV immune reconstitution. Additionally, the concomitant administration of other hepatotoxic medications, such as antituberculous agents, may also play a role.

In HIV disease, the immune reconstitution syndrome occurs when ART-induced immune recovery results in immune activity against antigens from resolved or ongoing infection. HBV-associated immune reconstitution has been reported and has been associated with clearance of both HBeAg and HBsAg. Importantly, immune reconstitution hepatitis has been reported even during lamivudine therapy.

Finally, the concomitant administration of other hepatotoxic drugs with ART, such as antituberculous therapy, has special implications for areas endemic for HIV, HBV, and TB. In one South African study, HBV infection increased the risk of hepatotoxicity in those receiving antituberculous therapy and ART.

Other Causes of Aminotransferase Elevation in HIV/HBV Coinfection
When evaluating the HIV/HBV-coinfected patient with elevated aminotransaminases, other important etiologies should also be considered. The differential diagnosis includes the hepatic flares associated with the natural immune clearance of hepatitis B; rebound viremia from either the inadvertent withdrawal of anti-HBV therapy or HBV resistance; and other etiologies such as alcohol abuse, coinfection with other hepatitis viruses (A, C, D, or E), and other opportunistic infections and malignancies.

HBV PATHOGENESIS AND GENETIC VARIANTS
The hepatitis B virus is a small, 3,200 kilobases (kb), hepatotropic DNA virus. The partially double-stranded circular DNA encodes four overlapping open reading frames: S for the surface gene, C for the core gene, P for the polymerase gene, and X for the X gene. The S gene encodes the viral envelope. The core gene produces the e antigen protein (HBeAg). The HBV virus enters liver cells (hepatocytes) and, after entry, is transported to the cell nucleus, establishing a persistent reservoir as covalently closed circular DNA (cccDNA) in the host hepatocyte. This cccDNA then acts as the stable template for viral protein translation and reverse transcription into genomic DNA (see Figure 2).

Hepatitis B-associated liver injury is immune mediated; the hepatitis B virus is itself noncytopathic. The pathogenesis of liver damage is related to B and T cell immune response to peptide antigens, production of cytopathic and noncytopathic cytokines, and the recruitment of nonspecific effector leukocytes.

Hepatitis B Genotypes
There are eight HBV genotypes (A–H), with a divergence of greater than 8% in the entire genomic sequence. The eight genotypes have a geographical distribution: A is prevalent in northwestern Europe, North America, and Africa; B and C are endemic in Asia; D predominates in the Mediterranean but has a worldwide distribution; E is found in West Africa; F is found in the aboriginal populations in South America; and G has been found only in France and the United States. In South Africa, HBV genotypes A and D can be further divided into subgenotypes A1 and A2, and D1–D3.

Genotypes are predictive of natural history progression. Genotypes B, C, and D are associated with the development of core and precore promoter mutations. Studies from Japan, Taiwan, and China indicate that genotype C, when compared with genotype B, is associated with more severe liver disease. In India, where genotypes
infection can be divided into HBeAg-positive and HBeAg-negative disease. Patients with HBeAg-negative disease do not express HBeAg because of mutations in the precore and core regions of the HBV genome.119-120

HBeAg-negative disease, defined as the absence of HBeAg production but with active HBV replication, is not thought to arise de novo but rather as the evolution of chronic HBV infection. HBeAg-negative disease is associated with a poorer long-term prognosis, and sustained spontaneous remission is rare. The precore and core promoter mutations are also associated with genotypes B, C, and D. It is not known whether there is an increased proportion of HBeAg-negative disease in HIV infection.

Precore and Core Promoter Mutations
HBeAg is generally regarded as a marker of HBV replication. A subset of patients with HBV infection have high levels of HBV replication in the absence of HBeAg production. Thus, chronic HBV infection can be divided into HBeAg-positive and HBeAg-negative disease. Patients with HBeAg-negative disease do not express HBeAg because of mutations in the precore and core regions of the HBV genome.119-120

HBeAg-negative disease, defined as the absence of HBeAg production but with active HBV replication, is not thought to arise de novo but rather as the evolution of chronic HBV infection. HBeAg-negative disease is associated with a poorer long-term prognosis, and sustained spontaneous remission is rare. The precore and core promoter mutations are also associated with genotypes B, C, and D. It is not known whether there is an increased proportion of HBeAg-negative disease in HIV infection.
MANAGEMENT OF HEPATITIS B IN THE SETTING OF HIV INFECTION

Goals, Predictors, and Duration of Therapy
The goals of hepatitis B therapy in HIV/HBV coinfection are similar to those in HBV monoinfection: to suppress HBV viral replication, promote HBeAg seroconversion (in those with HBeAg), and, ultimately, decrease the progression to cirrhosis and/or HCC. Loss or decrease in HBV DNA is considered an acceptable surrogate marker for successful HBV treatment. In HIV infection, an additional benefit of treatment of HBV infection may include the possibility of decreasing ART-associated hepatotoxicity.

In HBV monoinfection, the predictors of a favorable treatment response include low pretreatment HBV DNA levels, the presence of HBeAg, and evidence of liver inflammation demonstrated by liver biopsy or elevations in liver enzymes. The predictors of optimal treatment response in HIV and HBV coinfection are unknown.

The optimal duration of therapy for chronic hepatitis B in HIV infection is also unknown, but given the suppressive nature of therapy and the concomitant treatment of HIV with anti-HBV active therapy, the duration of therapy will likely be lifelong. Several studies have shown that markers of liver damage may improve with successful therapy in some patients. For example, Matthews et al. found that after approximately two years of treatment with tenofovir in cirrhotic HBV-HIV-infected patients, all markers of liver injury improved. Another study assessed improvement in liver damage with tenofovir therapy via biopsy, and yielded similar results.

Anti-HBV Therapy
Several agents are currently available for the treatment of chronic hepatitis B: lamivudine, adefovir, tenofovir, emtricitabine, entecavir, telbivudine, and interferon. Tenofovir and emtricitabine are not officially approved for hepatitis B infection but have been studied in its treatment. In resource-limited settings, as of this writing, lamivudine will likely be the most accessible agent, although tenofovir may be more widely available soon. Lamivudine, tenofovir, and adefovir are discussed in the following paragraphs.

Lamivudine, a nucleoside analogue, is currently the most widely available drug for hepatitis B in low-income settings. The dosage for chronic hepatitis B therapy is 100 mg daily, but the dosage in HIV infection, 300 mg daily, is the appropriate dosage if both HIV and HBV are to be treated. In HIV/HBV-coinfected patients, lamivudine monotherapy is associated with HBV DNA reductions to below 10^5 copies/mL in 40% to 87% of patients. A major limitation to single-agent lamivudine therapy for hepatitis B is the development of HBV lamivudine resistance (see the following subsection).

Although not formally approved for the treatment of hepatitis B, tenofovir disoproxil fumarate, a nucleotide analogue also used in the treatment of HIV, has been widely used and studied in HIV/HBV coinfection. Studies in high-income countries have demonstrated its activity against HBV in lamivudine-naive and lamivudine-resistant HIV/HBV-coinfected patients. Tenofovir may also become more accessible in resource-limited settings; tenofovir and coformulated tenofovir and emtricitabine were approved in South Africa in April 2007. In 54 HIV/HBV-coinfected individuals with HBeAg-positive chronic hepatitis B, tenofovir produced a median reduction in HBV DNA of 4.56 log_{10} copies/mL and 30% achieved an undetectable HBV viral load. In 11 treatment-naive and -experienced HIV/HBV-coinfected patients, tenofovir was effective in suppressing HBV replication.
Adefovir, a nucleotide analogue approved for the treatment of chronic hepatitis B, does not have known anti-HIV activity at the anti-HBV active dose of 10 mg daily. In lamivudine-resistant HIV/HBV-coinfected patients, the addition of adefovir resulted in sustained and significant reduction in HBV DNA levels.141

**Hepatitis B Drug Resistance**

When lamivudine is used as monotherapy for the treatment of HBV in the setting of HIV infection, lamivudine resistance approaches 100% at four years. Lamivudine resistance occurs when point mutations alter the highly conserved YMDD motif in the C domain of the HBV polymerase gene, preventing lamivudine binding. Lamivudine resistance is accompanied by rebound viremia, ALT elevation, and reversal of histologic improvement. In HIV/HBV coinfection and cirrhosis, HBV drug resistance can lead to fulminant hepatitis. In medication-compliant patients who experience a greater than 1 log10 copies/mL increase in serum HBV DNA from nadir, lamivudine resistance should be considered. The optimal treatment for lamivudine-resistant HIV/HBV-coinfected individuals is not well defined. Most experts recommend the addition rather than the replacement of a second anti-HBV agent. Both tenofovir and adefovir exhibit activity against lamivudine-resistant virus in HIV infection. Entecavir should be used with caution as background lamivudine resistance mutations facilitate entecavir resistance.

**Approach to the Management of HIV/HBV Coinfection in Resource-Limited Settings**

Because of resource limitations, including limitations in drug availability, the management of hepatitis B infection in resource-limited settings will differ from that in high-income settings. References for HBV treatment in high-income countries are listed here. As of this writing, there are no data on HBV management in HIV infection in resource-limited settings. The following are our recommendations, modified from previously published recommendations in resource-limited settings, but not yet proven through rigorous clinical trials.

HBsAg and transaminase testing should be available at the clinic level, both at the initiation and, in the case of transaminases, at follow-up evaluations. Additional follow-up laboratory tests such as HBeAg, anti-HBe, and HBV viral load could be reserved for district-level testing.

In HBV-endemic areas, we advocate screening for HBsAg and liver enzymes at primary health care centers and before the initiation of ART. Individuals with HIV/HBV coinfection should be asked about symptoms of severe liver disease, including hematemesis, hematochezia, and abdominal and leg swelling. Alcohol intake and family history of HCC should also be queried. Examination should include the evaluation of severe liver disease including jaundice, ascites, spider angioma, lower extremity edema, and palmar erythema. If available, HBeAg, anti-HBe, HBV DNA, prothrombin time, albumin, and a complete blood count should be obtained.

If HBsAg screening is not available, a reasonable, but unstudied, alternative may be to initiate ART therapy, monitoring for signs and symptoms of hepatotoxicity (i.e., abdominal pain, jaundice, scleritis). Should these symptoms develop, a history designed to exclude other causes of hepatotoxicity should be obtained, and subsequent laboratory evaluation should include ALT and hepatitis A and B serologies. The non-hepatitis differential diagnosis includes antiretroviral-related hepatotoxicity (with nevirapine being the usual agent), AIDS-related opportunistic infections that target the liver, lactic acidosis (with hepatic steatosis if stavudine or didanosine are included in the regimen), and hepatotoxicity from...
other medications (i.e., anti-TB medications). Hepatitis-related etiologies include acute infection with hepatitis A, B, or C, and, in the setting of HBsAg-positive disease, hepatitis B immune reconstitution and hepatic flares. If serologies demonstrate HBsAg positivity, then the addition of a second anti-HBV active drug (in most settings, tenofovir) should be considered.

When to Initiate Therapy
HBV therapy should be commenced concurrently with ART.

Management of HBV Disease in Patients on ART
If available, ART for coinfected patients should include two anti-HBV active agents. In the setting of HIV/HBV coinfection, combination nucleoside therapy is associated with more potent HBV suppression, and may be associated with the reduced incidence of drug resistance, although this protection against resistance has not been definitively established. If tenofovir is available, then we recommend combination therapy with tenofovir and lamivudine or emtricitabine. Coformulated tenofovir and emtricitabine, although not approved in the United States for the treatment of chronic hepatitis B, has also been used and retrospectively studied for the treatment of HIV and HBV coinfection. To maintain HBV suppression, anti-HBV therapy should be continued indefinitely.

Nevirapine should be avoided, because of the higher rates of hepatotoxicity in HIV/HBV coinfection. Additionally, use of didanosine and stavudine, individually or in combination, should be avoided if possible. Finally, lamivudine and emtricitabine should not be used concomitantly, as both share a similar mechanism of action.

If, at the time of HBsAg identification, HIV therapy has already been initiated and does not contain two anti-HBV active drugs, the optimal approach would include the addition of a second anti-HBV agent.

If a second-line ART regimen is necessary (i.e., due to toxicity, treatment failure, etc.), continuation with a regimen that contains an anti-HBV agent (e.g., lamivudine, tenofovir, emtricitabine) is recommended. If anti-HBe testing is available, this test should be performed every six months to a year. If anti-HBe seroconversion has occurred, then anti-HBV therapy may be discontinued six months after anti-HBe seroconversion. If anti-HBe testing is not available, then an HBV-active agent should be continued for the duration of ART. Early discontinuation of anti-HBV therapy can lead to rebound HBV viremia, elevated aminotransferase levels, and, in some immunosuppressed patients, hepatic failure.

Monitoring During Treatment
In HIV-positive and HBsAg-positive patients, liver enzymes should be evaluated at least once or twice in the first three months after ART initiation. If available, serum HBV DNA, HBeAg, and anti-HBe should be measured every six months. If lamivudine or emtricitabine is the only HBV-active drug in the regimen (i.e., HBV monotherapy), a rise in liver enzymes or HBV DNA should prompt the consideration of HBV drug resistance. Additional considerations include antiretroviral-related hepatotoxicity (nevirapine, efavirenz, stavudine, didanosine), concomitant hepatotoxic medications (i.e., anti-TB), other hepatotropic opportunistic infections, immune reconstitution/HBV flare, acute hepatitis from A/C/D/E, and/or alcohol abuse.

The optimal strategy to manage HBV drug resistance in HIV infection is unknown; in the setting of lamivudine resistance, most consensus panels recommend the addition of tenofovir.

In high-income countries, screening for HCC with biannual alpha-fetoprotein measures and liver ultrasounds is recommended.
Prevention of Further Liver Damage

Even without treatment, steps may be taken to prolong time to severe liver injury. Alcohol interacts synergistically with viral hepatitis to exert injurious effects on the liver. There are several mechanisms by which this may occur, including increased lipid peroxidation, less hepatocyte regeneration, alteration of key metabolic pathways, and reduced DNA repair capacity.149 Alcohol avoidance, while not necessarily reversing damage already incurred, will serve to soften the effects of viral hepatitis and drug interactions on an already compromised liver.

In addition, individuals with HBV infection who have not been exposed to hepatitis A should receive the hepatitis A vaccine.156 Acute infection with hepatitis A in hepatitis B-coinfected individuals can result in fulminant hepatitis.150

PREVENTION OF HEPATITIS B

Hepatitis B can be prevented through vaccination (children and adults) and through administration of hepatitis B immune globulin and vaccination (neonates).

Prevention of HBV Perinatal Transmission

In infants and children, the two major routes of HBV acquisition are via perinatal and horizontal transmission. In pregnant women who are HBsAg- and HBeAg-positive and who do not receive immunoprophylaxis, a newborn's risk for chronic HBV infection at six months is 70% to 90%.151-155 Infants born to mothers who are HBeAg-negative have a less than 10% risk of developing chronic hepatitis B. Predictors of HBV transmission include the presence of HBeAg and high-level HBV viremia.154 Breastfeeding in HBsAg-positive mothers is not thought to increase the risk of HBV acquisition.155

The current HBV perinatal exposure prophylaxis regimen in high-income countries includes the administration of hepatitis B immune globulin (HBIG) and HBV vaccine, both administered within 12 to 24 hours of birth, followed by the completion of the HBV vaccination series. This regimen is 85% to 95% effective in preventing chronic HBV infection in infants born to women with both HBsAg and HBeAg.156

In low-income countries where HBIG administration may be limited by cost and cold-storage availability, World Health Organization (WHO) recommendations note that hepatitis B vaccination alone, if administered within 24 hours of birth, is comparable to the combination of hepatitis B vaccination and HBIG administration in the prevention of mother-to-child transmission of hepatitis B.156

The use of nucleos(t)ide therapies as an alternative to HBIG and the HBV vaccination has been raised.97 To date, only two small studies have examined the administration of lamivudine to HBsAg-positive mothers in order to prevent HBV transmission to the infant.157-158 Both have suggested that lamivudine may be effective in reducing HBV transmission, but larger studies are needed, especially in HIV-coinfected women, where HBV viral loads may be higher than in their monoinfected counterparts.

Routine Hepatitis B Vaccination

Neonates and Children

In 1991, WHO called for routine global infant and childhood HBV immunization, initially targeting regions and countries with high HBV prevalence.1 Hepatitis B immunization strategies include routine infant vaccination, prevention of perinatal HBV transmission, and catch-up vaccination of older age groups.159

Routine infant HBV vaccination is encouraged in low-, intermediate-, and high-endemicity HBV countries, with the timing of vaccination differing between regions with varying endemicities. HBV vaccination at birth (provision of birth dose) in order to prevent perinatal HBV transmission
In HIV-positive individuals with well-preserved CD4 counts (defined as greater than or equal to 500 cells/mm³), a normal HBV vaccine dosing schedule is recommended. In those with evidence of immunosuppression, a more intensive schedule is suggested (20 µg at months 0, 1, 2, and 12). Those who do not respond to the first vaccination cycle should receive booster doses or undergo a second cycle with a double-dose regimen until titers greater than or equal to 100 IU/L are observed.\textsuperscript{126}

CONCLUSION
In summary, HIV/HBV coinfection is a common occurrence. HIV alters the natural history of hepatitis B disease, resulting in increased HBV viremia, increased HBV drug resistance, and increased mortality when compared to HBV infection alone. If possible, ART in HIV/HBV-coinfected patients should include two HBV-active agents. When lamivudine is the only HBV-active agent, lamivudine resistance occurs in the majority of HIV/HBV-coinfected patients on lamivudine-containing ART.

ACKNOWLEDGMENTS
We are grateful to Dr. Chloe Thio for her review of this manuscript.
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Prevention and Management of Malaria Infection in People Living with HIV

Paula E. Brentlinger and Christopher B. Behrens

Human malaria infection is usually caused by four parasites: Plasmodium falciparum, P. ovale, P. malariae, and P. vivax. The most common of the four are P. vivax and P. falciparum, with P. falciparum being the most lethal. In some regions of the world, a single parasite species predominates (e.g., P. vivax in Central America and P. falciparum in sub-Saharan Africa); in other regions, the geographic distributions of two or more species may overlap substantially. The global burden of malaria is immense. Snow et al, in an estimate that attempted to correct for deficiencies in case reporting, concluded that in 2002 alone, there were 513 million episodes (range: 300–660 million) of symptomatic P. falciparum malaria. Snow et al further estimated that 2.2 billion people were at risk of P. falciparum malaria, and that attack rates in the most highly endemic regions were 849 cases per 1,000 population per year. The distribution of malaria overlaps that of HIV-1 infection broadly, especially in sub-Saharan Africa.

Interactions between Malaria and HIV
Interactions involving P. falciparum and HIV have resulted in increases in the burden of both diseases. Reported interactions that are of interest to clinicians fall into the following broad categories:

1. Increases in HIV replication rate and/or viral load in the presence of acute malaria
2. Reversible decline in CD4 T-lymphocyte count in the presence of acute malaria
3. Increased incidence, prevalence, and severity of malaria in HIV-positive individuals (especially in pregnancy, where adverse consequences may affect both mother and fetus)
4. Increased likelihood of malaria treatment failure in HIV-positive individuals

Recent research on interactions between the malaria parasite, the human immune system, and HIV itself has begun to describe plausible mechanisms for some of the observed interactions. The existing data (which are restricted to interactions between HIV and malaria caused by P. falciparum, owing to lack of available data regarding other Plasmodium species) are summarized in Table 1. Similar interactions are likely to exist between HIV and the other Plasmodium species, but published studies do not yet describe them.
### Table 1. Selected Studies Describing Interactions between *P. falciparum* and HIV

<table>
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<tr>
<th>Setting</th>
<th>Finding</th>
<th>Patient population</th>
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<tr>
<td><strong>Malaria-related HIV viral load elevation and/or increases in HIV replication</strong></td>
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<tr>
<td>Malawi&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Median HIV-1 viral RNA 19.1 x 10^4 copies/mL with acute malaria, dropping to 12.0 x 10^4 copies/mL four weeks after antimalarial treatment</td>
<td>Nonpregnant adults</td>
</tr>
<tr>
<td>Malawi&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Median HIV-1 RNA at baseline 9.6 x 10^4 copies/mL, rising to 16.9 x 10^4 copies/mL with acute malaria infection, falling to 8.2 x 10^4 copies/mL six to eight weeks post treatment</td>
<td>Nonpregnant adults</td>
</tr>
<tr>
<td>Zambia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HIV-1 RNA concentration decreased by 0.1 log 28 days after treatment of symptomatic malaria.</td>
<td>Nonpregnant adults</td>
</tr>
<tr>
<td>Malawi&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Maternal malaria infection is associated with a significant increase in the proportion of CD16+ monocytes; these monocytes are in turn more likely to express CC chemokine receptor 5 (CCR5) and to harbor HIV.</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>Tanzania&lt;sup&gt;b&lt;/sup&gt;</td>
<td>The HIV receptor CCR5 is upregulated (fourfold) in the presence of maternal placental malaria infection.</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>In vitro&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Exposure to <em>P. falciparum</em> antigens results in increased HIV viral replication.</td>
<td>N/A</td>
</tr>
<tr>
<td>Malawi&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Malaria infection is associated with increased concentration of CCR5 in maternal macrophages, thus increasing the number of HIV target cells.</td>
<td>N/A</td>
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<tr>
<td><strong>Malaria-related CD4 lymphocyte decline</strong></td>
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<tr>
<td>Kenya&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Observed CD4 count decline in HIV-positive Ugandan patients was 40.5 cells/mm³ faster per malaria episode per year; estimated excess CD4 decline of 142 cells/mm³ per year in a person with three malaria episodes.</td>
<td>Nonpregnant adults</td>
</tr>
<tr>
<td>Zambia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28 days after successful treatment for symptomatic malaria in HIV-positive patients, median CD4 counts rose from 274 to 447 cells/mm³, and the proportion of patients with CD4 counts &lt;200 declined from 28.7% to 13.4%.</td>
<td>Nonpregnant adults</td>
</tr>
<tr>
<td><strong>Increased incidence or prevalence of malaria in the presence of HIV infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Malaria cases 57 per 1,000 person-years if CD4 ≥500, 93 if CD4 = 200 to 499, 140 if CD4 &lt;200</td>
<td>Nonpregnant adults</td>
</tr>
<tr>
<td>Uganda&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Odds ratio for clinical malaria (at routine visits) by CD4: 1.0 if CD4 ≥500, 3.23 if CD4 = 200 to 499, 6.12 if CD4 &lt;200</td>
<td>Nonpregnant adults</td>
</tr>
<tr>
<td>Malawi&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Hazard ratio for experiencing first malaria parasitemia episode in HIV-positive persons compared to HIV-negative persons: 1.8; hazard ratio for incidence of a second parasitemia episode: 2.5</td>
<td>Nonpregnant adults</td>
</tr>
</tbody>
</table>
### Table 1. Selected Studies Describing Interactions between *P. falciparum* and HIV (cont.)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Finding</th>
<th>Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased incidence or prevalence of malaria in the presence of HIV infection (cont.)</strong></td>
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<tr>
<td>Mozambique<em>10</em></td>
<td>The odds ratio for the association of maternal peripheral malaria parasitemia and HIV infection was 1.5. Prevalence of maternal peripheral malaria parasitemia ranged from 38.1% in HIV-positive multiparas (i.e., women who have given birth two or more times) to 75% in HIV-positive primigravidas (i.e., women who are pregnant for the first time) in the study site that experienced the most intense transmission.</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>Malawi<em>11</em></td>
<td>HIV infection is associated with decreased concentrations of antibodies to specific <em>P. falciparum</em> antigens in pregnant women; this finding is associated with low CD4 counts.</td>
<td>Pregnant women</td>
</tr>
<tr>
<td><strong>Increased severity of malaria with HIV infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa<em>2</em></td>
<td>Significantly higher likelihood of severe anemia, renal insufficiency, and metabolic acidosis in HIV-positive vs. HIV-negative patients with acute malaria; CD4 counts substantially lower (134 vs. 190 cells/mm³) in HIV-positive patients</td>
<td>Nonpregnant adults, hospitalized</td>
</tr>
<tr>
<td>South Africa<em>2</em></td>
<td>Significantly higher likelihood of confusion or drowsiness (26% vs. 17%, <em>P</em> =.01), renal insufficiency (27% vs. 15%, <em>P</em> =.01), coma (16% vs. 8%, <em>P</em> =.03), metabolic acidosis (15% vs. 6%, <em>P</em> =.015), and jaundice (9% vs. 1%, <em>P</em> =.001) in HIV-positive patients with acute malaria; odds ratio of 7.5 for association of mortality and HIV infection in hospitalized patients</td>
<td>Nonpregnant adults, hospitalized</td>
</tr>
<tr>
<td>South Africa*</td>
<td>Significantly higher incidence of severe malaria in HIV-positive children as compared to uninfected children (32 vs. 5 children, <em>P</em> =.05); odds ratio for the association between HIV infection and death from malaria was 10.2</td>
<td>Children under 14 years old with acute malaria</td>
</tr>
<tr>
<td><strong>Increased likelihood of malaria treatment failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya<em>12</em></td>
<td>HIV-negative patients treated for acute malaria: 87.7% cured, 7.6% relapsed, 4.3% reinfection; HIV-positive patients with CD4 &lt;200 cells/mm³: 68.0% cured, 20.5% relapsed, 11.5% reinfection</td>
<td>Nonpregnant adults</td>
</tr>
<tr>
<td>Uganda<em>13</em></td>
<td>In adults, but not in children, HIV-1 infection was associated with a greater than threefold risk (hazard ratio 3.28; 95% CI, 1.25–8.59) of clinical treatment failure after antimalarial therapy for symptomatic infection. Reinfection (HR 6.35; 95% CI, 1.64–24.5) rather than relapse (HR 1.51; 95% CI, 0.27–8.58) was implicated.</td>
<td>Children under 5 years of age and nonpregnant adults</td>
</tr>
</tbody>
</table>
From the Ground Up: Establishing a Framework for Success

Parasitemia are largely related to steadily worsening anemia. However, asymptomatic parasitemia has been observed to confer a fivefold elevation in the risk of symptomatic malaria in young children.28

Asymptomatic Placental or Maternal Peripheral Parasitemia
Asymptomatic malaria parasitemia (P. falciparum and/or others) has been noted in 10%–70% of pregnant women living in regions of stable malaria transmission.20,29 It is associated with maternal anemia, maternal mortality, and infant low birth weight.29 In a recent autopsy study of maternal mortality in Mozambique, evidence of recent or current malaria infection was detected in 66.2% of maternal deaths, though only 10.1% of deaths were thought to have been caused directly by severe malaria.30 Maternal malaria infection has recently been associated with reduced transfer of maternal tetanus antibodies to the fetus.31 Vertical transmission of HIV may be increased in the presence of maternal malaria, and placental malaria conferred a relative risk of 7.9 for vertical transmission in one study (although this finding has not been consistently replicated).32,33 There is also evidence of association between maternal malaria and eclampsia.34,35

Latent Infection
The life cycles of P. vivax and P. ovale include a liver-stage parasite known as a hypnozoite. If left untreated (the standard therapy is primaquine), latent infection may cause relapses of symptomatic malaria weeks to years after initial infection.25

Asymptomatic Parasitemia
Asymptomatic parasitemia is generally the consequence of P. falciparum infection in older children and adults living in regions of stable transmission. Morbidity and mortality in asymptomatic parasitemia are largely related to steadily worsening anemia. However, asymptomatic parasitemia has been observed to confer a fivefold elevation in the risk of symptomatic malaria in young children.28

Asymptomatic Placental or Maternal Peripheral Parasitemia
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Signs and Symptoms of Acute Uncomplicated Malaria, and Their Occurrence in Other HIV-Related Conditions
Malaria represents a daunting diagnostic challenge in the HIV-positive patient.36 Its clinical symptoms overlap with those of opportunistic infections (OIs),
adverse drug reactions (ADRs), immune reconstitution inflammatory syndrome (IRIS), other infectious entities that are common in resource-limited environments, and advanced AIDS itself. To further complicate matters, asymptomatic malaria parasitemia may coexist with OIs (and other disease entities) that share symptoms with malaria. Common signs and symptoms of malaria, with important considerations in differential diagnosis, are described below.

**Fever**

Fever without apparent source is a common clinical problem in HIV-positive persons; its observed incidence was 602.5 events per 1,000 person-years of observation in one adult cohort in Nairobi, Kenya. Most clinicians in malaria-endemic settings are quick to suspect malaria in the febrile patient. However, TB, cryptococcosis, bacteremia, typhoid fever, dengue, influenza, and various other entities (including ADRs and IRIS) may present in a similar fashion. More than one cause of fever may be present concurrently in the HIV-positive patient. Several groups of investigators have attempted to characterize the causes of fever in HIV-positive adults and children; the findings of selected studies are summarized in Table 2.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Finding</th>
<th>Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Côte d’Ivoire</td>
<td>In 269 episodes of fever in 144 patients, no specific etiology was identified in 135 instances. In the remaining cases, identified causes were as follows:</td>
<td>HIV-positive adults enrolled in cohort study</td>
</tr>
<tr>
<td></td>
<td>Bacterial disease in 77 (57%) cases (in descending order of frequency): pneumonia, skin abscess, sinusitis, bacterial enteritis, isolated bacteremia, otitis, pyelonephritis, epididymitis, peritonitis, pericarditis, prostatitis, pyosalpinx). In 7 of these cases, there was another concurrent infection.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malaria (P. falciparum) in 25 (19%) of cases. In 2 cases, there was another concurrent infection.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Other” identifiable causes of fever in 40 (30%) cases (in descending order of frequency): tuberculosis, herpes zoster, toxoplasmosis, atypical mycobacteriosis, Kaposi’s sarcoma, adverse drug reaction, cryptococcosis, acute hepatitis</td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>Identified causes of fever in 291 HIV-positive patients: M. tuberculosis 55 (5 coinfected with bacterial pathogens), non-typhi salmonella 44 (1 coinfected with S. pneumoniae), malaria 31, S. pneumoniae 13, E. coli 4. The cause of fever could not be identified in 34% of patients.</td>
<td>Hospitalized HIV-positive adults ≥14 years old with T≥37.4°C or history of fever</td>
</tr>
<tr>
<td>Malawi</td>
<td>In HIV-positive children, disease incidence per 100 person-years of observation:</td>
<td>HIV-positive children enrolled in cohort study</td>
</tr>
<tr>
<td></td>
<td>Malaria 59.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Septicemia 22.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever of unknown origin 11.1</td>
<td></td>
</tr>
</tbody>
</table>
presentation of malaria may easily be confused with that of an upper respiratory infection, bronchitis, pneumonia, or other conditions. Malaria and bacterial pneumonia may be clinically indistinguishable (especially in children) and may even occur simultaneously; concurrent infections have been described both in children and in HIV-positive adults.42,46-48

Vomiting and/or Diarrhea
Gastrointestinal symptoms are common in acute malaria, and may be confused with gastroenteritis (multiple opportunistic and other etiologies) or ADRs.

Nonspecific Complaints
Particularly in young children and infants, the signs and symptoms of malaria may include such
nonspecific complaints as lethargy, irritability, malaise, or fussiness. The differential diagnosis of these complaints is very broad.

**Anemia**

Anemia is a common consequence of malaria, and may be confused with anemia caused by hookworm, TB, bleeding lesions of the gastrointestinal tract (including lesions caused by OIs), ADR to zidovudine, recent obstetrical hemorrhage, and other entities. Anemia is commonly multifactorial. Of note is that malaria-related anemia may continue to progress, and erythropoiesis may be suppressed for days to weeks even after effective clearance of malaria parasitemia. Hence, continued decline in hemoglobin after malaria treatment does not rule out malaria as the primary cause of a patient's anemia.\(^{49,50}\)

**Signs and Symptoms of Severe Malaria**

**Seizures, Impaired Consciousness, Coma**

The clinical presentation of cerebral malaria overlaps with that of toxoplasomic and viral encephalitis, bacterial and cryptococcal meningitis, meningeal TB, and malignancy (e.g., primary central nervous system lymphoma).\(^5^1\) In pregnant women, cerebral malaria may be mistaken for severe pre-eclampsia or eclampsia.\(^5^2\) Altered mentation could also represent an ADR to efavirenz or other medications.

**Hypoglycemia**

Severe malaria is commonly accompanied by hypoglycemia, which may be exacerbated by quinine therapy.\(^5^3\) Hypoglycemia is also a common complication of sepsis in infants and in severely malnourished children.\(^5^4,5^5\)

**Pulmonary Edema**

Acute pulmonary edema caused by malaria may be confused with that provoked by cardiac failure in the setting of myocardial infarction or other cardiac disease.

**Respiratory Distress**

Respiratory distress caused by severe malaria (associated, for example, with metabolic acidosis) is easily confused with that caused by pulmonary infection, cardiac disease, or stavudine-induced metabolic acidosis.

**Lactic Acidosis**

The lactic acidosis that is common in severe malaria may be mistaken for an ADR to certain ARVs, especially stavudine or didanosine.

**Jaundice, Hepatomegaly, Transaminase Elevations, Abdominal Pain, Nausea, Vomiting, Diarrhea**

Severe malaria may present with jaundice, hepatomegaly (enlargement of the liver), moderate transaminase elevations, and/or significant abdominal pain and other gastrointestinal symptoms. The differential diagnosis of these signs and symptoms is very broad, and includes viral or drug-induced hepatitis (e.g., nevirapine hepatitis or stavudine steatohepatitis), cholelithiasis, pancreatitis (including drug-induced pancreatitis), cholangitis, and many other AIDS-related and other entities.

**Severe Anemia**

Severe anemia is a common complication of severe malaria. Notes on the differential diagnosis are given above.

**Intravascular Hemolysis with Hemoglobinuria**

Once thought to be a complication of severe malaria ("blackwater fever"), this particular manifestation of severe malaria is now thought to be an adverse effect of quinine or halofantrine therapy.\(^1\) In patients on indinavir, the combination of dark red urine and flank pain may suggest drug-related nephrolithiasis.
**Table 3. Diagnostic Accuracy of Clinical Diagnosis of Malaria: Summary of Selected Studies**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Finding</th>
<th>Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya56</td>
<td>79.3% of patients with no evidence of malaria parasitemia on microscopy were diagnosed clinically with malaria.</td>
<td>Patients over 5 years of age; observational study of clinical practice under field conditions</td>
</tr>
<tr>
<td>Uganda57</td>
<td>Malaria blood smear was positive for only 757 of 2,359 episodes of fever (all of which would ordinarily have been diagnosed with malaria); only 13 of 1,602 episodes of fever with negative smear occurred in people who subsequently developed detectable parasitemia.</td>
<td>Children between 1 and 10 years of age presenting with fever</td>
</tr>
<tr>
<td>Uganda58</td>
<td>Only 24.8% of patients who met clinical case definitions of malaria had demonstrable parasitemia; over 75% of patients were treated unnecessarily for malaria; the majority of patients without demonstrable parasitemia were not treated for alternative diagnoses.</td>
<td>Febrile pediatric and adult outpatients</td>
</tr>
<tr>
<td>Tanzania59</td>
<td>Only 46.1% of patients clinically diagnosed with severe malaria had <em>P. falciparum</em> infection on microscopy. Higher case fatality (12.1% vs. 6.9%, <em>P</em>&lt;.001) in smear-negative patients, associated with failure to provide treatment for alternative diagnoses to patients with negative malaria smears.</td>
<td>Hospitalized adults and children who met clinical criteria for diagnosis of severe malaria</td>
</tr>
<tr>
<td>Papua, New Guinea60</td>
<td>Positive predictive value (for malaria parasitemia of any level) of clinical diagnosis of malaria was 73% in children and 51% in adults.</td>
<td>Children and adults presenting for outpatient evaluation of fever</td>
</tr>
<tr>
<td>Sub-Saharan Africa (review)61</td>
<td>Sensitivity of clinical diagnosis estimated as 90% in high-transmission areas and 73% in lower-transmission areas; corresponding specificity 30% and 71%</td>
<td>Children (review of multiple studies)</td>
</tr>
<tr>
<td>Kenya62</td>
<td>Sensitivity of clinical diagnosis of malaria: 100%; specificity: 0% (compared to diagnosis by physician with access to results of blood smears)</td>
<td>Field trial of an algorithm for Integrated Management of Childhood Illness; children between 2 months and 5 years of age</td>
</tr>
<tr>
<td>Gambia63</td>
<td>Sensitivity of clinical diagnosis of malaria: 87%; specificity: 8% (compared to diagnosis by pediatrician with access to results of malaria smears)</td>
<td>Field trial of an algorithm for Integrated Management of Childhood Illness; children between 2 months and 5 years of age</td>
</tr>
</tbody>
</table>

**Thrombocytopenia**

Severe malaria may be accompanied by thrombocytopenia, with or without clinical bleeding. Malaria, as noted above, is often accompanied by anemia as well, and may occasionally cause leukopenia (leukemoid reactions have also been observed). Several
OIs are also associated with bone marrow suppression; examples include atypical mycobacterial infections and visceral leishmaniasis.

Signs of Asymptomatic Malaria Parasitemia

Anemia is the most common sign of asymptomatic malaria parasitemia. It is particularly common in pregnancy. If untreated, the progressive anemia caused by asymptomatic malaria parasitemia leads to diminished work capacity and elevated risk of infant low birth weight and/or maternal mortality. Anemia in general is considered to be a risk factor for AIDS-related disease progression and mortality. However, as noted above, the differential diagnosis of anemia in the HIV-positive person is quite broad.

Laboratory vs. Clinical Diagnosis of Malaria

Although malaria is commonly diagnosed purely on the basis of clinical signs and symptoms, this approach is unreliable even in patients without HIV infection. Table 3 summarizes the findings of selected studies of the sensitivity and specificity of clinical malaria diagnosis in both adults and children. Although we are not aware of any studies that have addressed the sensitivity or specificity of clinical diagnosis of malaria in HIV-positive persons, the inclusion of OIs, ARV-related ADRs, and IRIS in the differential is likely to render clinical diagnosis of malaria even less accurate in this setting. Both overdiagnosis and underdiagnosis of malaria are hazardous in HIV-positive patients. Overdiagnosis may increase the risk of adverse reactions to antimalarial drugs, drug-drug interactions involving antimalarials and ARVs, and morbidity and/or mortality caused by failure to diagnose and treat the true cause of symptoms. Underdiagnosis may lead to preventable morbidity and/or mortality from severe malaria and/or progressive anemia caused by asymptomatic parasitemia.

The current gold standard for diagnosis of malaria is inspection of a stained capillary blood smear by microscopy. This procedure, as performed under normal field conditions, is currently estimated to be approximately 70% sensitive and 65% specific for the diagnosis of malaria in children under five in sub-Saharan Africa, and permits both speciation of *Plasmodium* and quantification of parasitemia. However, many smaller health facilities operate without laboratories, and even in larger health facilities, microscopy may not be available at night, on weekends, or when limited by shortages of laboratory personnel, reagents, or equipment.

In response to the shortcomings of the existing network of laboratory facilities in malaria-endemic areas, several different types of rapid malaria diagnostic tests are increasingly being used. The advantages and disadvantages of the tests vary by test type, but in general, all of the tests have the advantage of being rapid and relatively simple to perform (as compared to microscopy). Important disadvantages (differing by test) include high cost compared to microscopy (though the difference in cost may be offset by cost savings resulting from decreased wastage of antimalarial drugs), limited capacity to speciate or quantify the infecting *Plasmodium* (particularly if not *P. falciparum*), propensity to yield false-positive results for weeks after clearance of infection (in the case of tests based on histidine-rich protein 2 [HRP-2] antigen), and the need for a “cold chain” of transport and storage. Depending on the test method, the sensitivity of rapid tests for diagnosis of symptomatic *P. falciparum* malaria in residents of endemic regions is thought to range from 62.7% to 92.1%, and the specificity from 98.4% to 99.6%, as compared to conventional microscopy performed under research conditions. A recent head-to-head comparison of two rapid tests based, respectively, on detection of HRP-2 and
plasmodium lactate dehydrogenase (pLDH) antigens, concluded that the HRP-2 test had the higher sensitivity (92% vs. 85%), while the pLDH had the higher specificity (100% vs. 93%); the latter difference was likely the result of more rapid clearance of pLDH from blood after successful antimalarial treatment. Further comparison of the performance of the two test types in settings with different levels of malaria transmission revealed that while the positive predictive values of both tests were consistently high (93% for HRP-2, 98% for pLDH), the negative predictive value of pLDH (but not of HRP-2) dropped to only 54% where transmission intensity was high.

In settings without regular access to microscopy, some national guidelines now recommend that the decision to treat for malaria be made on the basis of clinical impression and rapid-test results alone, but that a malaria smear be prepared for later examination elsewhere in order to permit speciation of parasites and longitudinal assessment of response to treatment.

Because the potential causes of malaria-like signs and symptoms are myriad in HIV-positive individuals, the World Health Organization (WHO) now recommends that, whenever possible, malaria infection be confirmed by laboratory testing before treatment of HIV-positive patients. This recommendation differs sharply from the standard Integrated Management of Childhood Illness (IMCI) and Integrated Management of Adolescent and Adult Illness (IMAI) recommendation that all febrile children, adolescents, and adults with a “high” risk of malaria be treated presumptively with antimalarials. It also conflicts with guidelines for many community-based malaria treatment programs, which recommend presumptive treatment with antimalarials for a range of acute symptoms (not always limited to fever).

Where there is no access to clinician evaluation or laboratory diagnosis, presumptive antimalarial treatment by a community-based health worker—with prompt referral of patients who fail to respond to first-line therapy—may indeed be the best course, and no conflict between disparate guidelines may exist at the practical level. However, where adequate capacity exists and is accessible to the HIV-positive patient, health-facility-based diagnosis and management is preferable. This is of particular importance in HIV-positive patients who receive cotrimoxazole (CTX) prophylaxis and use insecticide-treated bed nets, as these interventions reduce malaria risk dramatically (especially if combined), thus increasing the likelihood that febrile episodes will not be the result of acute malaria.

**TREATMENT OF MALARIA**

In theory, the correct regimen for treatment of malaria depends on the severity of the disease, the responsible *Plasmodium* species, the patient's other current medications and comorbidities, and local patterns of antimalarial drug resistance. In practice, the most effective available antimalarial regimen is often the best choice, regardless of theoretical considerations. National guidelines for first-line, second-line, and third-line antimalarial regimens vary broadly and revisions are frequent. Hence, we will present general recommendations for the choice of antimalarials for patients in specific circumstances rather than specific drug choices. These recommendations are based on our interpretation of the existing literature, not on formal clinical trials (except where indicated).

**Plasmodium falciparum**

*Asymptomatic HIV Infection without Comorbidity or Chronic Medications*

The HIV-positive patient who is not taking ARVs, CTX, TB treatment regimens, or other chronic medications, and who is not pregnant, can be treated with the standard national first-line regimen, assuming that it is known to be effective
(i.e., likelihood of response is not limited by drug resistance). If the national first-line regimen is comprised of only a single agent (monotherapy), or if it is known to have a substantial failure rate, an alternative first line should be defined for HIV-positive persons because of their increased risk of treatment failure, and clinicians should advocate for revision of malaria treatment guidelines for the population as a whole.\textsuperscript{12,13}

**Patients on Prophylactic CTX**

There is known cross-resistance between CTX and sulfadoxine-pyrimethamine (SP), and increased malaria resistance to SP may occur where CTX is widely used.\textsuperscript{75,76} Co-administration of CTX and SP has been associated with elevated risk of severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS).\textsuperscript{77} HIV-positive persons on CTX prophylaxis should not receive SP, or SP-based combination regimens, if better options are available.

**Patients on Antiretroviral Therapy and/or TB Treatment**

Patients on combination antiretroviral therapy (ART) or TB treatment may be at risk for drug-drug interactions; there is also the risk of diagnostic confusion when a patient receives antimalarials and ARVs that share overlapping ADR profiles. However, few published data are available to describe the pharmacodynamics or safety profile of antimalarial medications when given in combination with ART, or to describe the pharmacodynamics of antimalarials in the AIDS patient with severe malnutrition or wasting.

**Drug-drug interactions:** Primarily because of their effects on cytochrome P-450-mediated drug metabolism, various ARVs and anti-TB drugs (including most protease inhibitors [PIs], most non-nucleoside reverse transcriptase inhibitors [NNRTIs], and rifampin) are likely to increase or decrease clearance of quinine and halofantrine; these combinations should therefore be avoided.\textsuperscript{78,79} Co-administration of rifampin and quinine has resulted in markedly increased antimalarial treatment failure rates because of rifampin-induced reductions in quinine levels.\textsuperscript{79} Co-administration of efavirenz, artesunate, and amodiaquine has been associated with defective metabolism of amodiaquine in vitro and hepatotoxicity in vivo; in vitro studies suggest that co-administration of amodiaquine with saquinavir, lopinavir, and tipranavir is likely to yield similar results.\textsuperscript{80,81} There is controversy about the co-administration of PIs, NNRTIs, and lumefantrine; the manufacturer of lumefantrine and some reviewers have concluded that the combination should be avoided or be given only “with caution.” Other reviewers have concluded that careful studies have refuted these concerns.\textsuperscript{1,25,78} One pharmacokinetic study in healthy volunteers given ritonavir, lopinavir, and artemether-lumefantrine observed twofold elevation of lumefantrine levels without clinical toxicity.\textsuperscript{82} Early data also describe elevated risk of mortality in HIV-positive patients on zidovudine who were given high-dose pyrimethamine; the manufacturer continues to recommend against this combination.\textsuperscript{83} Finally, there was a high observed incidence of neutropenia (45%) in HIV-positive Ugandan children given the combination of artemether plus amodiaquine, often in combination with zidovudine and/or CTX.\textsuperscript{84} In general, published estimates of the incidence of drug-drug interactions with co-administration of ARVs and antimalarials are scarce. The Liverpool HIV Pharmacology Group maintains an online resource (http://www.hiv-druginteractions.org) that describes important drug-drug interactions involving ARVs and other medications commonly used in HIV care.\textsuperscript{78}

**Overlapping toxicities:** Both nevirapine and SP can cause SCAR, including SJS and toxic epidermal necrolysis. Because of the long half-life of
some ARV agents are active against *Plasmodium falciparum* and other species either in vivo or in vitro. Ritonavir, saquinavir, and lopinavir have been observed to have particularly potent antimalarial effects, but the clinical significance of these findings is as yet undefined.87

**The Pregnant HIV-Positive Patient**

The pregnant HIV-positive patient with symptomatic malaria may be treated in the same manner as the nonpregnant HIV-positive patient, except that medication choices during pregnancy—particularly the first trimester—are restricted by the paucity of available data on teratogenic effects of antimalarials. This issue has been recently reviewed.88 Chloroquine is considered safe in all trimesters but is largely ineffective due to widespread resistance. Quinine is also considered safe in all trimesters; the regimen of choice for acute malaria in the first trimester is now quinine + clindamycin, with artesunate + clindamycin as the second line. During the second and third trimesters, SP, mefloquine, clindamycin, and the artemisinins are also considered safe. The regimen of choice in the second and third trimesters is artemisinin-based combination therapy or artesunate + clindamycin; quinine + clindamycin is the second-line regimen. For severe malaria in pregnancy, intravenous artesunate + clindamycin is the preferred regimen (with quinine + clindamycin as a second choice).25 However, data on the pharmacodynamics of antimalarials in pregnancy are scarce.89 AIDS treatment programs should advocate for the clear definition of appropriate first- and second-line antimalarials for HIV-positive pregnant women.

The pregnant HIV-positive patient who is taking intermittent preventive treatment for malaria should not receive an SP-based regimen for the treatment of acute malaria sooner than one month after the last dose of preventive SP, unless better options do not exist.
*Plasmodium vivax*, *ovale*, *malariae*

The non-*falciparum* plasmodia are generally treated with a combination of chloroquine (to eradicate blood-stage parasites) and primaquine (to eradicate hypnozoites), except where drug resistance has developed. In the presence of chloroquine resistance, local first-line regimens vary, but may include artemisinin-based combinations, mefloquine, amodiaquine, or others.

**Chloroquine**

Thus far, we have been unable to locate reports of significant adverse drug-drug interactions involving chloroquine and ARVs, although theoretical concerns exist regarding interactions with ritonavir.\(^9\) Interestingly, chloroquine has been observed to inhibit HIV replication in vitro; this effect is enhanced in the presence of indinavir, ritonavir, and saquinavir.\(^9\) However, the clinical significance of chloroquine’s anti-HIV activity is as yet undefined.

**Primaquine**

Primaquine is contraindicated in pregnancy and in people with G6PD enzyme deficiency. We have not yet encountered reports of drug-drug interactions involving primaquine and ARVs. Primaquine has been used successfully (in combination with clindamycin) for treatment of *Pneumocystis* pneumonia.

**PREVENTION OF MALARIA IN THE HIV-POSITIVE PERSON**

Multiple methods exist for the prevention of malaria in HIV-positive persons, and may be used singly or in combination.

**Insecticide-Treated Bed Nets**

The insecticide-treated net (ITN) serves as a mechanical barrier to mosquitoes and also repels them through the action of its insecticide. The best nets are now made of fabric to which insecticide has been bonded prior to manufacture; the insecticide is released slowly throughout the life of the net, which does not require retreatment (“dipping”) with insecticide. In children of unknown (likely negative) HIV status living in regions of stable *P. falciparum* transmission, regular use of ITNs has been shown to reduce overall mortality and childhood anemia.\(^9\) In pregnant women, bed nets have been shown to reduce the overall burden of maternal anemia.\(^9\) In Uganda, bed nets provided additional antimalarial benefit in HIV-positive adult patients who were also taking CTX preventively.\(^9\) In HIV-positive Ugandan children, ITN use in combination with CTX prophylaxis was associated with a 97% reduction in malaria incidence.\(^9\) Where community-level coverage of ITNs is high (about 60% of households), households without bed nets derive some protection from malaria because of the insecticidal effect of their neighbors’ nets.\(^9\) In malaria-endemic regions, ITNs should be made available at the lowest possible price (preferably at no cost to the end user) to all HIV-positive persons, their family members, and their neighbors. Mass campaigns appear to be the most efficient means of achieving high levels of bed-net coverage quickly and equitably.\(^9\)

**Cotrimoxazole**

In cohort studies in sub-Saharan Africa, regular use of preventive CTX has been shown to reduce malaria incidence in nonpregnant adults by 72%–99%.\(^9\) CTX prophylaxis alone reduced malaria incidence by 39% in one cohort of HIV-positive Ugandan children (as noted above, the combination of CTX and ITNs was 97% effective in this cohort). No parallel studies have yet been conducted in pregnant women, or in regions where non-*falciparum* species predominate. The durability of CTX protection against malaria is unknown; CTX-resistant malaria has been documented, and
its prevalence is likely to increase in the presence of long-term drug pressure.\textsuperscript{103,104}

**Indoor Residual Spraying**

Indoor residual spraying (IRS) with a variety of insecticides has effectively reduced malaria transmission in a range of settings. For example, IRS progressively reduced malaria parasitemia prevalence in Mozambique during the first five years of implementation; the most dramatic reduction in prevalence was from 65\% to 4\%.\textsuperscript{105}

**Environmental Controls**

Environmental controls have included systematic application of larvicides to mosquito breeding grounds, elimination of standing water, and other methods. Often in combination with IRS, ITNs, and other strategies for transmission reduction, environmental controls have been an aid to the effective control of malaria. Using a combined strategy that included environmental controls, Eritrea succeeded in reducing estimated malaria incidence from 6,000 cases per 100,000 population per year to 1,100 cases per 100,000 between 1998 and 2003.\textsuperscript{106}

**Intermittent Preventive Treatment**

There are two basic types of intermittent preventive treatment (IPT): IPTp (for pregnant women) and IPTi (for young children). IPTp, with two or more treatment doses of an effective antimalarial (usually SP) given after the first trimester of pregnancy, has been shown to reduce maternal anemia and infant low birth weight in multiple prospective studies in regions of sub-Saharan Africa where \textit{P. falciparum} is endemic.\textsuperscript{107-114} IPTi, which involves giving treatment doses of antimalarials (often in conjunction with routine childhood immunizations in children under five), has been shown to reduce the prevalence of childhood anemia and the incidence of malaria episodes in some settings (effect sizes have been variable).\textsuperscript{115}

Neither intervention has yet been evaluated in pregnant women or children taking combination ART and/or preventive CTX, and few studies have been conducted in regions where \textit{P. vivax} transmission predominates. Specific IPTp and IPTi concerns relevant to the HIV-positive pregnant woman or child, on or off ARV or CTX therapy, are discussed below.

**IPTp**

Multiple studies have concluded that two-dose regimens of preventive SP (the most common IPTp regimen) are not as effective in HIV-positive women as in their HIV-negative counterparts, probably because HIV infection confers a higher risk of reinfection after a treatment dose of SP, and because SP is steadily losing efficacy throughout sub-Saharan Africa and other regions.\textsuperscript{114,116} Because HIV infection may also result in maternal anemia and infant low birth weight, measuring the impact of IPTp may be more difficult in these women. Some authors have concluded that the ideal regimen for the HIV-positive pregnant woman would consist of three doses of preventive SP after quickening; others have advocated for monthly administration of SP. Several experts have also observed that new agents are needed to replace SP for the indication of IPTp.\textsuperscript{117} Malaria prevention in the HIV-positive pregnant woman has other complexities beyond the frequency of SP dosing,\textsuperscript{118} including the following:

**IPTp in the pregnant woman on CTX prophylaxis:** CTX alone has been observed to prevent malaria infection in HIV-positive nonpregnant adults. However, no study has yet documented the effect of preventive CTX on incidence of severe maternal anemia, infant low birth weight, placental malaria parasitemia, or other obstetrical outcomes. Because CTX alone is believed to provide protection against malaria, and because the combination
of SP and CTX may result in increased incidence of toxicity, WHO currently recommends that women on CTX prophylaxis not receive preventive SP. However, owing to a lack of coordination between vertically implemented programs, some countries still recommend IPTp with SP (through national malaria control programs) as well as preventive CTX for HIV-positive pregnant women (through national AIDS control programs).

**Overlapping drug toxicities involving SP and nevirapine:** Nevirapine, when taken daily as a component of combination ART, has been associated with a substantial incidence of SCAR, particularly in women with high (greater than 250 cells/mm³) CD4 lymphocyte counts. For example, the incidence of SJS was 3% in one series of Mozambican pregnant women taking triple ART. Both nevirapine-associated and SP-associated SJS may manifest weeks after initiation of therapy, because of the long half-lives of these medications. SJS occurring in the pregnant woman who takes nevirapine daily and has had SP within the past month or so is likely to lead to diagnostic confusion. We know anecdotally that SJS has occurred in women on these regimens, but pharmacovigilance data are as yet inadequate to describe the incidence of this problem. It should be noted that SJS has not been documented in pregnant women who receive single-dose nevirapine to reduce the risk of HIV transmission to the infant.

**Overlapping toxicities involving SP and zidovudine:** The salutary effects of IPTp on maternal hemoglobin may be negated by adverse effects of antenatal zidovudine. One Mozambican study observed a severe anemia incidence of 20% in pregnant women who began daily zidovudine (as part of a triple-ARV regimen) and who had normal hemoglobins at study inception. In contrast, an Indian study failed to note an increased incidence of severe anemia in pregnant women on zidovudine monotherapy. The combination of SP and zidovudine has been previously associated with increased mortality and anemia. Further research is required to characterize the incidence of myelosuppression in HIV-positive women receiving zidovudine and SP concurrently. In the interim, close monitoring of hemoglobin levels—along with regular use of ITNs—is recommended for the pregnant woman who is vulnerable both to malaria and to the adverse effects of zidovudine and SP.

**Role of insecticide-treated bed nets:** ITNs have been shown to reduce maternal anemia, both when used alone and when used in conjunction with SP. Indeed, in one randomized controlled trial of IPTp with SP versus placebo in Mozambican pregnant women whose ITN use was estimated at 90%, SP conferred little advantage over ITN use alone. ITNs also have the advantage of reducing malaria incidence without causing drug-drug interactions. Therefore, pregnant women living in malaria-endemic areas should be urged to use ITNs nightly, and to continue consistent use even after delivery. Nets should be made available at the lowest possible cost to pregnant women and their neighbors. Ideally, HIV-positive women of reproductive age should begin ITN use well before pregnancy occurs.

**IPTp where malaria transmission is unstable or caused by non-*falciparum* species:** The role of IPTp in regions where malaria transmission is unstable, or where *P. falciparum* species are not predominant, has not yet been clarified even for HIV-uninfected women, although one study has now documented the success of IPTp with chloroquine against maternal *P. vivax* malaria.

**IPTi**

As in the case of IPTp, IPTi has largely been studied in HIV-uninfected individuals or in subjects of unknown HIV status; hence, it is unclear whether findings in these populations are generalizable to
the situation of the HIV-positive child. At present, IPTi is primarily implemented in the research setting, but it may become more widespread in the near future. Concerns about IPTi in the HIV-positive infant or young child include the following:

**CTX prophylaxis and IPTi:** As with adults, daily CTX prophylaxis may provide adequate protection against malaria parasitemia in children, although this has not been consistently demonstrated in published trials. It is not clear whether IPTi would confer any additional advantage over CTX alone, or the combination of CTX and ITNs.

Where the IPTi regimen consists of SP (with or without a second agent), children on CTX may be at increased risk of adverse reactions if SP is co-administered (as above). However, there are even fewer data on the incidence of SCAR in HIV-positive children than there are in adults. Where there is a risk that children on CTX may be stigmatized if their parents or guardians decline SP during mass campaigns because of concerns about effectiveness or safety, it may be prudent to devise ways to preserve the confidentiality of HIV-positive or HIV-exposed infants.

**ART and IPTi:** Children who are taking daily combination ART presumably incur risks of adverse reactions and drug-drug interactions similar to those cited above, but incidence data in this age group are sparse.

**IPTi where malaria transmission is unstable or caused by non-*falciparum* species:** The role of IPTi has not yet been clarified where malaria transmission is unstable, or where *P. falciparum* is not the predominant species.

**Malaria Vaccines**

There is as yet no commercially marketed malaria vaccine, although some promising candidate vaccines have now reached the clinical trial stage or are approaching clinical trials.

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**GAPS IN THE EXISTING EVIDENCE AND GUIDELINES**

People living with HIV comprise an important and vulnerable subgroup among people exposed to malaria infection. Carefully conducted studies have concluded that HIV-positive individuals are at higher risk of malaria infection, higher risk of malaria-related complications, higher risk of anti-malarial treatment failure, and higher risk of adverse effects and drug-drug interactions related to at least some antimalarials, especially if combined with specific ARVs or ARV classes or with rifampin. However, few published studies have evaluated the situation of the HIV-positive person on ART, or the HIV-positive person at risk of *P. vivax* or other non-*falciparum* infection. No studies have described validated algorithms for differential diagnosis in symptomatic HIV-positive persons who are simultaneously at risk for multiple OIs and ADRs whose signs and symptoms overlap those of malaria. Most malaria-prevention studies have focused on populations living where malaria transmission is stable, where *P. falciparum* is the predominant species, and where the status of study participants is unknown or thought to be predominantly negative. The gaps in the existing data are substantial. Our own suggested priorities for future research and policymaking include the following:

1. Description of the effectiveness of daily CTX prophylaxis for the prevention of malaria and its complications (including maternal anemia and infant low birth weight) in pregnant women, people living in regions of unstable malaria transmission, and people living in regions where the predominant species of malaria is not *P. falciparum*.

2. Description of the effectiveness of common first- and second-line ART regimens for the prevention of malaria (asymptomatic, symptomatic, *P. falciparum*, other species) in HIV-positive individuals.
3. Description of the incidence of specific clinical signs and symptoms and the severity of malaria in HIV-positive persons living in a range of malaria-transmission circumstances, and at different levels of immunosuppression. Key questions include the following: What is the actual incidence/prevalence of fever in the immunocompromised individual with acute malaria? What is the actual incidence of severe malaria in patients with WHO stage III or IV HIV disease?

4. Description of the positive and negative predictive values of common rapid malaria tests in HIV-positive persons with varying levels of immunocompromise. (Justification: HIV infection has been associated with increased incidence of false-positive and/or false-negative reactions to other laboratory tests. 126,127)

5. Estimates of the incidence of significant adverse reactions and drug-drug interactions in HIV-positive persons who are given common antimalarials in addition to ART, CTX, and/or anti-TB drugs. Special attention should be given to the safety profile of artemisinin-based combination regimens and common IPTp and IPTi agents.

6. Development of validated algorithms for the diagnosis (and exclusion of the diagnosis) of malaria in HIV-positive persons living in a range of malaria-transmission circumstances, and at different levels of immunosuppression. Of particular importance are guidelines for management of the HIV-positive patient with anemia, fever, or headache when laboratory tests for malaria are negative.

7. Adaptation of WHO staging criteria to include increased malaria incidence and/or severity as indicators of immunosuppression.

8. Adaptation of WHO staging criteria to reflect the apparent effect of acute malaria on CD4 lymphocyte count.

9. Tracking of malaria incidence and severity by HIV treatment programs, just as other important OIs would be tracked.

10. Evaluation of malaria vaccine efficacy in HIV-positive individuals at various disease stages as soon as clinical trials reach the appropriate stage.

GUIDELINES FOR PREVENTION, DIAGNOSIS, AND TREATMENT OF MALARIA IN THE HIV-POSITIVE PERSON

Based on the evidence cited above and our own professional judgment, we offer the following recommendations—which we acknowledge to be somewhat subjective, given the above-mentioned gaps in the evidence base—for prevention, diagnosis, and management of malaria in the HIV-positive person residing where malaria transmission occurs.

Prevention

All HIV-positive adults and children living in regions where malaria is transmitted should be urged to use ITNs regularly. ITNs should be provided as cheaply as possible, preferably without cost to the end user. Where HIV prevalence is high, entire communities or districts should be targeted, not just individuals. ITNs must be made available to HIV-positive persons in a manner that does not stigmatize them; for example, if ITNs are given at no charge to pregnant women who test positive for HIV, equivalent nets should also be given to HIV-uninfected pregnant women and to pregnant women who have not yet been tested for HIV.

All HIV-positive persons should also be instructed in household-level methods of environmental control of malaria, such as installment of window screens and drainage of standing water.

If preventive CTX is medically indicated (based on HIV disease stage, patient drug allergies, etc.) in
a patient who is at risk for malaria, its use should be further encouraged. If it is discontinued (because of ADR or immune reconstitution), the patient should be advised that malaria risk may increase.

Patients who are on preventive CTX should not also receive preventive SP or SP-based combination regimens (in the context of IPTi or IPTp).

National and regional HIV/AIDS control programs should advocate for population-level reduction of malaria transmission (through IRS, larvicides, or other means appropriate for the population in question) where both HIV and malaria are prevalent.

**Diagnosis**

Because so many other clinical conditions (OIs, ADRs, IRIS) may resemble malaria, and because of the importance of avoiding drug-drug interactions and ADRs, presumptive treatment of malaria in the HIV-positive patient should be actively discouraged *where better options are available*. This is particularly important in HIV-positive individuals who use ITNs regularly and receive CTX prophylaxis, as they are at substantially reduced risk of malaria. AIDS programs should ensure that HIV-positive persons have ready access to properly performed microscopy and/or rapid malaria tests. Patients should be counseled to avoid home treatment with antimalarials *where better options exist*. However, if malaria is likely and laboratory testing is unavailable or considered unreliable, antimalarial treatment should *not* be withheld, especially when severe malaria is suspected.

Acute fever should not be the only trigger for clinical suspicion of malaria. The HIV-positive patient at risk for malaria who has acute headache, myalgias, vomiting, or diarrhea; an acute neurologic syndrome (e.g., coma or seizures); pulmonary edema; severe anemia; jaundice; lactic acidosis; or other sign of malaria *even in the absence of fever*, should be evaluated for malaria.

**HIV programs should coordinate with programs advocating community-based (or household-based) presumptive treatment of malaria in order to devise appropriate policies for the management of HIV-positive persons.**

Where HIV seroprevalence is high but microscopy is unavailable, intensified efforts should be made to introduce rapid malaria testing to health facilities and selected community-level health workers.

**Treatment of Malaria**

Clinicians who may be confronted with HIV/malaria coinfection should know which *Plasmodium* species is (or are) transmitted locally, whether the transmission pattern is stable or unstable, and what the local patterns of antimalarial drug resistance are. Similarly, clinicians should be familiar with local and WHO policies for IPTp, IPTi, and diagnosis and treatment of symptomatic malaria infection.

If malaria infection is confirmed or strongly suspected (in the absence of laboratory facilities or in the presence of a negative laboratory result with no other likely cause of symptoms in the patient at high risk for malaria), the most effective available antimalarial should be given in adequate doses as soon as possible. If two or more regimens of roughly equivalent effectiveness are available, the regimen thought safest for the individual (based on pregnancy status, comorbidities, and concurrent medications, including regimens for IPT) should be chosen.

**Related Policy Considerations**

AIDS and malaria programs should collaborate at the national and international levels to define first-, second-, and third-line antimalarial regimens that are appropriate for HIV-positive persons taking daily CTX prophylaxis, daily combination ARVs, and/or rifamycin-based anti-TB regimens. Where
alternatives to the standard regimens are indicated, intensified efforts should be made to make the alternative regimens available to health facilities that care for HIV-positive patients.

Clinicians should be wary of the possibility of simultaneous malaria infection and OI, bacteremia, or other illness.

Like episodes of TB and herpes simplex (infections that occur in both healthy and immunocompromised persons, but with substantially higher incidence in the latter group), episodes of malaria in HIV-positive persons should be reported on the standard forms for the monitoring and evaluation of complications of HIV/AIDS.

Routine monitoring of CD4 lymphocyte counts should be postponed until several weeks after the resolution of an episode of symptomatic malaria. HIV viral load results should be interpreted with caution in the aftermath of a malaria episode.

We encourage AIDS clinicians working in malaria-prone environments to follow the malaria and malaria/HIV literature closely, because the evidence base for these and other recommendations is changing rapidly. Certain existing e-mail list servers may facilitate this.* We also encourage AIDS clinicians to report their own experiences with malaria-HIV coinfection and its treatment, in order to add to the evidence base that is so urgently required to confront the dual pandemics more effectively.

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* MalariaWorld (formerly the Multilateral Initiative on Malaria Communications Network, MIMCom) provides regular electronic malaria news updates to support malaria research in Africa and networking around the world. Subscribe/unsubscribe messages may be sent to inga@malaria-world.com.
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SEXUALLY TRANSMITTED INFECTIONS (STIs) are the second most important cause of loss of years of healthy life among women. A 1993 World Bank report estimated that STIs other than HIV accounted for almost 9% of the global disease burden in women aged 15 to 45; they accounted for only 1.5% of the global disease burden in similarly aged men. Globally, the World Health Organization (WHO) estimates that each year, 340 million new cases of curable STIs (gonorrhea, syphilis, chlamydia, and trichomoniasis) occur among sexually active men and women, with the majority of these infections occurring in developing countries. This figure does not include the millions of viral STIs other than HIV, such as herpes simplex virus (HSV), hepatitis B virus (HBV), and human papillomavirus (HPV).

The epidemiology of each STI is different and is shaped by multiple factors, including sexual mixing patterns (which may be moderated by preventive behaviors), the transmissibility of each pathogen, the duration of infectiousness (which is affected by access to effective care), demographics, and social conditions. For example, viral STIs are commonly found irrespective of the level of economic development in a given setting, whereas bacterial STIs remain the second leading cause of disease burden among women of reproductive age in developing countries. For both men and women, STIs are associated with an increased risk of HIV transmission.

The association between HIV and other STIs was first suggested in 1984, with the hypothesis that the presence of some STIs may facilitate the acquisition of HIV infection. Since then, several reviews have documented the association between HIV and both ulcerative and nonulcerative STIs. Overall the evidence points to an important bidirectional, positive relationship between HIV and other STIs. For instance, HSV type 2 (HSV-2) infection, which has become the predominant cause of genital ulcer disease (GUD) in many developing countries, is an important driver of the HIV epidemic in some settings. (For more on this topic, see the chapter entitled “HSV-2 Treatment Interventions to Control HIV: Hope for the Future?”)

STIs can give rise to significant complications. For example, HPV and sexually transmitted HBV infection can result in malignancies of the cervix and liver, respectively. Several STIs can also affect pregnancy outcomes or the health of newborns. For example, untreated early syphilis results in a stillbirth rate of...
25%, as well as a perinatal mortality rate of approximately 20%. Finally, reproductive tract infections can result in infertility, which may have significant social repercussions. The sections that follow detail each major STI, including its diagnosis, treatment, and management considerations for women living with HIV. (Note: HPV and HBV are not included, as they are covered elsewhere in this publication.)

**Cervicitis**

*Chlamydia trachomatis* is the most common bacterial STI worldwide. Cervicitis due to chlamydia generally affects women younger than 25 years of age. Asymptomatic infection is common, leaving women at risk for chlamydia-related morbidity through complications of pelvic inflammatory disease (PID), including chronic pelvic pain, ectopic pregnancy, and infertility. When symptoms of cervicitis exist, they are generally mild and may include an abnormal vaginal discharge or intermenstrual bleeding. Women with cervicitis may have a subclinical upper tract infection and should be assessed for signs of PID. Infection with *C. trachomatis* in men and women may be complicated by conjunctivitis or reactive arthritis. Neonates exposed to the mother’s infected cervix may develop conjunctivitis or pneumonia; thus, a chlamydial etiology should be considered for all infants aged 30 days or less who have conjunctivitis. Risk factors associated with cervicitis include age under 21 years, being unmarried, having more than one sexual partner within three months, having a new sexual partner in the prior three months, having a current partner with an STI, and having a partner who recently used condoms.

**Diagnosis of Cervicitis**

Cervicitis is characterized by the following diagnostic signs: (1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen, and (2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os. Vaginal discharge is poorly predictive of cervical infection. Leukorrhea (>10 white blood cells [WBCs] per high-power field on microscopic examination of vaginal fluid) has been associated with chlamydial and gonococcal infection of the cervix; when trichomoniasis is not found, this may be a sensitive indicator of cervical inflammation with a high negative predictive value in the absence of inflammatory vaginitis.

Because microscopy is time consuming and requires special training, its use is generally not recommended at the primary-care level in resource-limited settings. However, if Gram staining can be performed efficiently, as in a referral clinic, it should be performed when women present with vaginal discharge. The most sensitive and specific test available for *C. trachomatis* is nucleic acid amplification testing (NAAT), which can be performed on vaginal, cervical, or urine samples. Other laboratory tests, including culture, direct immunofluorescence, enzyme immunoassay (EIA), and nucleic acid hybridization tests, are available for detection of *C. trachomatis* on endocervical specimens. However, as with NAAT, their use in resource-limited settings is restricted by cost, time, and technical expertise. When laboratory testing is not available, risk assessment should be performed among women presenting with discharge and should be used, along with knowledge of local prevalence of gonorrheal and chlamydial infections, when deciding whether to treat.

**Treatment of Cervicitis**

Coinfection with *C. trachomatis* frequently occurs among patients who have gonococcal infection. Such patients should be presumptively treated for chlamydia. Recommended regimens for chlamydia cervicitis are doxycycline 100 mg orally twice daily for 7 days, or azithromycin 1 g orally in a single
dose. Alternative regimens include erythromycin base 500 mg orally four times a day for 7 days, erythromycin ethylsuccinate 800 mg orally four times a day for 7 days, ofloxacin 300 mg orally twice a day for 7 days, or levofloxacin 500 mg orally once daily for 7 days. Sex partners should be evaluated, tested, and treated if they have had sexual contact with the patient during the 60 days preceding onset of symptoms in the patient or diagnosis of chlamydia. The most recent sex partner should be evaluated and treated, regardless of the time of last sexual contact.

**Chlamydia Infection in Pregnancy**

In pregnant women, chlamydia infection has been associated with a number of adverse outcomes, including increased risk of ectopic pregnancy, preterm delivery, spontaneous abortion, low birth weight, premature rupture of membrane, perinatal mortality, and postpartum endometritis.12-18 In a cohort study, Ryan et al19 showed an increased risk in the incidence of premature rupture of membranes in patients with positive chlamydia cultures who did not receive treatment, as compared with patients with negative chlamydia cultures. Cohen et al20 demonstrated that patients with chlamydia who were successfully treated had a lower risk of premature rupture of membranes than those who were treated but had either persistent or recurrent chlamydia at the end of pregnancy.

Doxycycline (and other tetracyclines), ofloxacin, and levofloxacin are contraindicated in pregnant women. However, data suggest that azithromycin is safe and effective in pregnancy.21-23 Test of cure three weeks after completion of therapy is recommended for all pregnant women, especially considering the potential sequelae in the mother and neonate if infection persists. Erythromycin estolate is contraindicated during pregnancy because of drug-related hepatotoxicity; therefore, only erythromycin base or erythromycin ethylsuccinate should be used.

**Chlamydia Infection in the Setting of HIV Infection**

As previously mentioned, chlamydia infection in pregnancy has been associated with premature rupture of membranes. Although chlamydia infection itself has not been directly associated with an increased risk of perinatal HIV transmission, several studies have demonstrated an increased risk of perinatal transmission with increased duration of ruptured membranes.24-27 Treatment regimens for HIV-positive women are not different from those for HIV-negative women.

**Lymphogranuloma Venereum**

Infection with *C. trachomatis* serotypes L1, L2, and L3 results in the invasive disease lymphogranuloma venereum (LGV). At the site of inoculation, a self-limited papule or genital ulcer may occur. Among heterosexuals, typical presentation of LGV involves unilateral tender inguinal and/or femoral lymphadenopathy (buboes). Rectal exposure results in proctocolitis, with symptoms of mucoid and/or hemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenesmus. Untreated LGV proctocolitis progresses to chronic colorectal fistulas and strictures, and genital lesions may result in genital elephantiasis; either condition may result in secondary bacterial infections. Coinfection with other STIs is not uncommon. LGV is endemic in parts of Africa, Asia, South America, and the Caribbean, though it is rare in industrialized nations. Its epidemiology is not well defined because its clinical presentation overlaps with other causes of genital ulcer disease with bubo formation; therefore, definitive laboratory diagnosis is difficult.28

**Diagnosis of LGV**

Diagnosis of LGV is generally based on clinical features, epidemiology, and the exclusion of other diagnoses. Swabs of ulcers or aspiration of buboes may be tested for *C. trachomatis* by culture, direct
immunofluorescence, or nucleic acid detection where available. However, specific LGV diagnostic testing is not feasible in resource-limited settings, where LGV is most prevalent.

**Treatment of LGV**

Treatment of choice is doxycycline 100 mg orally twice daily for 21 days. Azithromycin 1 g daily for 21 days has been proposed as a therapeutic alternative as well, though data on its efficacy are lacking. Patients with a clinical syndrome consistent with LGV in the appropriate epidemiologic setting should receive treatment in the absence of diagnostic testing. Buboes should be aspirated through healthy skin to prevent the formation of ulcerations. Incision and drainage or excision of nodes may delay healing, and sequelae, such as strictures or fistulae, may require surgery. Erythromycin base 500 mg orally four times daily for 21 days is an alternative regimen and is the treatment of choice for pregnant or lactating women, as tetracyclines are contraindicated in pregnancy. Patients who have had sexual contact with a person with LGV within 60 days before onset of the patient’s symptoms should be examined, tested for urethral or cervical chlamydial infection, and treated with a standard chlamydia regimen, such as azithromycin 1 g single-dose orally or doxycycline 100 mg orally twice a day for 7 days.

**LGV in the Setting of HIV Infection**

Treatment for HIV-positive people with LGV remains the same as for HIV-negative people, although prolonged therapy may be required. Symptoms may resolve more slowly than in those who are HIV negative.

**Gonorrhea**

Gonorrhea is caused by *Neisseria gonorrhoeae*, a Gram-negative diplococcus. Infections in men are typically symptomatic and include a purulent urethral discharge associated with dysuria. Among women, gonorrhea is a major cause of cervicitis, urethritis, and PID. The presence of a gonococcal infection does not usually produce symptoms until complications, such as PID, occur. Other complications from gonorrhea in women include tubal scarring, which is a major cause of infertility and/or ectopic pregnancy. Gonorrhea can also cause accessory gland infection (Skene’s gland, Bartholin’s gland) that is often unilateral. An additional unique manifestation in women is gonococcal perihepatitis (Fitz-Hugh-Curtis syndrome), which is associated with inflammation of the liver capsule. Finally, women can acquire gonorrhea in the anorectal area.

Other manifestations seen in both men and women include pharyngeal infection, conjunctivitis, and disseminated gonococcal disease. Delivery through an infected birth canal can result in ophthalmic and respiratory disease in the newborn. Although the disease’s clinical manifestations are broad, community surveys suggest that there is a substantial pool of asymptomatic *N. gonorrhoeae* among men and women.²⁹,³⁰

**Diagnosis of Gonorrhea**

The diagnosis of gonorrhea can be made by several laboratory methods, including the following:

- Gram stain on a smear of genital discharge
- Culture on selective media
- Nonamplified tests, such as EIA, DNA probe, or direct fluorescent antibody (DFA)
- Amplified tests, such as polymerase chain reaction (PCR) or ligase chain reaction (LCR)

**Treatment of Gonorrhea**

It is generally accepted that the treatment for gonorrhea should be safe, highly effective, single dose, and affordable. Single-dose oral therapies improve compliance; given the large number of patients who
are treated but who get reinfected, safety remains an important concern.

The standard approach to therapy has been to treat both *N. gonorrhoeae* and *C. trachomatis*, because patients are often coinfected. The standard of care in high-income countries has been to use cephalosporins or quinolones. However, the recent widespread emergence of quinolone-resistant *N. gonorrhoeae* (QRNG) infection has resulted in more stringent treatment therapies, thus reducing the options for oral treatment.31

**Gonorrhea in the Setting of HIV Infection**

Little has been published regarding the presentation or response to gonorrhea treatment in patients with HIV disease. There are no data to suggest that the complications of gonorrhea are more common among patients living with HIV than in those who are HIV negative, nor does there appear to be an altered natural history in the setting of HIV-induced immunosuppression.32 As with other inflammatory STIs, the presence of gonorrhea can increase the risk of sexual transmission of HIV. Thus, people with gonorrhea should receive HIV counseling and testing.

**Trichomoniasis**

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. Symptoms of trichomoniasis in women include a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation. However, some women have minimal or no symptoms. Trichomoniasis is a risk factor for development of posthysterectomy cellulitis, tubal infertility, and cervical neoplasia.33-37

Several studies have investigated the prevalence of trichomoniasis among women in Africa. Buvé et al38 performed a cross-section study in four African cities—two with a high prevalence of HIV infection (Kisumu, Kenya, and Ndola, Zambia) and two with a relatively low prevalence of HIV (Cotonou, Benin, and Yaoundé, Cameroon). They found that the prevalence of trichomoniasis was significantly higher in the high-HIV-prevalence cities (29.3% in Kisumu and 34.3% in Ndola) than in Cotonou (3.2%) and Yaoundé (17.6%). Surprisingly, in Ndola, a high prevalence (40%) of trichomoniasis infection was found in women who denied having ever had sex. In a study conducted among 5,221 women in rural areas of eastern Zimbabwe, antibodies to *T. vaginalis* were detected by EIAs, and 516 (9.9%) women were seropositive for *T. vaginalis*, with increasing seroprevalence seen with age among younger women.39

A population-based study of a village population in Tanzania found that *T. vaginalis* vaginitis was the most common reproductive tract infection among participants aged 15 to 44 years (24.7%).40

**Diagnosis of Trichomoniasis**

Diagnosis of vaginal trichomoniasis is usually performed by microscopy of vaginal secretions, requiring immediate evaluation of wet preparation slide for optimal results. Sensitivity of wet prep is in the range of 60%-70%.41 Culture of vaginal secretions is the most sensitive and specific commercially available method of diagnosis. It should be performed when trichomoniasis is suspected yet unconfirmed using microscopy. PCR testing for *T. vaginalis* may be available through commercial laboratories. Several point-of-care diagnostic assays are available for diagnosis of trichomoniasis in women, including OSOM Trichomonas Rapid Test, an immunochromatographic capillary flow dipstick technology, and Affirm VPIII, a nucleic acid probe test that evaluates for *T. vaginalis*, *Gardnerella vaginalis*, and *Candida albicans*. Both tests are performed on vaginal secretions and tend to be more sensitive than wet prep, with a sensitivity greater than 83% and a specificity greater than 97%.42 The results of the OSOM Trichomonas Rapid Test are available in approximately 10 minutes, whereas results of the Affirm VPIII are available within 45 minutes. False
positives may occur in both, particularly in low-prevalence populations.

**Treatment of Trichomoniasis**

Treatment of choice is a single 2 g dose of oral metronidazole or tinidazole. Treatment of sex partners of patients with trichomoniasis is recommended. Patients should be instructed to avoid sex until therapy has been completed and symptoms have resolved for both the patients and partner(s). Although low-level metronidazole resistance has been identified in 2% to 5% of vaginal trichomoniasis cases, high-level resistance is rare. Use of topically applied antimicrobials (such as metronidazole gel) are not recommended, as they are unlikely to achieve therapeutic levels in the urethra or perivaginal glands. Cure rates using metronidazole gel are less than 50%, which is considerably less efficacious for the treatment of trichomoniasis than oral preparations of metronidazole (cure rates of 90%-95%) or tinidazole (86%-100%). In cases of treatment failure with 2 g oral metronidazole, once reinfection has been excluded, options include oral metronidazole 500 mg twice daily for seven days or single-dose tinidazole 2 g. Patients who fail these regimens may be treated with a five-day course of 2 g daily metronidazole or tinidazole.

**Trichomoniasis during Pregnancy and Lactation**

Adverse pregnancy outcomes, such as premature rupture of membranes, preterm delivery, and low birth weight, have been associated with *T. vaginalis* vaginitis. Treatment of vaginal trichomoniasis in pregnancy may prevent respiratory or genital infection of the newborn. However, a reduction in perinatal morbidity with treatment has not been found. Several studies have suggested an association between metronidazole treatment and low birth weight or prematurity, and some recommend deferring therapy in asymptomatic pregnant women until after 37 weeks’ gestation. Treatment with 2 g metronidazole in a single dose may be offered after a discussion with the patient of the potential risks and benefits of treatment. Metronidazole is pregnancy category B, while tinidazole is pregnancy category C; the safety of tinidazole in pregnancy has not been evaluated. For women who are lactating, interruption of breastfeeding is recommended during treatment and for 12 to 24 hours after the last dose if using metronidazole and for three days after the last dose for tinidazole.

**Trichomoniasis in the Setting of HIV Infection**

Patients living with HIV who have trichomoniasis should receive the same treatment regimen as those who are HIV-negative. The incidence, persistence, and recurrence of trichomoniasis in HIV-positive women are not correlated with immune status. A prospective study conducted in women in Mombasa, Kenya, suggested that trichomoniasis was associated with an increased incidence of HIV infection.

**Syphilis**

Syphilis emerged in Europe in the Middle Ages, probably related to the confluence of multiple endemic treponemal infections. Syphilis results from infection by *Treponema pallidum*, a corkscrew-shaped bacteria whose inoculation occurs via microscopic abrasions of the skin or mucous membranes, almost always via sexual contact. A high prevalence of the disease is found in resource-limited settings, as well as among men who have sex with men in urban centers of high-income countries. Notably, the collapse of Eastern Europe’s public-health system following the end of the Soviet Union spurred an epidemic of congenital syphilis.

Primary syphilis typically presents as a solitary chancre, a painless lesion that progresses from a macule to papule to ulcer. The chancre represents the bacteria’s site of entry. Multiple chancres are present in up to 40% of primary syphilis cases. Chancres typically occur on the penis or perineum of men and in the vagina of women, with painless
inguinal lymphadenopathy. Thus, women often are not aware of the disease at this stage. The chancre resolves spontaneously within three to six weeks, signaling the end of the disease’s primary stage.

After hematogenous dissemination, generalized or local skin and mucous membrane eruptions can occur and are often accompanied by generalized lymphadenopathy, signaling the onset of secondary syphilis. Although the rash of secondary syphilis is not specific in appearance, it is notably non-pruritic. Classically, it involves the palms of the hands and soles of the feet.

The host immune response plays a key role in early disease, though it often does not completely eradicate the infection. The subsequent latent period is characterized by a lack of clinical manifestations. Latent syphilis is the presence of positive serology in the absence of clinical disease. Early latent disease is syphilis of less than one year in duration, whereas late latent is defined as disease acquired more than one year prior to the diagnosis of latency. One-third of infections will typically resolve, with no evidence of disease and with negative serology. Another third will continue to have positive serology with no signs or symptoms of the disease. The final third will go on to develop tertiary syphilis, which can present with a variety of chronic illnesses, including granulomatous lesions of the skin, as well as cardiovascular and neurological disease.

Diagnosis of Syphilis
No culture is available for syphilis. In primary, secondary, and early congenital syphilis, dark-field examination is the quickest and most direct laboratory method of establishing the diagnosis. Nonetheless, dark-field examination has several disadvantages—namely, it requires a specialized microscope condenser and lens and an experienced microscopist. In addition, it must be read immediately, as motility is important to identify. Given these challenges, the diagnosis is typically established via serologic tests, which fall into two primary categories: nontreponemal and treponeme specific.

Nontreponemal assays include commonly used tests such as the rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) tests and are typically used to screen for past or present syphilis infection. They are also useful in evaluating the efficacy of syphilis therapy, as well as determining the likelihood of reinfection. Any positive nontreponemal test must be confirmed with a treponeme-specific assay, as biologic false-positive reactions can occur for a variety of reasons, including HIV infection, pregnancy, or other spirochete infections. False positives can also occur in individuals with a history of injection drug use.

Treponeme-specific assays are typically used to confirm a syphilis diagnosis in a patient with a reactive nontreponemal assay. Thus, they are used to reduce the likelihood of a biologic false-positive RPR or VDRL test. Commonly used assays include the fluorescent treponemal antibody (FTA) absorption test, *T. pallidum* particle agglutination assay (TPPA), and microhemagglutination assay (MHA-TP), or an IgG EIA.

Treatment of Syphilis
Penicillin remains the drug of choice for treating syphilis at all stages. Doxycycline is an alternative for penicillin-allergic patients. However, there is no alternative to penicillin therapy for pregnant women and people with neurosyphilis. Primary, secondary, and early latent syphilis are generally treated with one dose of penicillin G benzathine (2.4 million units intramuscularly). Patients with late latent disease should be provided three weekly doses of 2.4 million units of intramuscular penicillin G (7.2 million units total). The efficacy of nonpenicillin regimens (e.g., doxycycline and tetracycline) in HIV-positive individuals has not been well studied and must be considered with caution.
Primary syphilis may have a more aggressive presentation in people living with HIV. For example, multiple chancres, which occur in only 25% of primary syphilis cases, appear to be more common in people living with HIV.61

No significant differences have been noted in the progression to secondary or latent syphilis in the setting of HIV disease. However, rapid progression from the primary chancre to gummatous lesions has been observed in some HIV-positive individuals.62 Other potentially early manifestations of tertiary syphilis in HIV-positive individuals include aortitis63 and neurosyphilis, as noted previously.

The diagnosis of syphilis in HIV-positive individuals does not differ significantly from that in HIV-negative individuals. Both nontreponemal and treponemal tests are accurate and reliable for diagnosis and for response to treatment. However, recent studies suggest that patients with HIV may respond less well serologically.59 Thus, titers may decline more slowly than in patients without HIV infection when treated for early syphilis. Given the reports of rapid progression of syphilis in the setting of HIV infection, a cerebrospinal fluid (CSF) evaluation is recommended in patients with syphilis of unknown duration or in cases greater than one year in duration.

Recommended treatment regimens for each stage of syphilis remain the same, regardless of HIV infection status. However, because treatment failures with the current recommended regimens have been reported in HIV-positive patients, close follow-up is necessary for all those who are HIV positive, regardless of the treatment regimen used.59 Finally, recent data suggest that syphilis in HIV-positive individuals can increase serum HIV load, with a resultant decrease in CD4 count; however, these parameters do improve with standard syphilis therapy.64,65

There is no test of cure available for syphilis. Response to therapy is defined as resolution of clinical signs and symptoms (if present) and a two-dilution (i.e., fourfold) decrease in a nontreponemal serologic titer.

**Syphilis in Pregnancy**

Syphilis can be transmitted from the mother to the fetus at any stage of maternal infection, though the risk is higher in mothers with more recently acquired syphilis. It appears that the risk of fetal infection is greatest if disease is acquired late in pregnancy. Children born with congenital syphilis have a wide range of clinical findings, including dermatologic abnormalities, hepatosplenomegaly, osteochondritis, and a variety of central nervous system abnormalities. Most important, pregnancies in women with syphilis may result in stillbirths.

Data on coinfections with syphilis and HIV at the time of pregnancy are limited. Two prospective studies found no clinical differences in presentation, disease course, and response to therapy, though there was a lag in serological improvement after therapy in patients living with HIV.55,56 A retrospective analysis, however, did find a higher treatment failure among HIV-positive pregnant women.57 Currently, there are insufficient data to recommend a specific regimen for HIV-positive pregnant women,58 although some recommend a longer course of treatment for these patients.

**Syphilis in the Setting of HIV Infection**

Although reports are somewhat contradictory, an altered natural history of syphilis has been reported in the setting of HIV disease. For example, an early study noted rapid progression from early syphilis to neurosyphilis in HIV-positive patients, some of whom received appropriate therapy for early syphilis.59 A subsequent study, however, reported no association between HIV stage and syphilis progression or treatment failure.60
Genital Herpes

Both herpes simplex virus 1 and herpes simplex virus 2 (HSV-1 and HSV-2) infect the ano-genital area, with HSV-2 causing most episodes of recurrence. Genital herpes typically presents as prodromal local pruritus and paresthesia, followed by a red macule and vesicles, which subsequently ulcerate. Most patients with genital HSV have undiagnosed disease, only recognizing disease after they have been educated on the spectrum of presentations. Nonetheless, unrecognized HSV infection can cause serious disease in patient contacts, including primary disease, meningitis, erythema multiforme, and neonatal herpes.

The prevalence of HSV-2 is higher in some regions than in the United States. Recent studies suggest that the overall prevalence of HSV-2 in the United States is approximately 17%, somewhat lower than previous studies have suggested. However, HSV-2 prevalence rates among the adult general populations of sub-Saharan Africa range from 30% to 80% in women and from 10% to 50% in men. Likewise, HSV-2 prevalence rates among women in Central and South America range from 20% to 40%, and in low-income Asian countries, from 10% to 30%. Worldwide, HSV-2 seropositivity is uniformly higher in women than in men and increases with age. In general, HSV-2 seroprevalence is high in populations that have a high risk of acquiring other STIs, such as in populations of STI clinic attendees and sex workers. Some studies from African countries report greater than 80% HSV seropositivity among sex workers. In the United States, HSV-2 is the most common cause of genital ulcers.

Diagnosis of Genital Herpes

Genital infections due to HSV typically present as multiple painful ulcers. Primary HSV infection follows an incubation period of two to four days and is often accompanied by painful regional lymphadenopathy. Urethritis can also be present, presenting as dysuria and a clear urethral discharge. Other findings include a sacral radiculopathy and urinary retention. Diagnosis is confirmed by fluorescent antibody staining and culture of swabs. Lower yields on culture occur once the lesions have crusted over.

Treatment of Genital Herpes

Acyclovir, valacyclovir, and famciclovir are all recommended and can shorten the duration of pain, systemic symptoms, and viral shedding in initial HSV infections. Acyclovir, the least expensive option, is taken at a dose of 400 mg orally three times daily. Although famciclovir and valacyclovir have less frequent dosing (see Table 1), they are more expensive. The regimen for HIV-positive individuals is the same as for those who are HIV-negative. There is no consensus about the use of long-term suppressive therapy for HSV in HIV-positive individuals.

Genital Herpes in the Setting of HIV Infection

Genital HSV disease in individuals with advanced HIV infection can be severe, producing disfiguring disease that responds slowly to therapy. These severe ulcerative lesions typically appear in patients with very low CD4 counts. Infection with acyclovir-resistant HSV occurs uncommonly; it is almost exclusively limited to HIV-positive individuals, primarily due to strains that are thymidine-kinase deficient. Therapy with intravenous foscarnet can be used in these situations. Many additional studies have shown an association between prevalent and incident HSV-2 infection and the risk of HIV acquisition. HSV-2 has been associated with high amounts of HIV-1 in plasma and genital secretions, suggesting that HIV replication can be reduced with antiviral therapy directed solely at HSV-2.
<table>
<thead>
<tr>
<th>Infection</th>
<th>Recommended Regimens</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chlamydia trachomatis</strong></td>
<td></td>
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<tr>
<td>Cervicitis</td>
<td>Doxycycline 100 mg orally twice daily for 7 days or Azithromycin 1 g orally in a single dose</td>
<td>Erythromycin base 500 mg orally 4 times daily for 7 days or Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days or Ofloxacin 300 mg orally twice daily for 7 days or Levofloxacin 500 mg orally once daily for 7 days</td>
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<tr>
<td>Lymphogranuloma venereum</td>
<td>Doxycycline 100 mg orally twice daily for 21 days</td>
<td>Azithromycin 1 g daily for 21 days or Erythromycin base 500 mg orally 4 times daily for 21 days</td>
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<tr>
<td><strong>Neisseria gonorrhoeae</strong></td>
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<tr>
<td>Gonorrhea</td>
<td>Ceftriaxone 125 mg intramuscular (IM) in a single dose or Cefixime 400 mg orally in a single dose or Ciprofloxacin orally in a single dose* or Ofloxacin 400 mg orally in a single dose* or Levofloxacin 250 mg orally in a single dose* and Treatment for chlamydia if chlamydial infection is not ruled out</td>
<td>Spectinomycin 2 g IM in a single dose</td>
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<tr>
<td><strong>Trichomonas vaginalis</strong></td>
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<tr>
<td>Trichomoniasis</td>
<td>Metronidazole or tinidazole 2 g orally in a single dose</td>
<td>Metronidazole 500 mg orally twice daily for 7 days</td>
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<tr>
<td><strong>Treponema pallidum</strong> (syphilis)</td>
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</tr>
<tr>
<td>Primary, secondary, and early latent syphilis</td>
<td>Penicillin G benzathine 2.4 million units IM single dose</td>
<td></td>
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<tr>
<td>Late latent syphilis, latent syphilis of unknown duration, or tertiary syphilis</td>
<td>3 doses of penicillin G benzathine 2.4 million units IM each at 1-week intervals (7.2 million units total)</td>
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<tr>
<td>Neurosyphilis</td>
<td>Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days</td>
<td>Procaine penicillin 2.4 million units IM once daily and Probenecid 500 mg orally 4 times daily—both for 10–14 days if compliance ensured</td>
</tr>
</tbody>
</table>

*Quinolones should not be used in areas of high quinolone-resistant Neisseria gonorrhoeae prevalence.*
### Table 1. Treatment of Sexually Transmitted Infections (cont.)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Recommended Regimens</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herpes simplex viruses</strong> (Genital herpes)</td>
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<tr>
<td>First clinical episode</td>
<td>Acyclovir 400 mg orally 3 times daily for 7–10 days</td>
<td>Valacyclovir 1 g orally twice daily for 7–10 days</td>
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<td></td>
<td>or Acyclovir 200 mg orally 5 times daily for 7–10 days</td>
<td>or Famciclovir 250 mg orally 3 times daily for 7–10 days</td>
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<td></td>
<td>or Famciclovir 125 mg orally twice daily for 5 days</td>
<td>or Famciclovir 1 g orally twice daily for 1 day</td>
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<td></td>
<td>or Acyclovir 800 mg orally 3 times daily for 2 days</td>
<td>or Valacyclovir 500 mg orally twice daily for 3 days</td>
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<td></td>
<td>or Famciclovir 125 mg orally twice daily for 5 days</td>
<td>or Valacyclovir 1 g orally once daily for 5 days</td>
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<td></td>
<td>or Acyclovir 800 mg orally 3 times daily for 2 days</td>
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<tr>
<td>Recurrent episodes</td>
<td>Acyclovir 400 mg orally 3 times daily for 5 days</td>
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<tr>
<td></td>
<td>or Acyclovir 800 mg orally twice daily for 5 days</td>
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<tr>
<td></td>
<td>or Acyclovir 800 mg orally 3 times daily for 2 days</td>
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<tr>
<td></td>
<td>or Famciclovir 125 mg orally twice daily for 5 days</td>
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<td>or Famciclovir 1 g orally twice daily for 1 day</td>
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<td></td>
<td>or Valacyclovir 500 mg orally twice daily for 3 days</td>
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<td></td>
<td>or Valacyclovir 1 g orally once daily for 5 days</td>
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<tr>
<td>Suppressive therapy</td>
<td>Acyclovir 400 mg orally twice daily</td>
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<td></td>
<td>or Famciclovir 250 mg orally twice daily</td>
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<td></td>
<td>or Valacyclovir 500 mg orally once daily</td>
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<tr>
<td></td>
<td>or Valacyclovir 1 g orally once daily</td>
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<tr>
<td><strong>Calymmatobacterium granulomatis</strong></td>
<td>Granuloma inguinale (donovanosis)</td>
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<tr>
<td></td>
<td>Azithromycin 1 g weekly for at least 3 weeks and until all lesions have healed</td>
<td>Ciprofloxacin 750 mg orally twice daily for at least 3 weeks and until all lesions</td>
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<td></td>
<td></td>
<td>have healed</td>
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<td></td>
<td></td>
<td>or Erythromycin base 500 mg orally 4 times daily for at least 3 weeks and</td>
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<td></td>
<td>until all lesions have completely healed</td>
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<td></td>
<td></td>
<td>or Trimethoprim-sulfamethoxazole 1 double-strength (160 mg/800 mg) tablet orally</td>
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<tr>
<td></td>
<td></td>
<td>twice daily for at least 3 weeks and until all lesions have completely healed</td>
</tr>
<tr>
<td><strong>Haemophilus ducreyi</strong></td>
<td>Chancroid</td>
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<td></td>
<td>Azithromycin 1 g orally in a single dose</td>
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<tr>
<td></td>
<td>or Ceftriaxone 250 mg IM in a single dose</td>
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<tr>
<td></td>
<td>or Ciprofloxacin 500 mg orally twice daily for 3 days</td>
<td></td>
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<tr>
<td></td>
<td>or Erythromycin base 500 mg orally 3 times daily for 7 days</td>
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</tbody>
</table>
Granuloma Inguinale (Donovanosis)
Granuloma inguinale, also known as donovanosis, typically causes painless genital ulcers that bleed readily to the touch. The etiologic agent is *Calymmatobacterium granulomatis*, a Gram-negative pleomorphic bacterium. However, it has been proposed that *C. granulomatis* should be reclassified with the genus *Klebsiella* based on phylogenetic similarities.73 Donovanosis is typically found in marginalized populations in diverse settings in Africa, South Asia, and New Guinea. Indeed, the largest epidemic was reported in Papua New Guinea; between 1922 and 1952, 10,000 cases were identified in a population of 15,000.74 Although recent data are unavailable, older data suggest that between 1989 and 1990, donovanosis was the second most common cause of GUD (after HSV-2) in Papua New Guinea.75 A donovanosis epidemic emerged in Durban, South Africa, during the late 1980s. In one study conducted there among women presenting with a genital ulcer, Donovan bodies were identified in 16% of the women.76 More recent reports suggest that the epidemic in Durban peaked in 1997.77

The incubation period for donovanosis is poorly defined and has been reported to be as long as 360 days.77 Experimental lesions induced in humans occurred approximately 50 days following inoculation. Thus, 50 days probably represents a more accurate incubation period.78 Manifestations typically begin as a firm papule or subcutaneous nodule that ulcerates. Typically, the nodule evolves into one of four types of disease:

- Ulcer granulomatous, the most common type, appears as beefy, red, nontender ulcers that bleed readily to the touch
- Hypertrophic or verrucous ulcers with an irregular edge; often dry
- Necrotic, foul-smelling deep ulcers.
- Dry, sclerotic, or circular lesions with fibrous and scar tissue

The genital region is affected in 90% of cases, with the remaining occurrences in the inguinal area.

Diagnosis of Donovanosis
The diagnosis is typically made by identifying intracellular Donovan bodies within large mononuclear cells. Tissue for such studies usually comes from smears obtained directly from tissue or biopsies. PCR testing has been used, but is not widely available in resource-limited settings.79

Treatment of Donovanosis
Azithromycin is currently the treatment of choice. The Centers for Disease Control and Prevention (CDC) recommends 1 g weekly for at least three weeks or until all lesions have healed. Other antibiotics that have been used include cotrimoxazole, erythromycin, and ciprofloxacin. The doses of these therapeutic alternatives are noted in Table 1.

Donovanosis in the Setting of HIV Infection
Given the relationship between genital ulcer disease and HIV acquisition, reports have emerged that HIV transmission is increased in the setting of donovanosis. For example, rates of HIV increased dramatically in Durban, South Africa, during the donovanosis outbreak.80 As yet, there is no evidence of a significant bidirectional impact on the natural history of either donovanosis or HIV in the setting of both infections. However, ulcers secondary to donovanosis have been reported to have a longer duration to resolution in HIV-positive individuals,81 and case reports have suggested failure to respond to conventional treatment in Brazil.77 Nonetheless, most authorities recommend no difference in the standard of care in HIV-positive patients diagnosed with granuloma inguinale.
**Chancroid**

Chancroid is an acute infection that presents as deep genital ulcerations accompanied by inguinal adenopathy and buboes. The etiologic agent is *Haemophilus ducreyi*, a Gram-negative coccobacillus. A tender papule may develop five to seven days after infection, followed by progression to the pustular stage. These pustules can rupture two to three days later, forming painful, shallow ulcers with granulomatous bases and purulent exudates. Lesions typically occur on the vulva, cervix, and perianal area of women.

Chancroid frequently coexists with other STIs. It occurs sporadically in high-resource settings, but remains endemic in resource-limited areas. In urban areas, it is often associated with commercial sex work. For example, in a study of female sex workers in Nairobi, the prevalence of genital ulcers ranged from 5% to 25%, and *H. ducreyi* could be cultured from about half the ulcers.

**Diagnosis of Chancroid**

Diagnosis requires special culture media that are not widely available. Even when such diagnostic resources are used, the sensitivity of culture is less than 80%. Thus, the diagnosis is often made by exclusion, assuming that the following criteria are met:

- One or more painful genital ulcers
- No evidence of *T. pallidum* infection by dark-field examination of the ulcer exudate or by a serologic test for syphilis performed at least seven days after the onset of ulcers
- Clinical presentation of genital ulcers and regional lymphadenopathy
- Negative test for HSV on the ulcer exudate

Several DNA-amplification techniques have been developed. However, these require access to specialized laboratories that are often not available in the regions where chancroid is most prevalent.

**Treatment of Chancroid**

Effective treatment of chancroid cures the infection and prevents transmission to others. If buboes are large and painful, they may require drainage by aspiration. Recommended antibiotics include azithromycin 1 g orally in a single dose or ceftriaxone 250 mg intramuscularly (IM) in a single dose. Dosages for alternative therapies are listed in Table 1.

**Chancroid in the Setting of HIV Infection**

The effect of coexisting HIV infection on the natural history of chancroid is unclear. Some data suggest that HIV-positive individuals have increased numbers of genital ulcers, which may not heal as fast as in patients without HIV disease. In addition, chancroid ulcers contain CD4 lymphocytes, which may increase the susceptibility of an individual with chancroid to subsequent infection by HIV. Of further concern, some reports state that single-dose therapy is associated with reduced healing of genital ulcers and persistence of *H. ducreyi* in the lesions in the presence of HIV disease.

**Pelvic Inflammatory Disease**

Pelvic inflammatory disease (PID) refers to a spectrum of inflammatory disorders of the upper genital tract in women. It may involve the uterus, oviducts, and ovaries, as well as neighboring pelvic organs. PID may include any combination of endometritis, salpingitis, oophoritis, tubo-ovarian abscess, perihepatitis, and pelvic peritonitis. Most commonly, PID is caused by an STI, though it may also be caused by medical procedures, pregnancy, or other primary abdominal processes. Etiologic agents include sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*; however, vaginal flora—such as anaerobes *G. vaginalis* and *H. influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*—have also been associated with PID. In addition, cytomegalovirus (CMV), *Mycoplasma hominis*,

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*OPPORTUNISTIC INFECTIONS, CANCERS, AND COINFECTIONS*
Diagnosis of PID

Clinical manifestations of PID are varied, making diagnosis difficult. Symptoms suggestive of PID include abdominal pain, dyspareunia, vaginal discharge, menometrorrhagia, dysuria, nausea, and vomiting. All sexually active women presenting with lower abdominal pain should be evaluated for evidence of PID, and routine bimanual and abdominal examination should be conducted for all women with a presumed STI, because women with PID or upper genital tract infection may not complain of lower abdominal pain. Signs of PID on physical examination include adnexal tenderness, cervical motion tenderness, abnormal cervical or vaginal mucopurulent discharge, and fever. Enlargement or induration of one or both fallopian tubes, a tender pelvic mass, and direct or rebound tenderness may also be present. Laboratory tests that support PID diagnosis include the presence of white blood cells on saline microscopy of vaginal secretions, documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*, elevated erythrocyte sedimentation rate, and elevated C-reactive protein. Laparoscopy can be used to aid in diagnosis; however, it will not detect endometritis or subtle inflammation of the fallopian tubes. Its use is also limited by cost and lack of availability. Thus, diagnosis of PID is usually based on clinical findings. Potential long-term morbidities associated with PID include tubal factor infertility, ectopic pregnancy, and chronic pelvic pain.

Many episodes of PID go unrecognized, due to poor provider recognition of its mild and often subtle symptoms. In general, clinicians should maintain a low threshold for the diagnosis of PID and should err on the side of overdiagnosing and treating suspected cases. Delay in diagnosis and treatment of PID is associated with a higher risk of long-term complications, such as infertility or ectopic pregnancy. Sexually active young women and other women at risk for STIs with unexplained
pelvic or lower abdominal pain and either cervical motion tenderness, uterine tenderness, or adnexal tenderness should be empirically treated for PID.31

Treatment of PID

Treatment of PID involves immediate empiric, broad-spectrum antibiotic therapy, which covers the most likely etiologic pathogens. The antibiotic regimen must be effective against *N. gonorrhoeae*, *C. trachomatis*, anaerobic bacteria, facultative Gram-negative rods, and *M. hominis*. Because negative endocervical screening for *N. gonorrhoeae* and *C. trachomatis* does not rule out upper tract disease, treatment regimens must include coverage of these pathogens. Although some have advocated inpatient management for all women with PID, women with mild to moderate disease may receive outpatient therapy. Hospitalization is recommended in the following cases:

- Uncertain diagnosis
- Surgical emergencies, such as appendicitis or ectopic pregnancy
- Suspected pelvic abscess or tubo-ovarian abscess
- Severe illness, nausea and vomiting, or high fever
- Pregnancy
- Inability of the patient to follow or tolerate an outpatient oral regimen
- Failure to respond to outpatient therapy7,43

Oral Treatment may be considered for women with mild to moderate disease. Women who do not respond to oral therapy within 72 hours should be reevaluated to confirm the diagnosis and should be administered parenteral therapy on either an outpatient or inpatient basis. A number of different recommended outpatient oral regimens are available, including the use of single-dose therapy for uncomplicated gonorrhea (i.e., parenteral third-generation cephalosporin, such as ceftriaxone 250 mg IM or cefoxitin 2 g IM in a single dose plus probenecid 1 g orally administered concurrently in a single dose) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. If use of a parenteral cephalosporin is not feasible, a 14-day course of fluoroquinolone may be substituted if the risk of gonorrhea is low; in such cases, testing for gonorrhea is recommended before initiating therapy.

Parenteral Treatment. When using parenteral treatment, doxycycline may still be given orally due to its excellent bioavailability. Therapy may be changed to an oral regimen 24 hours after clinical improvement to complete a total of 14 days of therapy with doxycycline; many providers add either 14 days of clindamycin or metronidazole when a tubo-ovarian abscess is present. Recommended parenteral regimens are cefotetan disodium 2 g intravenously (IV) every 12 hours; or cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours; or clindamycin 900 mg IV every 8 hours may be used with weight-based IV or IM gentamicin every 8 hours. Alternatively, ampicillin/sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours can be used.

Male sex partners of women with PID should be examined and treated for *N. gonorrhoeae* and *C. trachomatis* if they have had sexual contact with the patient during the 60 days preceding onset of symptoms. All women diagnosed with PID should be offered HIV testing.

**PID in the Setting of HIV Infection**

It is not entirely clear whether the clinical manifestations of PID differ between HIV-positive and HIV-negative women. A case-control study performed in Abidjan, Ivory Coast, among women with PID found that HIV infection was associated with more severe clinical manifestations of
AWARENESS OF HIV TRANSMISSION RISKS) WITH A HEALTH PROMOTION CONTROL GROUP (WHICH Addressed medication adherence, nutrition, and provider interaction skills). AT THE 12-WEEK FOLLOW-UP, WOMEN IN THE WILLOW PROGRAM REPORTED FEWER EPISODES OF UNPROTECTED VAGINAL INTERCOURSE (1.8 EPISODES VS. 2.5; P = .022), WERE LESS LIKELY TO REPORT NEVER USING CONDOMS (OR 0.27; P = .008), AND HAD A LOWER INCIDENCE OF CHLAMYDIA AND GONORRHEA INFECTIONS (OR 0.19; P = .006).110 OTHER POPULATION-BASED INTERVENTIONS HAVE PRIMARILY FOCUSED ON STI TREATMENT AND PREVENTION AS A MEANS OF REDUCING INCIDENT HIV INFECTION. KAMALI ET AL.111 RANDOMIZED ALL ADULTS LIVING IN 18 COMMUNITIES IN MASAKA, UGANDA, TO RECEIVE BEHAVIORAL INTERVENTIONS ALONE, BEHAVIORAL INTERVENTIONS AND SYNDROMIC MANAGEMENT OF STIS, OR ROUTINE GOVERNMENT HEALTH AND COMMUNITY DEVELOPMENT ACTIVITIES. THEY FOUND NO DIFFERENCE IN HIV INCIDENCE AMONG THE GROUPS. INCIDENCE OF HSV-2 WAS LOWEST IN THE BEHAVIORAL INTERVENTION ONLY GROUP, WHEREAS INCIDENCE OF SYPHILIS AND PREVALENCE OF GONORRHEA DECREASED IN THE COMMUNITY DEVELOPMENT ASSISTANCE ARM.

Periodic Presumptive Treatment

Treatment given for presumed infection at regular intervals is known as periodic presumptive treatment. This approach saves the cost of diagnostic tests and reaches a greater proportion of people than treating only those who are symptomatic. To be effective, treatment must be given at a short enough interval to avoid reinfection. Periodic presumptive treatment may be used as a temporary strategy to reduce prevalence of infection while other strategies for establishing preventive services are being implemented. IN UGANDA'S RAKAI DISTRICT, A RANDOMIZED, CONTROLLED, SINGLE-BLINDED TRIAL COMPARED HIV INCIDENCE AMONG 10 COMMUNITY CLUSTERS ASSIGNED TO RECEIVE EITHER THE INTERVENTION (MOTHER TREATMENT WITH AZITHROMYCIN, CIPROFLOXACIN, OR METRONIDAZOLE) OR THE CONTROL (VITAMINS/ANTIHELMINTIC
drugs) every 10 months. At 20 weeks, the prevalence of syphilis and trichomoniasis was lower in the intervention group, but there were no differences in the prevalence of chlamydia and gonorrhea. There was also no difference in new syphilis seroreactivity or reports of urethral discharge, vaginal discharge, or genital ulcers, nor was there a decrease in the incidence of HIV infection. In a subanalysis of the Rakai trial, Gray et al investigated the effect of presumptive STI treatment during pregnancy on the outcomes of maternal-infant STIs (including HIV) and infant outcomes. Reductions in multiple STIs, including T. vaginalis, N. gonorrhoeae, C. trachomatis, and infant ophthalmia, were observed, as were improved infant outcomes, such as reductions in rates of neonatal death, low birth weights, and preterm deliveries. There was no effect on maternal HIV acquisition or perinatal HIV transmission.

**Structural Interventions**

Structural interventions include changes to policies, guidelines, laws, or environmental factors. Several community-level, nonrandomized trials have demonstrated a reduction in STIs due to structural interventions. In the United States, Lonczak et al studied the effects of the Seattle Social Development Project intervention on fifth-grade students. The intervention had multiple components, including teacher training in classroom instruction and management, child social and emotional skills development, and parent training. When the cohort reached 21 years of age, self-reported sexual behavior, pregnancies, births, and STI outcomes were compared with those of a control group. Although the intervention did not have a significant effect on STI diagnosis among the general study population, the African American members of the intervention group experienced a reduced probability of contracting an STI (by self-report) by age 21 years (OR 0.11; P<1). In northern Thailand, Celentano et al compared HIV and STI incidence in cohorts of 19- to 23-year-old male conscripts in 13 military bases from 1991 to 1993 and from 1993 to 1995 to determine the effectiveness of the 100% Condom Program that began in 1991. This public-health strategy consisted of a public awareness campaign promoting the reduction of high-risk sexual practices, such as commercial sex, and motivating condom use during commercial sex. As part of this strategy, free condoms were distributed to sex workers during periodic STI examinations, and universal condom use in commercial sex was promoted during these visits. In addition, commercial sex establishments visited by men treated for STIs were identified in order to enforce compliance with these recommendations. Investigators found a dramatic decline in the rates of STIs, including HIV infection, associated with these activities. For instance, they observed a 10-fold decrease in STI incidence from 1991 to 1995 and a decline in HIV incidence from 2.48 per 100 person-years in 1991-1993 to 0.55 per 100 person-years in 1993-1995.

**Population Screening**

Population screening for chlamydia takes place in several high-income countries, including Sweden, England, and the United States. However, no national screening program has been assessed in a randomized, controlled trial. In the United States, Scholes et al conducted a study among enrollees of a health maintenance organization. In this study, women who were deemed to be at increased risk for chlamydial infection (according to study criteria) were randomly assigned to either a screening group or usual care. At the end of the one-year follow-up, there was a 56% reduction in the incidence of PID associated with chlamydia screening. Similar reductions in the risk of PID linked to chlamydia screening have been demonstrated in Denmark, where home sampling kits were used to obtain vaginal flush samples that were then mailed...
back to the laboratory facility. Outcomes were then compared with standard of care.118

**Vaccination Programs**

Immunization of at-risk populations is a highly effective tool in the control of infectious diseases. The first vaccine to protect against an STI was the hepatitis B vaccine. More recently, in 2006, a vaccine offering high-level protection to previously unexposed women against HPV types 16 and 18 (which both cause cervical cancer) and types 6 and 11 (which both cause genital warts) has been licensed in the United States and in Europe.119-121

Although the availability of both HBV and HPV vaccines is currently limited in resource-limited settings, such vaccines could be a valuable tool in the control of these STIs. A vaccine against HSV-2 has been tested, showing partial effectiveness among women who had never been infected with either HSV-1 or HSV-2.122

**SPECIAL ISSUES**

**Syndromic Management**

Etiologic diagnosis of STIs remains problematic in resource-limited settings, due to a scarcity of cheap and accurate diagnostic tests. Laboratory testing requires time and financial resources, as well as costly equipment, well-trained personnel, and external quality controls. A syndromic approach to the management of STIs in resource-limited settings has been developed and is a core intervention in the WHO strategy for control of STIs in regions where access to diagnostic testing is limited. Syndromic management involves the identification of a group of symptoms and easily recognizable signs (syndromes) and the provision of treatment that covers the most likely and most serious causes of the syndrome through the use of simple flowcharts.7 Syndromic management can be implemented at many levels of health care and is valid and feasible for the treatment of urethral discharge in men and of genital ulcers in men and women.123,124 HSV-2 is emerging as the most common cause of GUD in developing countries; WHO guidelines recommend the incorporation of acyclovir in the syndromic management when more than 30% of genital ulcers are caused by HSV-2.7

Syndromic management does not work as well for the management of vaginal discharge, which is poorly predictive for gonorrheal or chlamydial cervicitis. Attempts to improve the sensitivity and specificity of the algorithm by incorporating risk assessment and/or speculum exam have been unsuccessful.123,125 A study conducted among 726 women in West African countries presenting with vaginal discharge found that the prevalence of *N. gonorrhoeae* was only 1.9% and of *C. trachomatis* only 3.2%. Risk factors previously recommended by WHO were not associated with the presence of cervical infection, with the exception of the number of sex partners in the past three months. When taken together, WHO risk factors had a positive predictive value of only 6.4% for identification of cervical infections in this population.126

The effect of syndromic management on HIV transmission has been studied. Grosskurth et al127 conducted a randomized, controlled trial implementing improved syndromic management of STIs versus standard of care in six communities in Mwanza, Tanzania, and comparing HIV incidence between the groups. The Mwanza study demonstrated a 38% reduction in HIV incidence in the intervention group, with the greatest impact in women aged 15 to 24 and men aged 25 to 34. A reduction in syphilis seroprevalence and a borderline reduction in new syphilis cases and symptomatic urethritis were also observed in the intervention group, though no effect was seen on gonococcal or chlamydial infection among women receiving antenatal care.127,128
Cost of Treatment
Few studies have been done assessing the costs and benefits of treating STIs. Perhaps the most comprehensive review was published in 2006 and served as a systemic review of the costs of treating curable STIs in low- and middle-income countries. This report reviewed 53 primary studies. The median STI treatment cost was US$17.80 per treatment per person. Clinical settings serving symptomatic patients were consistently less expensive than were outreach services. Notably, services using syndromic management protocols had lower costs, and these costs decreased with scale.

SUMMARY

Key Points
- Early treatment for STIs is important. Most standard recommended regimens are effective for people living with HIV.
- Continuous access to improved STI services is likely to have greater impact on HIV transmission than an intermittent mass treatment approach to STI control.
- Affordable, effective screening strategies for cervical cancer, such as visual inspection aided with acetic acid, are sensitive and cost effective.
- Meaningful involvement of women living with HIV is instrumental in facilitating effective responses. This includes healthy living and healthy sexual activity for people living with HIV. More information can be obtained from specific publications, such as those published by the International AIDS Alliance.

Recommendations
- Systematic screening for STIs should be part of clinical evaluations for women living with HIV and should include thorough medical history taking; clinical examination; and, when resources permit, laboratory examination for syphilis, gonococcal, and chlamydial infections.
- HIV-positive women whose sexual partners are infected with STIs should be offered treatment, even if the women are asymptomatic.
- Cervical screening for STIs should be offered more frequently, using the same tests as for HIV-uninfected women.
- Health workers should be made more aware of the importance of screening for STIs in women living with HIV and of the importance of follow-up in special cases, such as the management of syphilis and PID.
- Regular and systematic screening and treatment for syphilis should be an integral part of antenatal care. This is particularly important and cost effective in pregnant women on treatment interventions for the prevention of mother-to-child transmission of HIV. Reagents and treatment to prevent congenital syphilis are cheap and affordable, even in limited-resource settings.
- More research is needed to formulate effective strategies for scaling up the provision of vaccines for the prevention of oncogenic HPV infections to prevent cervical cancer, especially among adolescents and women living with HIV.

CONCLUSION
Although STIs cause substantial morbidity and mortality worldwide, their impact is often unrecognized. Effective diagnostic tests, antibiotics for bacterial and protozoal STIs, suppressive antivirals, and vaccines against HBV and HPV are often not widely available in resource-limited settings. Syndromic management remains the core intervention for individual case management in resource-limited settings where laboratory testing is not available. Inexpensive, accurate, point-of-care tests are vital for the diagnosis of STIs that are undiagnosed or misdiagnosed by syndromic approaches, particularly in women. A public-health approach to the control of STIs is essential.
This approach should include improvement in surveillance, such as monitoring of sexual behavior and implementation of evidence-based strategies.

The prevention and care of STIs in HIV-positive women should be an integral part of comprehensive sexual and reproductive health services provided to women. The control of STIs, even among HIV-positive individuals, is feasible. Policymakers and health-care providers should be made aware of the special requirements of people living with HIV, such as regular screening for STIs and provision of information, counseling, and treatment for STIs. Pregnant women living with HIV should be provided with services for the prevention of mother-to-child transmission of both HIV and syphilis to prevent babies from being saved from HIV infection only to die from preventable congenital syphilis.


17. Witkin SS, Ledger WJ. Antibodies to Chlamydia trachomatis in sera of women with


51. McClelland RS, Sangare L, Hassan WM, et al. Infection with *Trichomonas vaginalis* increases...


110. Wingood GM, DiClemente RJ, Mikhail I, et al. A randomized controlled trial to reduce HIV transmission risk behaviors and sexually


126. Pépin J, Deslandes S, Khonde N, et al. Low prevalence of cervical infections in women with vaginal discharge in west Africa: implications...


Epidemiological data show a high burden of cervical cancer in high-HIV-prevalence settings, and cervical cancer has been designated as an AIDS-defining illness by the Centers for Disease Control and Prevention (CDC). Yet how two sexually transmitted viruses, human papillomavirus (HPV) and HIV, impact morbidity and mortality in coinfected women in resource-limited settings is virtually unknown. For instance, women living with HIV in South Africa typically present with cervical cancer 10 to 15 years earlier (between the ages of 35 to 40) than HIV-negative women, who usually present with this condition in their early 50s.1,2

With increasing access to antiretroviral therapy (ART), women living with HIV in developing countries are expected to live longer, and morbidity and mortality associated with opportunistic infections are expected to decrease. However, the burden of cervical disease is anticipated to increase in populations where Pap smear-screening programs and colposcopy (microscopic visualization of the cervix) are limited.3,4,5 Further, little is known about the epidemiology and pathology of HPV-related cervical disease in HIV-positive women in resource-limited settings.

This review is intended to update primary healthcare providers on the disease process, including the relationships between HPV and cervical cancer and between HPV and HIV; cervical cancer screening; prevention of HPV infection; and diagnosis and treatment of cervical dysplasia in HIV-positive women in resource-limited settings.

Natural Disease Process

HPV and Its Relationship to Cervical Cancer

Human papillomavirus is a DNA virus with more than 100 identified types. Between 30 and 40 types are sexually transmitted through skin-to-skin or mucosa-to-mucosa contact, leading to anogenital infections in both men and women.6

HPV is the etiological agent for cervical cancer and precursor lesions.6 The lifetime risk for HPV infection among sexually active men and women is at least 50%, and 80% of women will have acquired HPV infection by 50 years of age.7 The individual infectious nature of the various HPV types is unknown, but because of their common route of transmission, many HPV types may be transmitted simultaneously during one sexual exposure.5
Early sexual debut and having multiple sex partners increase the risk of HPV infection. Despite their potential danger, most HPV infections are transient; in a study of 608 HIV-negative college women in the United States, 91% of HPV infections cleared within two years. However, some HPV infections do evade the immune system through a complicated cascade of events, leading to a persistent infection. The natural history of cervical dysplasia is a process of gradual change once the HPV genome is integrated into the human epithelial DNA. Persistent infection of the high-risk types of HPV (16, 18, 31, 33, 35, and 45) is a crucial step in the process of cervical dysplastic changes. Worldwide, HPV types 16 and 18 account for most cervical cancers. However, one or more of these oncogenic types can be found in 90% of high-grade intraepithelial precursor lesions. The E6 and E7 proteins of oncogenic HPV types are known to facilitate the degradation of the tumor suppression proteins of p53 and retinoblastoma tumor suppression protein, respectively. With the loss of the suppression of these oncogenes, apoptosis (cell self-destruction) and cell cycle arrest is disrupted. Changes in the epithelium cells occur with the increase of the nucleus-to-cytoplasm ratio. These precursor changes often occur at the transition zone in the cervix, where the squamous epithelium meets the endocervical columnar epithelium.

Factors that increase the risk of persistent HPV infection and cell dysregulation include immune suppression; cigarette smoking; hormonal contraceptive use; and possibly other sexually transmitted infections, such as chlamydia. The development of cervical cancer can be thought of as a four-step process: (1) transmission of an oncogenic HPV type, (2) persistence of the HPV infection, (3) transformation of HPV-infected epithelial cells, and (4) loss of inhibitory cell replication control causing invasion. Interruption of any of these stages can result in prevention of cervical cancer.

Relationship between HPV and HIV

The natural history of cervical dysplasia is a process of progression or regression, partially mediated by local cervical immunity, which is still poorly understood. Clear immune markers for clearance of HPV infection have not been well defined. Because HPV infections are frequent and usually kept in a latent state by a functional immune system, they can be reactivated under immunosuppressive conditions. In HIV-positive women, the local mucosal immunity seen in cervical intraepithelial neoplasia (CIN) was associated with suppression of markers of both pro- and anti-inflammatory pathways (i.e., gamma interferon, macrophages, neutrophils, and natural killer cells) in CIN 2 or CIN 3 lesions, which was not the case for the local mucosal environment of HIV seronegative women with CIN 2 or CIN 3 dysplasia. Besides the possible increased immune-escape pathway in HIV immunosuppressed women, a direct viral-viral interaction may exist between HIV and HPV, given that both viruses infect macrophages and that expression of the HIV Tat protein might increase the expression of HPV E1 and L1 viral genes and HPV type 16 E7 transcription. It is uncertain, however, whether HIV increases the risk of HPV replication or transcription, leading to the development of more-persistent HPV infections. The effect of the systemic immune system is not well known in HIV-positive women; but in HIV-negative women in several populations, the HLA marker DRB1*1301 may be protective against cervical disease.

Many of the low-grade lesions in immunocompetent HIV-negative women will regress without treatment. However, with HIV-related immunosuppression, progression of cervical dysplasia occurs more frequently and regression decreases. One study found a significant difference in progression of cervical dysplasia in HIV-positive and HIV-negative women after only six months.
of observation. Progression of cervical dysplasia was seen in 14% of HIV-seropositive women compared with 7% in HIV-seronegative women after an abnormal smear. Regression to a normal Pap smear in six months was observed in 43% of HIV-seropositive women and 66% of HIV-seronegative women. In another study, only 45% of HIV-seropositive women had cytological regression of cervical dysplasia after a median of 2.7 years. Women whose lesions regressed were younger, had higher CD4 counts (336 cells/mm\(^3\) vs. 230 cells/mm\(^3\)), longer time on ART, and lower viral loads (4,850 copies/mL vs. 14,000 copies/mL); the regression rate in HIV-positive women was lower than the rate in HIV-negative women. In the same study, presence of HPV, irrespective of type, was associated with higher rates of lesion progression and lower rates of lesion regression. In another study, HIV viral load was not associated with lesion progression.

Studies have begun to show that HIV-positive women are presenting with cervical cancer 10 to 15 years earlier (at a median age of 35 years) than HIV-negative women. Early data are also beginning to show that the prevalence of cervical dysplasia is much higher among women in resource-limited settings and among HIV-positive women. Two studies in South Africa found low-grade squamous intraepithelial lesions (LGSIL) in 18%, high-grade squamous intraepithelial lesions (HGSIL) in 8%, and infiltrative cancer in 0.8% of the general population of women using public-sector health facilities. That study did not look at the HIV status of the source patient. In a cohort of only HIV-seropositive women, 54% were found to have abnormal cytology on their Pap smears. Two-thirds of those lesions were LGSIL and one-third were HGSIL. Those findings are at least 2 to 10 times higher than the rates of cervical dysplasia typically found in the general South African population, adding to the evidence that progression of lesions occurs more frequently among HIV-positive women and, it is believed, more rapidly. Regression of LGSIL occurs less frequently in HIV-positive women.

**Epidemiology of Human Papillomavirus**

Worldwide, HPV types 16 and 18 account for the majority of cervical cancers, and one or more of these types can be found in 90% of high-grade intraepithelial precursor lesions in HIV-negative women. Preliminary data from Brazil, South Africa, and Thailand show high rates of oncogenic HPV infection in 38.6%, 85%, and 51% of HIV-positive women, respectively. Studies conducted in Zambia found that cervical disease was present in up to 76% of all women, and 98% of HIV-positive women harbored at least one type of HPV (85% had a high-risk HPV type), with a median of four types per participant. A study in South Africa, which included 148 HIV-positive women, showed similar results, with 95% of HIV-positive women harboring HPV, a median of three HPV types per participant, and 85% of HIV-positive women with one or more oncogenic HPV types. Data from developing countries also show a large diversity of oncogenic HPV types (including 16 and 18) in addition to other types, such as 33, 35, 52, and 81. The studies from Thailand and Brazil are notable for their findings of a large diversity of high-risk HPV types, including 16 and 18, with high percentages of other high-risk types also seen (i.e., 33, 35, 52, and 81).

It should be noted that the vaccine targeting HPV types 6, 11, 16, and 18 might reduce the acquisition of infection and clinical disease caused by these HPV types in HIV-positive women in developing countries. However, with the diversity of oncogenic types seen in this population, studies are needed in HIV populations in resource-limited settings to determine the efficacy and safety of available vaccines.
Other Risk Factors for Cervical Dysplasia

The known risk factors for cervical dysplasia, besides HPV and HIV infections, are smoking, multiple sex partners, and early sexual debut. Other less well-defined but probable risk factors are associated sexually transmitted infections and the use of hormonal contraceptives. In HIV-seropositive women coinfected with HPV, the contribution of other risk factors to the development of cervical dysplasia is unknown. One study in South Africa, among a cohort of 148 women coinfected with both HPV and HIV found that only the number of sex partners was slightly statistically significant for independently increasing the risk of cervical dysplasia. Age of sexual debut, use of hormonal contraceptives, age, and use of tobacco products (including snuff—a practice of chewing tobacco seen in South African women of various tribal backgrounds) were not statistically associated with increased risk of dysplasia. More research in resource-limited settings is needed, but findings to date may imply that HIV-HPV coinfection may play a greater role in the development of cervical cancer than other traditionally known risk factors for cervical cancer.

CERVICAL CANCER SCREENING

Only one set of cervical cancer guidelines specifically targets HIV-positive women. Developed by CDC, the guidelines state that HIV-positive women should be screened every six months for two consecutive smears. If cytology results are normal for the two smears, a woman may then revert to having a Pap smear once a year. However, if one or both of the initial Pap smears is abnormal, colposcopy should be performed and then followed with a Pap smear every six months until two consecutive tests are normal. Some specialists advocate that a colposcopy be performed at the initial screening visit. Although appropriate for developed countries, these guidelines may be impossible for developing countries to follow because of inadequate infrastructure and human and financial resources. Guidelines for cervical cancer screening developed by the World Health Organization (WHO), do not account for HIV-HPV coinfection and its potential effect on cervical disease progression. WHO recommends that a woman undergo her first Pap smear at 30 years of age, followed by two more smears at 10-year intervals. Although this recommendation has been shown to reduce the lifetime risk of cervical cancer in HIV-negative women, the low frequency of screening may not be effective in preventing cervical dysplasia or cancer in HIV-positive women. A study in South Africa shows that 20% of the women who had CIN 2 or CIN 3 were 30 years of age or under, illustrating the need for much earlier screening in these HIV-seropositive women (unpublished data).

For a Pap smear, also called conventional cytology, a clinician collects endocervical cells via a brush or spatula and places the cells on a microscopic slide for cytological review. For many years, the Pap smear has been widely integrated into the public-health cancer prevention agenda in many developed countries and is credited for the reduction of cervical cancer in those countries. The cytology screening has been improved with the standardization grading of the 2001 Bethesda System (Table 1).33 Despite the success of the Pap smear in reducing cervical cancer mortality, access to this system in most resource-limited countries is limited at best. Some middle-income countries (e.g., South Africa and Brazil) are equipped to provide Pap smears, cytological review, and colposcopy in tertiary research centers but not in other areas; and in low-income countries, these procedures are not available because financial resources and trained personnel are lacking. Further research is being done to determine the best approach to providing effective, adequate screening and prevention for
Table 1. The 2001 Bethesda System Classifications

<table>
<thead>
<tr>
<th>Specimen Adequacy</th>
<th>General Categorization (optional)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfactory for evaluation</td>
<td>Negative for intraepithelial lesion or malignancy</td>
<td><strong>Results</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative for Intraepithelial Lesion or Malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organism (list organism or changes consistent with organism)</td>
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<tr>
<td></td>
<td></td>
<td>Other non-neoplastic findings (optional to report; i.e., reactive cellular changes associated with inflammation, radiation, intrauterine device, or atrophy)</td>
</tr>
<tr>
<td>Unsatisfactory for evaluation (reason specified)</td>
<td>Epithelial cell abnormality</td>
<td>Other HGSIL encompassing moderate and severe dysplasia, carcinoma in situ, CIN 2, CIN 3</td>
</tr>
<tr>
<td>Specimen rejected or not processed (reason specified)</td>
<td>Other</td>
<td>HGSIL encompassing moderate and severe dysplasia, carcinoma in situ, CIN 2, CIN 3</td>
</tr>
<tr>
<td>Specimen processed and examined but unsatisfactory for evaluation (reason specified)</td>
<td>Squamous cell carcinoma</td>
<td>Squamous cell carcinoma</td>
</tr>
</tbody>
</table>

**Source:** Adapted from Solomon et al.33
women living with HIV in settings with shortages of skilled providers and limited resources.

Visual inspection of the cervix with acetic acid (VIA) has been shown in several studies to be an effective alternative to the Pap smear in resource-limited settings. VIA is a simple procedure involving a speculum examination and a cervical swab with 5% acetic acid. Dysplastic changes on the cervix appear white in color after a few minutes of exposure to acetic acid, while the normal squamous cells remain pink and the columnar epithelium is dark pink to red. The change of color is thought to be caused by the cellular changes in the cervical squamous epithelium, which involves an increase in the nuclear proteins and cytokeratins. VIA can also be performed during menses, if the flow is not heavy. The convenience and relative simplicity of VIA makes it preferable to the Pap smear in many settings, especially because it does not require the client to return to the clinic for her results. VIA can also be performed during a routine gynecological visit, such as prenatal and postpartum care. Another advantage of VIA is that unlike the Pap smear, it does not lose sensitivity in women over 50 years of age.34

VIA has been shown to be at least as sensitive as or even more sensitive than the Pap smear but not as specific.35,36,37 A study in India reports an 88% sensitivity and a 78% specificity for VIA compared with the gold standard of colposcopy with biopsy.38 One study performed in Nicaragua shows that VIA detected up to twice as many invasive cancers but that for every diagnosis, eight false positives were identified at the referral center.39 At least two studies found that primary health-care nurses can perform this procedure, thus increasing the capacity for cervical screening in settings where most primary providers are nurses.35,36 In one study in the Philippines, women actually preferred the VIA method to the cervical cytobrush used during Pap smears. All these studies were conducted among the general population; and despite taking place in settings with a high prevalence of HIV, none of the studies looked at VIA specifically in HIV-positive women. Therefore, how HIV coinfection influences the sensitivity and specificity of VIA is unknown.

PREVENTION OF HPV INFECTION

HPV Vaccine (Preventive and Therapeutic)

Given the enormous burden of HIV-HPV coinfection, other methods for treating and preventing cervical dysplasia in resource-limited settings are needed. One possibility is the development of preventive or therapeutic HPV vaccines. Two preventive HPV vaccines have so far been approved by the U.S. Food and Drug Administration: the GlaxoSmithKline vaccine, Cervarix, which produces antibodies to types 16 and 18; and Gardasil, a new quadrivalent HPV vaccine from Merck. The quadrivalent HPV vaccine consists of viruslike particles generated by the expression of the major capsid protein L1 from HPV types 6, 11, 16, and 18, with an aluminum adjuvant. During studies of Gardasil, all women in the vaccine arm developed detectable antibody responses to the vaccine types, and the titers were substantially higher than in women who received the placebo or had a prior history of natural HPV infection. The combined incidence of persistent infection or disease caused by HPV types 6, 11, 16, and 18 fell by 90% in women receiving the vaccine compared with women who received the placebo (0.7 vs. 6.7 incidence per 100 patient-years at risk). Ten women in the placebo arm developed HPV-related diseases (seven cases of CIN and four instances of external genital lesions), and no HPV-related diseases occurred among the vaccinated women.41

Despite its effectiveness, Gardasil has not been tested in HIV-positive women or in women
residing in sub-Saharan Africa, and several questions remain:
1. Will the vaccine be effective in preventing HPV disease given the diversity of high-risk oncogenic HPV types seen in HIV-positive women?
2. Will the vaccine confer enough immunogenicity in HIV-positive women, and at what CD4 level and HIV viral load?
3. Will the vaccine be effective in the majority of women living with HIV who are already infected with more than one type of HPV?
4. Would a preventive vaccine be effective in areas where at least 80% of women are already infected with one or more types of HPV? Could this preventive vaccine improve regression and clearance of the HPV virus in HIV-positive women who were treated for their HPV, and prevent reinfection or reactivation?

One study found that in HIV-negative women, a preventive vaccine candidate (a viruslike protein to the Lp1 capsid protein AS04) was not effective in reducing HPV clearance in women already infected.42

Another HPV vaccine in trials is the therapeutic vaccine. This type of vaccine is directed at the oncogenic proteins E6 and E7 of the HPV virus and would be given to women already infected with HPV. The hope is that a vaccine directed at these proteins will block the action of the oncogenic proteins, thereby preventing progression and improving regression of cervical lesions. A therapeutic vaccine could be given after diagnosis of HPV oncogenic infection or after LLETZ (large loop excision of the transformation zone)/LEEP (loop electrosurgical excision procedure) or cone biopsies to prevent recurrence. This type of vaccine is in the early phases of testing.43,44

**Condom Use**
The effectiveness of condom use in preventing transmission of genital HPV was considered questionable until a study reported that condoms were in fact effective in reducing the spread of HPV. Despite the small numbers of participants (N=82), this study shows a decrease in the rate of genital HPV infection from 89.3 per 100 patient-years at risk in women reporting inconsistent partner condom use to 37.8 patient-years at risk in women reporting 100% partner condom use. Also, no cervical squamous intraepithelial lesions were diagnosed in the women who reported condom use with their partners compared with 14 lesions found in women whose partners did not wear condoms consistently.45 There is also evidence that consistent use of condoms increases the clearance of HPV and increases the rate of regression in HIV-seronegative women.46

The impact of condom use on HPV infection is unknown in HIV-positive women. However, abstinence from sexual activity is the only action that can completely prevent HPV transmission. The findings of some studies suggest that HPV is easily transmissible. Correlated HPV types have been found on the external genitals and cervixes of women with no history of intracoital sexual activity47; and among couples reporting monogamy, HPV infection has been reported.48,49 HPV infection, carriage, and transmission in circumcised men might be lower than in uncircumcised men, possibly because of the epithelium changes that occur following circumcision.50

**DIAGNOSIS AND TREATMENT OF CERVICAL DYSPLASIA**

**Colposcopy**
Confirmation of high-grade cervical dysplasia with colposcopic biopsy is done after a Pap smear. In expert hands, the correlation between the Pap smear and the biopsy can be as high as 90%, but correlations as low as 50% are possible when staff are inadequately trained. The cost of a colposcope without cameras varies between US$10,000
and US$15,000. Therefore, not only is colposcopy cumbersome, inefficient, and time consuming, but it also may be too expensive for use in resource-limited settings.

**Cryotherapy, LLETZ/LEEP Biopsy, and Cone Biopsy**

If the screening test and the colposcopy results are correlated, the patient is further treated and evaluated with either cryotherapy, LLETZ or LEEP biopsy, or cone biopsy. Cryotherapy can be done after the VIA procedure, during the same visit. No electricity is required for cryotherapy, but the procedure does demand a consistent supply of nitrous oxide or carbon dioxide and a low-temperature probe to freeze the epithelium changes. Cryotherapy has the drawback of not reaching lesions spreading to the endocervical canal and may not completely treat larger lesions.\(^4\)

A LLETZ or LEEP biopsy is an outpatient procedure that requires local anesthesia but can be done rather efficiently in an outpatient setting. The procedure uses a thin electrified wire to remove a sample up to 7 mm in depth from the transitional zone. Treatment failure rates can be up to 15% for the LLETZ or LEEP procedure, so follow-up screening of the patient within one year is required.\(^34,51\) However, the failure rate of the procedure among HIV-positive women in resource-limited settings according to preliminary data is roughly 50%; therefore, aggressive follow-up should occur within three to four months.\(^53-55\)

Another older modality of treatment is the cone biopsy. It is an effective mode of treatment but requires a referral to a center with a skilled gynecological surgeon, inpatient admission, and operating room availability.\(^51\)

Hysterectomy is not recommended for the treatment of cervical dysplasia. This surgical procedure is performed only when carcinoma is found in situ by the LLETZ or LEEP biopsy and the margins of the biopsy are not cleared of the pathology.\(^51\)

**Antiretroviral Therapy**

Because HPV infection is an immunomodulated disease, the more aggressive HPV oncogenic types and HGSIL are commonly seen in patients with lower CD4 lymphocyte counts. However, findings of reversal of cervical dysplasia in HIV-positive women receiving ART have been quite controversial. Some initial studies\(^52,53\) report that antiretroviral drugs (ARVs) may improve outcomes in cervical dysplasia in HIV-positive women, much as they have done in patients suffering from Kaposi’s sarcoma.\(^54\) However, some cohort studies conducted in developing countries show that ART has no effect on cervical dysplasia.\(^23,55\) One hypothesis is that the effect of ART is so variable and difficult to elucidate in cervical dysplasia and invasive cervical cancer (ICC) in HIV-seropositive women because of the multitude of oncogenic HPV types seen in these women. HPV type 16 is more elusive of the immune systems, because women infected with this HPV type develop cancer without the immunosuppression seen in HIV. However, other dysplastic changes seen with other HPV types may occur in the more immunosuppressive state seen in HIV. In a study in South Africa, 50%–70% of patients with CIN 2 or CIN 3 did not have HPV type 16.\(^56\) Changes related to other oncogenic HPV types may be more responsive to immune reconstitution. Larger prospective cohort studies need to be conducted in resource-limited settings to assess the effectiveness of ARVs in preventing cervical cancer in the large population of women with HPV-HIV coinfections.

**Other Modes of Therapy**

The potential role of micronutrients and vitamins in reducing the risk of cervical dysplasia and cancer has not been studied in HIV-positive women. Therefore, no definitive data demonstrate that
supplementation of tocopherols (vitamin E), carotenoids (vitamin A), ascorbic acid (vitamin C), and other micronutrients affect the progression or regression of cervical dysplasia. Antiviral agents such as ganciclovir and cidofovir have not shown any positive effect on the treatment of cervical dysplasia and should not be recommended.51

CONCLUSION
Because both HIV and HPV are common in many developing countries, great care, as well as further thought and research, is needed to find ways to efficiently screen and treat coinfected women. With the progressive scale-up of comprehensive HIV treatment throughout Asia, Africa, and South America, HIV-positive women will be surviving well into middle age and will therefore be at an increased risk of developing HPV-related disease. Clearly elucidating and defining the role that ART may play in the regression of cervical disease in coinfected women is crucial, yet this mode of treatment, if viable, may or may not be the best way forward in resource-limited settings. Vaccination in a preexposed population is likely the most efficient method of prevention for women in developing countries. However, for the millions of women already HPV/HIV coinfected, more research is needed into accessible, adequate, and affordable cervical dysplasia screening and treatment methods.


ANCER OF THE CERVIX IS THE second most common female malignancy in the world. Each year, more than 80% of the 493,000 new cases and 274,000 deaths associated with cervical cancer occur among women who reside in developing regions of the world, that is, sub-Saharan Africa, Latin America, the Caribbean, south-central Asia, and Southeast Asia. In these resource-limited settings, cervical cancer accounts for 15% of all female malignancies and is a significant cause of years of life lost. In a recent analysis of cancer and years of life lost conducted by Yang et al., cervical cancer was found to be responsible for 2.7 million (age-weighted) years of life lost worldwide. Furthermore, it was the largest single cause of years of life lost from cancer in the developing world, making a greater contribution than such diseases as tuberculosis, maternal conditions, or AIDS. Of all annual global deaths from cervical cancer, 20% occur in sub-Saharan Africa, a region of the world where this preventable disease continues to be the number one cause of cancer-related death among women. According to the database of the International Agency for Research on Cancer (IARC), cervical cancer incidence and mortality in the eastern African region of sub-Saharan Africa are the highest on the African continent and rank among the highest in the world, led by Tanzania (68.6 and 55.6 per 100,000, respectively), Zambia (53.7 and 44.0 per 100,000), and Zimbabwe (52.1 and 43.1 per 100,000).

Sub-Saharan Africa is also the epicenter of the global HIV/AIDS crisis, particularly as it relates to women. According to the 2006 Joint United Nations Program on HIV/AIDS / World Health Organization (WHO) report, of the 30.5 million people in the world living with HIV two-thirds reside in sub-Saharan Africa; of the 17.3 million women in the world living with HIV, approximately 75% (13.2 million) reside in sub-Saharan Africa.

Given the excess risk of cervical cancer in women with HIV/AIDS, all resource-constrained

Building a Cervical Cancer Prevention Program into the HIV Care and Treatment Infrastructure in Zambia

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countries of the world which suffer excess burdens of both diseases should become focal points for intense cervical cancer prevention efforts. An example is Zambia, one of the world’s poorest nations, which has both a high prevalence of HIV (adult HIV prevalence 16.5%) and a cervical cancer incidence that is the second highest in Africa and the sixth highest in the world. It is estimated that one million Zambians are currently living with HIV, more than 50% of whom are women.

CERVICAL CANCER AND HIV
Cervical cancer is an AIDS-defining illness. In Western Europe and the United States, record linkage studies of population-based registries of people diagnosed with both HIV/AIDS and cancer have estimated excessive cervical cancer risk for people living with HIV, as compared to the general population. In sub-Saharan Africa, where cervical cancer incidence is among the highest in the world, epidemiological studies of the relationship between HIV and cervical cancer risk have been controversial. While some studies have shown no excess risk for cervical cancer in the setting of HIV infection, others have indicated such a link. Given the present high prevalence of HIV in sub-Saharan Africa and the association of HIV infection with the development and progression of cervical intraepithelial neoplasia (CIN), even small increases in cervical cancer risk may have significant public-health implications. A recent study of cervical cytology among HIV-positive women in sub-Saharan Africa revealed an excessively high prevalence of high-grade squamous intraepithelial lesions (HGSIL). In that study, which the authors performed in Zambia, the majority of women were first-time seekers of HIV care and treatment and were severely immunosuppressed (mean CD4 count 165 cells/µL). While 33% had cytologic evidence of HGSIL, 20% had cytologic findings compatible with squamous cell carcinoma. Such results may even suggest an impending epidemic of cervical cancer among severely immunosuppressed HIV-positive women in resource-limited settings of the developing world, where cervical cancer screening is not readily available.

CIN AND HIV
HIV infection and HIV-induced immunosuppression are markers of CIN, the precursor to cervical cancer. In HIV-positive women, CIN is more prevalent, has a higher incidence, progresses more rapidly, and is diagnosed at a higher grade than in HIV-uninfected women. The strength of these associations increases with the degree of immunosuppression, which is possibly explained by the following biological mechanisms:
- Enhancement of the effectiveness of human papillomavirus (HPV) proteins, and possibly cell cycle disruption, by HIV proteins (e.g., Tat-1)
- Dysregulation of the cellular arm of the local and systemic immune systems by HIV, worsening the natural course of CIN
- An increase in target cells and proinflammatory cytokines at the site of HPV-induced CIN lesions, which in turn increases the probability of heterosexual acquisition of HIV and subsequent alteration of the progression rates of HPV and CIN
- Diminished rates of clearance of HPV in HIV-positive women

CERVICAL CANCER IN THE ERA OF ANTIRETROVIRAL THERAPY
Until recently, HIV-positive women living in developing countries had a shorter than average life expectancy, making it unlikely that invasive cervical cancer would have time to develop from a persistent infection with oncogenic HPV, a process that can take from 10 to 20 years. In other words, it is supposed that HIV-positive women in these settings died as a result of AIDS-related complications
and other associated conditions before they could develop invasive cervical cancer.\textsuperscript{39,40} This theory is supported by the results of a recent preliminary report\textsuperscript{41} on the natural history of CIN and HPV in a cohort of 400 HIV-positive South African women. All women were antiretroviral therapy (ART) naive at baseline. During the first 18 months of the study, almost 20% of the participants died. Their median age was 28 years, almost 25 years younger than the mean age at which HIV-negative South African women are diagnosed with cervical cancer.\textsuperscript{42} Predictors of death were median values of CD4 counts and HIV viral loads.

In a recent report\textsuperscript{40} from the U.S. Census Bureau, the life expectancies of individuals living in Zambia, Angola, and Swaziland, from the time of birth, were reported as 38 years, 37 years, and 32.5 years, respectively. Life expectancy rose to 55 years for Zambian men and women when deaths from AIDS were removed from the calculations. A 2006 epidemiologic study\textsuperscript{49} performed in KwaZulu-Natal, the epicenter of South Africa’s HIV/AIDS pandemic, revealed an inverse relationship between HIV/AIDS mortality and invasive cervical cancer prevalence over two time periods. Supporting evidence indicated this was due to competing mortalities related to HIV/AIDS-related illnesses.

Recent efforts have made ART available on a scale unthinkable even a few years ago. Through efforts such as the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR)\textsuperscript{45} and the Global Fund to Fight AIDS, Tuberculosis and Malaria, there has been a massive scale-up of HIV treatment and care in developing countries. As a result of this increased access to affordable and effective therapy for both HIV and HIV-related opportunistic infections, the lives of HIV-positive women living in these countries may be prolonged. However, living for longer periods of time in immunocompromised or partially immunocompromised states potentially puts HIV-positive women on ART at increased risk of prolonged exposure to oncogenic HPV, the viral progenitor of cervical carcinogenesis.\textsuperscript{38} Consequently, the early detection and treatment of HPV-induced cervical cancer precursors is of increasing importance to prevent cervical cancer deaths in this very high-risk category of women.

**METHODS**

The discussion that follows outlines the authors’ experiences establishing Zambia’s first single-visit “see and treat” cervical cancer prevention program. This program was designed as a fully integrated component of existing PEPFAR-funded HIV care and treatment services within the country.

**Choosing the Proper Screening Test**

One of the major challenges we initially faced in setting up our cervical cancer prevention program in Zambia was the selection of a screening test that would be effective yet appropriate for our setting. Cytology, the screening test most commonly used in developed countries, requires multiple visits by clients, screening at regular intervals, and sufficient laboratory infrastructure, including cytologists and pathologists. In Zambia, medical and technical resources are scarce (i.e., there is currently no formally trained and certified cytotechnologist, there is only one full-time pathologist at the university, and the national physician density is only 0.12 physicians per 1,000 population).\textsuperscript{45} These and other factors led us to conclude that the main emphasis of our program should be placed on the extent of screening coverage rather than on the frequency of examinations. A highly specific screening test such as cytology, while useful in settings where there is low disease prevalence, is not the most useful test for countries like Zambia that have high disease prevalence. HPV DNA testing has gained popularity in the United States and Western Europe. However, the present cost of the test, its
laboratory-based nature, the necessity for patient recall, and the test’s relatively low specificity make it inappropriate for conditions such as those found in Zambia.

Over the past 10 years, unaided visual inspection of the cervix following the application of dilute (3%–5%) acetic acid (VIA) has been proposed as a promising alternative to the Pap smear, particularly in settings with scarce resources. Its sensitivity is greater than that of the Pap smear, and it is cheap, easy to learn, simple, safe, efficacious, acceptable, real-time in nature, and easily adaptable for use in developing countries. VIA has been recently shown to significantly reduce the incidence of CIN and cervical cancer as well as the mortality rates of the latter in developing-country settings. However, despite its many positive attributes, VIA has several serious shortcomings that need to be addressed before its performance can be optimized:

- Low specificity, most commonly due to the inability of VIA to distinguish between some forms of dysplasia and acetowhite, benign “look-alike” entities (e.g., immature squamous metaplasia, acanthosis, severe cervicitis, glandular hyperplasia, cervical hyperplasia, keratosis, etc.), which can turn white when exposed to dilute acetic acid (i.e., acetowhite).
- Limitations in delineating the morphologic characteristics used to determine whether acetowhite cervical lesions are potentially dysplastic or not (e.g., sharpness of the borders between acetowhite and normal epithelium, degree of opaqueness, lesion size, and lesion location in relationship to the squamocolumnar junction).
- The inability to consistently visualize abnormal vascular architecture that is often compatible with high-grade lesions or invasion (e.g., coarse punctations, mosaicism, atypical blood vessels).
- The difficulty of performing quality control, monitoring and evaluation performance measures (quality of VIA services), and assessment of appropriateness of decisions made by providers, outside controlled settings.
- The requirement of an on-site clinic visit by a consultant, and possibly a repeat clinic visit by the client, if the primary screener deems the VIA result “indeterminate.”

While colposcopic magnification and colposcopy provide many of the solutions to the aforementioned shortcomings of VIA, their costs and training requirements are prohibitive, making them unsustainable in resource-limited settings. For this reason, we chose to use VIA and adjunctive digital cervicography when establishing Zambia’s first single-visit “see and treat” program in January 2006. Digital cervicography was selected as an adjunct because of its low-tech nature, simplicity, reproducibility, availability, and ability to be used as a tool for (1) assessment of provider decision-making skills, (2) continuing education of providers, (3) education of patients, (4) distance consultation, (5) record keeping, (6) global wireless communication, and (7) improvement of the sensitivity and specificity of VIA.

“See and Treat”
VIA is based on the white appearance of dysplastic cervical epithelium after exposure to dilute 3%–5% acetic acid (vinegar) for two to three minutes. The mechanism underlying the change is thought to be secondary to acetic acid’s dehydrating effect on cellular cytoplasm and its ability to coagulate cellular proteins, the latter of which are usually found in larger amounts in dysplastic epithelium. The result is less transmission and greater reflection of incandescent light off the surface of dysplastic epithelium, recorded as a white appearance to the human eye. The establishment of “see and treat” cervical cancer prevention programs in developing countries, which use specially-trained nurses and paramedical workers to screen with VIA and treat...
with cryotherapy while triaging complicated cases for expert evaluation by consultants, is particularly beneficial given the chronic shortage of highly skilled medical manpower in such settings. In the very near future, it may be possible to use a low-cost, rapid HPV DNA test as a screening modality. Even so, some form of visual assessment of the cervix will still be necessary in order to characterize HPV-positive lesions and make appropriate treatment decisions.

**Training**

All providers were licensed Zambian nurses or nurse-midwives who were trained to perform VIA followed immediately by digital cervicography and cryotherapy. Nurses were chosen as the program’s primary providers because they are in large supply in Zambia and most are familiar with performing pelvic exams and functioning independently in the clinic setting. Providers initially attended a three-day didactic training workshop on cervical cancer prevention, which included the following topics:

- Embryology, anatomy, and physiology of the female reproductive tract
- Epidemiology and natural history of cervical carcinogenesis
- HIV and cervical carcinogenesis
- Cervical cancer screening methods: cytology, VIA, HPV DNA testing, and digital cervicography
- Treatment of CIN: cryotherapy, LEEP (loop electrosurgical excision procedure), cold-knife conization (benefits, side effects, and complications of each)
- Cervical cancer staging and treatment
- The potential utility of the HPV vaccine in developing nations
- Syndromic treatment (WHO) of pelvic infections
- How to educate the community about cervical cancer screening

Following didactic training, nurses spent eight weeks in clinics gaining hands-on experience in VIA, digital cervicography, cryotherapy, and indications for referral, initially under the guidance of a gynecologist. At the end of the eight-week practicum, each nurse-in-training had successfully performed a minimum of 100 visual examinations, 100 digital photographs, and 35 cryotherapies. The first group of trained nurses was used to train subsequent groups of nurses, with monitoring by gynecologists (i.e., the training-of-trainers model).

**Screening and Treatment Protocol**

VIA was performed by applying 5% acetic acid to the cervix for two to three minutes, after which time the cervix was immediately inspected with the naked eye with the aid of a gooseneck halogen lamp. After manually recording results by drawing on a diagram of the cervix, the cervix was again washed with 5% acetic acid for two to three minutes, after which time a digital photograph (cervigram) was taken. The digital camera was a handheld, battery-operated model outfitted with a macro conversion lens (10x zoom), adapter tube, and automatic flash. Visualization of the cervix on a television or laptop monitor was used to focus the image prior to taking the photograph.

The still photograph of the cervix was immediately uploaded onto a laptop or television monitor, magnified 30x and rotated 360 degrees to better characterize the lesion’s extent, thickness, margins, vascular patterns, and vicinity to the squamocolumnar junction. Nurses then used the cervigram to explain the findings to the patient.
Cryotherapy was performed if there was, at a minimum, an acetowhite lesion with well-circumscribed borders within the transformation zone and originating at the squamocolumnar junction. Cryotherapy was performed using the 3-5-3 minute (freeze-thaw-freeze) technique with compressed nitrous oxide gas. Patients were extensively counseled regarding post-cryotherapy care and informed about the warning signs of infection, serious bleeding, and so on. They were also given a pamphlet in their native language explaining these issues and another pamphlet specifically designed for their sexual partners. They were then scheduled for return visits after 1, 6, and 12 months.

**Referrals**

Patients with lesions judged by nurses to be too complex for treatment with cryotherapy were referred for histologic evaluation to the Cervical Cancer Prevention Outpatient Unit at the University Teaching Hospital of Zambia, where three Zambian gynecologists and a nurse were trained to perform cervical biopsy, LEEP, and exam under anesthesia (EUA). Criteria established for referral were as follows: (1) large-volume lesion (occupying three or more quadrants of the transformation zone or unable to be completely covered by the largest available cryoprobe), (2) extension into the endocervical canal beyond visualization, (3) suspicion of invasion (fungating, exophytic, ulcerative, necrotic, extremely raised, contact bleeding, abnormal vasculature), or (4) persistence at 6 or 12 months post-cryotherapy.

**Quality Control and Nursing Education**

Once a week, all nurses were required to participate in a digital cervicography quality-control meeting. During the meeting, they displayed the cervigrams from all patients they had examined during the prior week on a large screen (using an LCD projector), and explained or defended their management decisions. Any discrepancies between a nurse's management decision and that of the expert consultant in attendance were assessed and judged by the consultant. A cervigram-histology correlation review session was included in the weekly meetings for the purpose of increasing nurses’ understanding of the myriad of visual (cervicographic) manifestations of different types of underlying histology (e.g., normal/benign [cervicitis, squamous metaplasia, nabothian cysts, endocervical polyp, glandular hyperplasia, inflammation, cervical hyperplasia, keratosis, etc.], CIN1/HPV, CIN2, CIN3, microinvasive cancer, and invasive cancer).

**Distance Consultation**

Nurses functioned independently during daily operations in the clinic; cervigrams about which they were uncertain were classified as “indeterminate.” All such cervigrams were immediately uploaded onto a laptop computer and instantly transmitted to the on-call consultant for review (i.e., digital telecervicography), followed by either a text message or cell phone call indicating that a consultation was being requested. Distance consultations were performed while patients were still in the clinic and, in some cases, still on the examination table. If no computer or cell phone connection was available or the wireless communication system was malfunctioning, nurses downloaded “indeterminant” cervigrams onto flash drives and transported them to the consultant by car.

**Record Keeping**

Each nurse’s cervigrams were uploaded onto the hard drive of his or her laptop computer and maintained as permanent patient records. Cervigrams were backed up on the hard drive of a desktop computer on a regular basis.

**Initiation of the Program**

Most developing countries lack population-based cervical cancer screening programs of any kind.
Common reasons often cited are extreme poverty, health-care issues with higher priorities (e.g., malaria, tuberculosis, HIV), shortages of material resources, lack of trained manpower, a dysfunctional health-care infrastructure, and disenfranchisement of women (Sten Vermund, MD, personal communication, December 2007).

We found that one way to cross these long-standing barriers was to integrate cervical cancer prevention services into PEPFAR-funded HIV care and treatment services. In Zambia, a major partner in the Zambian government’s effort to provide PEPFAR-funded HIV care and treatment services is the Center for Infectious Disease Research in Zambia (CIDRZ), a nongovernmental organization (NGO) formed jointly by the Zambian Ministry of Health and the University of Alabama at Birmingham. HIV care and treatment services facilitated and managed by CIDRZ are tightly integrated into Zambian government-operated public health clinics. By collaborating with CIDRZ and modeling our cervical cancer prevention services after its PEPFAR-funded HIV care and treatment services, we were able to successfully initiate a cervical cancer prevention program in Zambia. CIDRZ provided the funding and much of the strategic guidance for the development of the cervical cancer prevention program. Another major collaborating partner in this effort was the Lusaka Urban District Health Management Team, which operates all public health clinics in Lusaka, and the University Teaching Hospital of Zambia (UTH), the referral site for all patients within Lusaka with complex cervical lesions that need further evaluation. Cohesive linkages between collaborators permitted the sharing of financial resources, infrastructure, manpower, and information technology while allowing female clients access to much-needed specialized preventive health-care services. Such linkages and subsequent resource sharing considerably lowered start-up and maintenance costs while facilitating rapid program initiation and expansion.

During the first year of our program, we established six cervical cancer prevention clinic sites. An additional eight were established in the second year, for a total of fourteen. We also established a Cervical Cancer Prevention Outpatient Unit on the campus of the University Teaching Hospital. While HIV-positive women have remained our target population, we were very careful not to stigmatize the program. All cervical cancer prevention examination rooms were physically located a distance away from ART clinics, and screening services were offered to all women regardless of their HIV status.

Community Sensitization
As we neared the completion of the eight-week nurse training program, we contacted key stakeholders in the community and explained the problem of cervical cancer in their communities; its causes; the synergistic relationship between HIV, HPV, and cervical cancer; and the importance of screening and treatment. Our discussions were thorough and open, had no time limits, and incorporated the use of pictures, diagrams, and PowerPoint presentations. All meetings were held in community centers within the communities where new clinics were to be established. Light refreshments were served after the meetings, and attendees from the community were reimbursed for their travel expenses. Meetings were not segmented by gender, age, ethnic group, or any other characteristic. Presentations were led by a gynecologist from either Zambia or the United States. Educational material in the appropriate languages was distributed after each meeting, and the presenter always stayed as long as necessary for questions and answers.
Clinic Staff Education
Within two weeks following the community sensitization meeting, a similar educational meeting was held for the entire staff of the government-operated clinic in which the cervical cancer prevention services were to be located. This meeting was always organized through the “nurses in charge” of the clinics, due to their immense responsibility and tremendous influence, both in the clinic and community. The staff education consisted of a lecture on the subject of cervical cancer prevention. Topics included in the lecture were as follows:
- What is cancer?
- Basic anatomy of the female reproductive tract
- Cancer of the cervix—its origin and natural history
- Epidemiology of cervical cancer globally, in resource-constrained developing nations, in sub-Saharan Africa, and in Zambia
- Risk factors for cervical cancer, with emphasis on HIV
- How cervical cancer can be prevented—primary prevention (HPV vaccine, lifestyle changes) and secondary prevention (screening—HPV DNA testing, cytology, VIA, digital cervicography)
- HPV in men
- Cervical cancer screening in Zambia
- The role of the clinic staff in promoting cervical cancer prevention
- Questions and answers

Continuing Community Sensitization
Peer Educators
An essential component of community education and encouraging clients to be screened involved peer educators (community-based health promoters). It is important to select peer educators from the community where the clinic will be located. Their knowledge of the local environment increases their overall effectiveness as community educators and client advocates. Living in the community that surrounds the clinic also increases their availability to friends and neighbors who may have questions about screening and prevention. Several times a day, peer educators talked with groups of people in the community as well as potential clients who were sitting in waiting rooms of HIV care and treatment sites and other medical clinics. Their activities included the distribution of educational pamphlets in the clinics and the surrounding community. When nurse-midwives became very busy, peer educators helped administer intake questionnaires to clients, particularly those unable to read and/or write. For each of our clinic sites, we hired two volunteer peer educators who receive monthly reimbursements for travel and other work-related expenses. It is important to note that in resource-limited settings such as Zambia, where unemployment rates are extremely high, volunteers often consider their positions as actual jobs, as this may be their single or major source of income.

Drama Groups
Community-based drama groups created skits using key messages about cervical cancer and HPV, as well as announcing the availability of new screening and treatment facilities. All members of our cervical cancer team had input into the development of the content and method of delivery of the skits. Drama performances were held within the various communities once per quarter. Peer educators from the respective clinics were always in attendance at the drama group sessions in order to answer questions from members of the community.

Radio
Public radio spots permit information sharing about cervical cancer as well as describing the screening process. Any member of the cervical cancer team may appear as a guest, but the personal perspectives of women who have been screened and of clinic nurses have been especially
Effective. If the program is a call-in talk radio show, listeners can ask questions, increasing the interactive nature of the exchange. Radio often reaches a wide audience in places where people do not own televisions or have access to newspapers and educational brochures.

**Television**

In those areas where many people have televisions, it can be helpful to request a spot on a health education program. Many news stations have short health segments from time to time, so it can help to contact the news stations with information about the services being offered.

**EARLY OUTCOMES**

Between January 2006 and October 2007, we established 14 prevention sites in outlying government-operated public health clinics and a modern outpatient evaluation center (Cervical Cancer Prevention Outpatient Unit). During this 22-month period, 8,823 women were screened (Figure 1). Their mean age was 33.4 years (standard deviation ±9.4) and their median age was 32 years (interquartile range: 26–39). VIA test results were recorded and positive in 51% of women screened and negative in 44% (Figure 2, next page). Fifteen specially trained nurses independently managed 95% of clients in the outlying clinics and referred the remaining 5% for further evaluation. Four physicians managed the outpatient evaluation center, performing punch biopsy or LEEP, the latter with minimal intra- and post-operative complications.

**Interpretation of Early Outcomes**

Although our cervical cancer screening program targeted HIV-positive women, it had the collateral
women with high-grade or severe cervical cytological abnormalities (OR 8.0; 95% CI, 1.7-37.4; \(P=0.008\)). HPV viral diversity in high-grade lesions and squamous cell carcinoma on cytology suggests that vaccines based on HPV 16 and 18 may not be adequately polyvalent to induce protective immunity in this population. Our results add to the findings reported in a recent meta-analysis of HPV types among HIV-positive women\(^{60}\) and the recent data from diverse international settings that reflect the increased preponderance of HPV types other than 16 or 18 among HIV-positive women.\(^{61-64}\)

If cross-reacting immunity is not induced across viral types by existing vaccines, this will limit vaccine efficacy in immunosuppressed women in developing countries where prominent high-risk HPV types may be other than 16 and 18. However, these findings in Zambia may not be generalized to all developing countries. The differences in prevalence and diversity of HPV genotypes in HIV-positive women from different geographic origins can perhaps be explained by their differing behavioral, nutritional, and socioeconomic

**WILL THE HPV VACCINE WORK IN AFRICA?**

We recently screened 145 HIV-positive, nonpregnant women at a tertiary care center in Lusaka, Zambia.\(^{59}\) Liquid-based cytology and HPV genotyping with PGMY09/11 biotinylated primers (Roche Linear Array HPV genotyping test) maximized sensitivity of cytology and HPV assessments. Among high-risk types, HPV 52 (37.2%), 58 (24.1%), and 53 (20.7%) were more common overall than HPV 16 (17.2%) and 18 (13.1%) in women with HGSIL or squamous cell carcinoma on cytology. High-risk HPV types were more likely to be present in women with CD4 cell counts <200 cells/\(\mu\)L (OR 4.9; 95% CI, 1.4-16.7; \(P=0.01\)) and in

![Figure 2. HIV status/VIA test results](image-url)
CONCLUSION

In Zambia we have successfully created, rolled out, and scaled up a single-visit “see and treat” cervical cancer prevention intervention using the infrastructure previously established by a successful HIV care and treatment program (CIDRZ). Following the HIV care and treatment program’s model of health-care service delivery, we tightly integrated and linked our cervical cancer prevention services to government-operated public health clinics, placed the primary responsibility for screening and treatment in the hands of nonphysicians (nurses), and made liberal use of community-based health promoters (peer educators) to educate the community. The method of screening we chose to use was VIA and adjunctive digital cervicography. The latter was used to provide visual documentation for medical records, a measure of quality control,
patient and nursing education, and a form of wireless, digital distance consultation (telecervicography). Trained nurses bore the major responsibility for screening, treatment (cryotherapy), and referral for physician evaluation, with backup from a minimal number of physician consultants. A Cervical Cancer Prevention Outpatient Unit was created to manage referrals.

Using all these elements, we built—from the ground up—a thoroughly modern but practical cervical cancer prevention infrastructure that supported and promoted the development of innovative approaches that allowed us to bypass many of the historic barriers to cervical cancer prevention in resource-limited settings (e.g., shortages of highly skilled medical specialists such as gynecologists, cytologists, etc.). Integrating our prevention program into the preexisting HIV care and treatment program infrastructure facilitated a rapid initiation, rollout, and scaling up of our services. Digital-based visual imaging (digital cervicography) provided the tool necessary for training, continuing education, monitoring and sustaining of provider skills, quality control, distance consultation, and education of patients. We recently screened our twenty-five-thousandth patient (in approximately three years), opened our first clinics in rural provinces of Zambia, and assisted in the development of sites in other African countries (Cameroon, South Africa, Botswana) and China. The major challenges we now face are sustainability and innovative adaptation of this low-tech (VIA) / high-tech (digital cervicography and Internet) / high-touch (peer educator) hybrid form of community-based cervical cancer prevention in the face of increasing demand for our services. This form of electronic Cervical Cancer Control (“eC3”) represents a new paradigm that has the inherent flexibility to function in low-resource environments and yet take advantage of ultramodern means of communication which are now rapidly expanding across the developing world.
REFERENCE LIST


PREVENTION AND MANAGEMENT OF TUBERCULOSIS
TUBERCULOSIS (TB) IS THE SECOND leading cause of infectious disease deaths worldwide after HIV/AIDS\(^1\) and the leading cause of death from a curable infectious disease.\(^2\) Since 2003, the number of new TB cases per capita has stabilized in the European region and fallen in five World Health Organization (WHO) regions, with the exception of African countries with low HIV prevalence.\(^3\) In 2006, in the sub-region of Africa with high HIV prevalence, both the annual change in TB incidence and the change in HIV prevalence were falling (see Figure 1). In that same year, there were a total of 9.2 million new cases of TB globally, with 1.7 million resultant deaths. Of these, 700,000 cases and 200,000 deaths were among those living with HIV. It is estimated that 31% of deaths associated with TB occur in Africa, despite the continent having only 11% of the world’s population.\(^3,4\)

Much of the increase in TB infection seen since 1980 is a result of the spread of HIV, especially in eastern and southern Africa, where between 34% and 70% of TB patients are also coinfected with HIV.\(^2,5\) This increase is especially pronounced in countries with generalized HIV epidemics (i.e., where antenatal HIV prevalence is greater than 1% in urban areas).\(^5,6\)

The African region has the highest TB case notification rate in the world, at 356 per 100,000 population.\(^2\) In the six southern African countries with HIV prevalence of over 20% in the adult general population, TB case notification rates are 461 to 719 per 100,000 population (compared with the U.S. rate of 5 per 100,000).\(^4\) In African populations, TB incidence is eight times higher among those who are HIV-infected than among those who living with HIV.\(^2\) HIV-related TB is now acknowledged as one of the four recognized TB epidemiological patterns and is the primary TB challenge in Africa, causing immense strain on the delivery of TB control programs throughout the continent.\(^4,7\)

TB-HIV COINFECTION

HIV infection is a significant risk factor for the development of TB. As HIV-related immune suppression progresses, HIV-infected individuals with latent TB infection (LTBI) are 20 times more likely to progress to active TB disease than those who are HIV-uninfected.\(^5,6\) To illustrate this point, the lifetime risk of developing TB in HIV-negative individuals is 10%, while in HIV-positive individuals this risk increases to 5% to 10% per year\(^5\) (see Figure 2).
Figure 1. Time trends in estimated TB rates and the annual change in incidence rates in the African subregion, based on low and high HIV prevalence settings

Source: WHO3
Figure 2. Natural history of *Mycobacterium tuberculosis* infection in HIV-infected and uninfected individuals

Source: Sharma et al
HIV-infected patients with TB are less infectious than HIV-negative individuals because they tend to have fewer bacilli in their sputum and a shorter duration of infectiousness due to more rapid disease progression and higher mortality. At the same time, HIV-infected patients are highly susceptible to TB acquisition from HIV-negative patients, who have a longer period of infectivity and a higher smear-positive rate. Thus, despite recent declines in HIV prevalence, the driving force behind the TB epidemic in Africa is still the high incidence rate of TB in people living with HIV.

A high index of suspicion is required to diagnose TB in HIV-infected patients, as they may not present with respiratory symptoms but rather with weight loss and fever. HIV-infected patients also often present with atypical symptoms. TB has been isolated from patients with short duration (i.e., less than two weeks) of cough, acute pneumonia, febrile illness, and diarrhea. In various African countries, TB was detected at autopsy in up to 47% of cases but diagnosed antemortem in only half. As an opportunistic infection, TB can present at any level of CD4 lymphocyte count. Experience in sub-Saharan Africa in the 1990s showed that most people presenting for care with HIV-associated pulmonary TB (PTB) had CD4 counts ranging from 250 to 500 cells/mm³. However, recent data suggest that patients are now presenting with more advanced immune suppression; the median CD4 count of 2,232 TB patients with PTB and/or extrapulmonary TB (EPTB) enrolling in antiretroviral therapy (ART) clinics in Lusaka, Zambia, was 123 cells/mm³ (interquartile range 61-195). Studies in Malawi and Zambia showed that 80% to 90% of patients with previous or active TB were eligible for ART. In Lusaka, Zambia, 83% of TB-HIV coinfected patients undergoing diagnostic counseling and testing at TB clinics had CD4 counts of less than 350 cells/mm³, and 75% of TB patients enrolling in HIV care and treatment had CD4 counts of less than 200 cells/mm³.

The clinical presentation of TB in HIV-infected individuals depends on the level of immune dysfunction; those with more intact immune systems (i.e., CD4 counts greater than 200 cells/mm³) typically present with more classic signs and symptoms of post-primary TB (i.e., pulmonary disease with cough, sputum production, hemoptysis, chest pain, and upper lobe cavitation). Those with CD4 counts of less than 200 cells/mm³ are more likely to present with EPTB (i.e., hilar and mediastinal adenopathy, and miliary TB). EPTB is a WHO stage IV diagnosis, and these patients have a high risk of disseminated disease and death. In non-HIV-uninfected patients, 80% present with PTB and 20% with EPTB, while in HIV-infected patients, this proportion changes to 30% with PTB alone, 20% with EPTB alone, and 50% with both PTB and EPTB (see Figure 2).

Prompt and accurate diagnosis of TB in coinfected patients is critical to (1) assess the need for co-treatment with anti-TB and antiretroviral (ARV) drugs, (2) reduce the incidence of immune reconstitution inflammatory syndrome (IRIS), (3) improve treatment outcomes, (4) reduce nosocomial spread, and (5) promote timely initiation of appropriate prophylaxis against opportunistic infections. Patients enrolling for HIV care and treatment represent a unique opportunity to screen, diagnose, and treat TB in a high-risk population. Also, HIV screening in TB clinics is a critical intervention that provides coinfected patients with access to HIV counseling and testing. However, inconsistent screening and limitations in the existing TB diagnostic technology (e.g., sputum smear, chest radiography, and culture) result in many TB cases among HIV-positive adults remaining undiagnosed, especially in sub-Saharan Africa.
PTB IN HIV-INFECTED PATIENTS

Presentation and Diagnosis
In the past, a cough lasting at least three weeks was the minimum symptom duration for considering a PTB diagnosis. However, recent studies suggest that a shorter duration of cough can signify TB in HIV-infected patients. WHO currently recommends investigation for TB among those with a cough of more than two weeks in duration (see Figure 3).

The most important nonrespiratory symptoms to signal TB investigation are persistent fever, unexplained weight loss, severe undernutrition, suspicious nodes, or sweats. Other respiratory symptoms include chest pain, hemoptysis, and shortness of breath. Systemic symptoms include fatigue, loss of appetite, and secondary amenorrhea (see Table 1).

Sputum smear microscopy by the Ziehl-Neelsen method is the primary TB diagnostic technology used in sub-Saharan Africa. Although highly

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Late HIV Infection (CD4 &lt;200 cells/mm³)</th>
<th>Early HIV Infection</th>
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</thead>
<tbody>
<tr>
<td>Pulmonary-to-extrapulmonary disease ratio</td>
<td>50:50</td>
<td>80:20</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Often resembles primary TB</td>
<td>Often resembles post-primary TB</td>
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<tr>
<td>Chest radiograph</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Intrathoracic lymphadenopathy</td>
<td>Common</td>
<td>Rare</td>
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<tr>
<td>Lower lobe involvement</td>
<td>Common</td>
<td>Rare</td>
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<tr>
<td>Cavitation</td>
<td>Rare</td>
<td>Common</td>
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<tr>
<td>Sputum smear positivity</td>
<td>Less common</td>
<td>Common</td>
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<tr>
<td>Adverse drug reactions</td>
<td>Common</td>
<td>Rare</td>
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<tr>
<td>Relapse after treatment</td>
<td>Common</td>
<td>Rare</td>
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</tbody>
</table>

Source: Sharma et al

Figure 3. TB screening questions in HIV-positive individuals
Source: Adapted from Ministry of Health, Zambia

Table 1. Clinical Presentation of TB in HIV-Infected Patients
specific, smear microscopy is technically limited, with a sensitivity of 50% to 60%, especially in patients with low concentrations of mycobacteria (as is commonly the case in HIV-positive individuals).\textsuperscript{21,22} Thus, the usefulness of smear microscopy is relatively limited in high-prevalence settings such as sub-Saharan Africa, where WHO estimates that only 54% of smear-positive cases are detected.\textsuperscript{23} The quality of sputum microscopy is further limited by inadequate sputum collection, storage, and staining, as well as reading errors\textsuperscript{24} associated with heavy workloads and staff shortages, since the effectiveness of sputum microscopy is highly dependent on the diligence of the microscopist and time spent per smear.\textsuperscript{25} In a review of 15 studies, the proportion of smear-negative results in HIV-infected patients ranged between 24% and 61%.\textsuperscript{24} Despite these limitations, sputum smear microscopy is still the first step in the diagnosis of patients with suspected TB, pending new TB diagnostics appropriate for resource-limited settings.

The technique used for sputum collection is critical to improving diagnostic yield (see Box 1). At least two specimens should be examined for acid-fast bacilli (AFB), with one specimen produced in the early morning after an overnight sleep.\textsuperscript{17,20} A smear-positive TB case in an HIV-infected patient (or a patient with strong clinical evidence of HIV infection) is defined as a case with at least one sputum smear positive for AFB (see Figure 4). These patients require immediate referral to the national TB program for directly observed therapy (DOT) and follow-up.
Figure 4. Algorithm for the diagnosis of TB in ambulatory patients

Source: Adapted from WHO17
Approach to Smear-Negative PTB

Smear-negative PTB in HIV-infected patients (or patients with strong clinical evidence of HIV infection) is defined as symptomatic illness with at least two negative smears for AFB and TB indicated by chest X-ray (CXR) abnormalities consistent with active TB and a decision by a clinician to treat with a full course of anti-TB medications or a sputum culture positive for Mycobacterium tuberculosis (MTB). HIV-infected patients with smear-negative TB are more likely to die (hazard ratio 2.2) than those with smear-positive TB, before and after diagnosis, due to severe immunosuppression or delays in treatment initiation associated with prolonged diagnostic workups. Diagnostic algorithms used to date, if followed without delay, can require up to 30 days or longer for a diagnosis to be made, and this delay can lead to increased mortality. In addition, multiple diagnostic steps can lead to high patient attrition. Current WHO guidelines recommend a maximum of four visits for ambulatory patients from initial presentation to diagnosis, while minimizing the number of days required to establish a diagnosis (see Figure 4). Thus, in the 2007 WHO algorithm for the diagnosis of smear-negative TB, the emphasis is on expediting the diagnostic process so that treatment can be initiated as soon as possible. In addition, some experts suggest that ART should be started soon after TB diagnosis, but final recommendations await the results of ongoing randomized trials. Consequently, ambulatory HIV-infected patients with suspected TB should be assessed as follows:

First visit (day 1): Sputum smear microscopy for AFB is performed.

Second visit (day 2): If one smear is AFB-positive, the patient should be treated for TB. If negative, all investigations available at the site should be initiated during this visit, including a repeat AFB smear, CXR, and culture. Follow-up should be organized as soon as possible to review investigations. Repeat clinical examination at this point may enable a decision to treat with anti-TB drugs. Cotrimoxazole preventive therapy should be provided to all HIV-infected TB patients who are not already taking it.

All investigations should be available at this visit (except culture), and patients with suspected TB should be initiated on treatment. Disseminated TB should be suspected in any HIV-infected patient with rapid or marked weight loss, fever, and night sweats. If a decision is made to not treat TB at this time, then one course of broad-spectrum antibiotic (not fluoroquinolones) to treat both typical and atypical bacterial infection or treatment of Pneumocystis carinii pneumonia (PCP) should be initiated.

Third visit (day 7): During this visit, response to initiated therapy, whether anti-TB treatment or antibiotics, is monitored. Even if an immediate response to broad-spectrum antibiotics is observed, superimposed TB must still be considered. Those who do not respond to treatment should be reassessed for the presence of TB and, if indicated, anti-TB therapy should be initiated. Although nonresponse to antibiotics increases the likelihood of TB, a response to antibiotics does not exclude TB, as many HIV-positive patients are coinfected with bacterial pathogens. The primary role of antibiotics is not as a diagnostic aid but to treat concomitant bacterial infection in patients with cough. If the patient is initiated on anti-TB therapy without confirmatory tests, close monitoring is required to confirm that the patient is responding clinically. If TB is still suspected, repeat AFB smears.

Fourth visit (day 8): Reassess repeat AFB smears. In cooperation with the TB laboratory, systems should be in place to ensure that TB culture results are received and reviewed by a clinician. This should include mechanisms to trace patients not on TB treatment who subsequently develop positive cultures, so that appropriate treatment can be initiated.
Patients should be classified as seriously ill and referred to higher-level care if one or more of the following signs are present: unable to walk unaided, respiratory rate greater than 30 breaths per minute, fever over 39 degrees Celsius, pulse rate over 120 beats per minute.

**Chest Radiography**

Although HIV reduces the specificity of CXR presentation, radiographic presentations in people living with HIV are now well described and should no longer be considered “atypical” for TB in HIV-prevalent settings. Although CXRs are not routinely available in all settings, where available, they should be performed early in symptomatic patients, as they can potentially shorten the time to diagnosis and treatment initiation. The value of routine chest radiography in asymptomatic patients has been questioned. CXR characteristics depend on the level of immunosuppression. If TB occurs in the early stages of HIV, the CXR shows more typical findings, including cavitation and upper lobe disease, and sputum smears are more likely to be positive. With more advanced HIV disease (i.e., CD4 count less than 200 cells/mm$^3$), patients often present predominantly with radiographic signs consistent with primary TB, including lower lobe involvement, absence of cavitation, and air-space disease similar to bacterial pneumonia; smears tend to be negative (see Table 1). In addition, patients with severe immunosuppression are more likely to have EPTB presentations on CXRs, such as intrathoracic lymphadenopathy, and markers of disseminated disease, such as miliary disease. Ten percent to 20% of coinfected patients can have normal CXRs.

**EPTB IN HIV-INFECTED PATIENTS**

The diagnosis of EPTB in an HIV-infected patient (or a patient with strong clinical evidence of HIV infection) is defined by one specimen from an extrapulmonary site that is smear AFB or culture positive, or the presence of histological or strong clinical evidence consistent with active EPTB. EPTB is not often diagnosed microbiologically, but rather on clinical or symptomatic features without confirmation. In a Tanzanian study, only 18% of EPTB patients had laboratory confirmation. In Côte d’Ivoire, disseminated TB was found at autopsy in 44% of patients presenting with wasting syndrome; none had been diagnosed antemortem. In Malawi, 10% of patients presenting with severe anemia had disseminated TB in the bone marrow.

Overall, approximately one-third of deaths in sub-Saharan Africa among people living with HIV are due to disseminated TB, but only 50% are actually diagnosed prior to death. Especially in patients with fever and wasting, a high index of suspicion and presumptive therapy are often required. In Malawi, MTB was the most common cause of bloodstream infection, occurring in 17% of febrile adult patients on the medical ward of a central hospital. In 77% of these patients, TB was diagnosed by routine investigation (i.e., sputum smear, CXR), but in 11%, TB was not suspected and was diagnosed only by blood culture. EPTB is one of the most common causes of fever of unknown origin in HIV-infected patients. Mycobacteremia should be suspected in patients with anemia, HIV infection, cough, chronic fever and weight loss, and clinical diagnosis of AIDS. In most patients, the presentation of disease is characteristic enough to allow diagnosis without bacteriologic or histologic confirmation. With the exception of lymph node aspiration, investigations will often mislead or delay the diagnosis and are usually expensive or not available (see Figure 5).

Common forms of EPTB, discussed below, include pleural effusion, pericardial effusion, tuberculous ascites, TB lymphadenitis, and TB meningitis.
Presentation and Diagnosis of Pleural Effusion

Pleural effusions are usually unilateral but may be bilateral. In Africa, 95% of unilateral pleural effusions are TB related, and it is the most common EPTB presentation in HIV-infected patients.\(^3^5,^36\) Patients may present with pleuritic chest pain, a nonproductive cough, and shortness of breath. Clinical signs include decreased breath sounds and dullness to percussion, both of which can be confirmed by CXR. Suspicion is highest if associated with night sweats, weight loss, or fever.\(^9\) Unlike in HIV-negative patients, pleural effusions in HIV patients do not resolve spontaneously and remain culture positive for prolonged periods.\(^3^7\)

The diagnosis of pleural effusion is usually presumptive, as most settings do not have the capacity to provide a microbiologic or histologic confirmation. If thoracentesis is not available, TB treatment should be started, especially if the patient is suspected or confirmed to be HIV-infected. If a pleural tap is performed and the fluid is clear, straw-colored, and clots on standing in a plain tube, then the patient can be treated presumptively as having TB. Lab analysis of pleural fluid consistent with TB should have protein greater than 30g/L and greater than 50% lymphocytes.\(^1^7,^3^8\) In HIV-infected cases, pleural fluid is positive for AFB in approximately 20% of cases, and culture is positive in less than 30% of cases.\(^9,^3^9\) Neither method, however, is required to make the diagnosis. Pleural biopsy is invasive, not routinely available, and requires histologic examination, but does show characteristic features of TB (e.g., granulomatous inflammation, caseating

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### Signs and symptoms in patients with suspected EPTB
- Cough for 2 weeks or more
- Unintentional weights loss with
  - Night sweats and
  - Temperature $\geq 37.5\,^\circ$C
- Shortness of breath
- Enlarged lymph nodes in neck/axilla
- Chronic headache or altered mental state

### Chest X-ray
- Miliary pattern
- Enlarged heart
- Pleural effusion
- Enlarged mediastinal lymph nodes

### Physical signs in patients with suspected EPTB
- Lymph node swelling in neck or axilla
  - Possible TB lymphadenitis
  - (may also present with other types of TB and may be only way to make a diagnosis)
- Signs of fluid in chest
  - Reduced or absent breath sounds
  - Dull to percussion
  - Possible TB pleural effusion
- Signs of fluid around heart
  - Distant heart sounds
  - Peripheral edema (right heart failure)
  - Tachycardia
  - Distended neck veins
  - Possible TB pericarditis
- Signs of meningitis
  - Neck stiffness
  - Confusion
  - Abnormal eye movements
  - Possible TB meningitis

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**Figure 5. Diagnosis of extrapulmonary tuberculosis**

*Source: Adapted from WHO*\(^1^7\)
CXRs can show active PTB in 30% of cases and pleural effusion in 40% to 60% of cases. Due to the high prevalence of pericardial TB in African countries, patients should not undergo diagnostic pericardiocentesis, but should instead be treated empirically with anti-TB medications. In most cases, a presumptive diagnosis is safer and more expeditious than investigating pericardial fluid for AFB; culture is not required. Therapeutic pericardiocentesis should be undertaken only by someone who is experienced and only if there are signs of cardiac tamponade. If the clinician is unsure of the diagnosis, ultrasound is a noninvasive method that can assist by showing pericardial fluid with strands crossing between visceral and parietal pericardium. Steroids may have benefits, but the clinical trials published to date are too small to demonstrate an effect. Kaposi’s sarcoma should always be considered in patients with pleural or pericardial effusions and advanced HIV.

Presentation and Diagnosis of Pericardial Effusion

In Africa, 90% of pericardial effusions in HIV-infected patients and 70% in non-HIV-infected patients are due to TB. Pericardial effusion is usually associated with systemic symptoms (e.g., night sweats, fever, and weight loss) and evidence of TB elsewhere. Patients can present with cough, shortness of breath, and, if severe, signs of right heart failure (i.e., right hypochondrial pain due to liver congestion, abdominal distension due to ascites, or peripheral edema). Cardiac signs include tachycardia, hypotension, pulsus paradox, and elevated jugular venous pressure. Pericardial effusion usually develops slowly, is another presentation of exudative effusion, and should be suspected in anyone with signs of an enlarged cardiac silhouette on the CXR (present in 90% of cases), congestive heart failure, or cardiac tamponade or pericardial constriction.

Presentation and Diagnosis of Tuberculous Ascites

Patients with tuberculous ascites present with constitutional symptoms and palpable abdominal masses from mesenteric lymph nodes. Ascites may be less common than in HIV-negative patients. Patients may also present with bowel obstruction or fistulae formation between bowel, bladder, and abdominal wall. A CXR may show evidence of PTB. A peritoneal tap will show clear yellow exudative fluid with predominantly lymphocytes and protein greater than 30g/L. Ultrasound is not necessary but may show hepato-splenic focal lesions or enlarged mesenteric or retroperitoneal lymph nodes. Diagnosis can be made presumptively if the above investigations are not available. Other causes of exudative ascites are malignancy and infection. Causes of transudative ascites that should be considered are necrosis, or AFB) in 50% to 97% of cases. If the pleural fluid is cloudy or bloody or bilateral, this should prompt further investigations and the consideration of alternate diagnoses. Diagnoses to consider include malignancy (e.g., pulmonary Kaposi’s sarcoma if the patient has advanced-stage HIV), post-pneumonic effusion, pulmonary embolus, pancreatitis, and amoebic liver abscess. Untreated tuberculous effusions, in those without HIV infection, will resolve spontaneously in 4 to 16 weeks, with the subsequent development of EPTB or PTB in 43% to 65% of cases over the next several years. The use of steroids in HIV-associated pleural effusions is not currently recommended. Newly developing or worsening pleural effusion may represent an IRIS presentation (see section “Immune Reconstitution Inflammatory Syndrome” later in this chapter) or an unmasking of TB in someone not yet diagnosed with disease.
congestive cardiac failure, nephrotic syndrome, liver cirrhosis, or schistosomiasis.\(^9\)

**Presentation and Diagnosis of TB Lymphadenitis**

Asymmetric lymphadenopathy is a common problem in HIV-infected patients. TB is the most likely diagnosis, but other reactive, HIV-associated infections and malignancies can also present in a similar fashion. TB lymphadenitis more often presents with nodes that are asymmetric, firm, greater than 2 cm, and usually in the cervical region.

The diagnosis of TB lymphadenitis can be obtained rapidly in up to 85% (studies vary)\(^{44,45}\) of patients with wide-needle aspiration (using an 18-gauge needle). In one study, the use of needle-core biopsy (using a 16-gauge needle) was found to be diagnostic in 88% of patients, and CXRs were abnormal in 85%\(^{46}\). TB treatment should be started immediately if needle aspiration cannot be performed, results are delayed, or the patient is unlikely to return or has other features of disseminated TB\(^9\).

**Presentation and Diagnosis of TB Meningitis**

TB meningitis is usually gradual in onset; symptoms include headache, decreased level of consciousness, and cranial nerve palsies. Patients may also present with constitutional features. Meningeal signs (e.g., stiff neck) may not be present in HIV-infected patients. Tuberculomas and vascular occlusion may result in focal neurological deficits or seizures and may be more common in HIV-infected patients.\(^{47}\)

Lumbar puncture (LP) is the primary diagnostic tool for TB meningitis and is usually safe if there are no focal neurologic signs indicating a possible space-occupying lesion, and ophthalmoscopy reveals no signs of raised intracranial pressure. With focal signs, a computed tomography (CT) scan of the head is required before LP can be performed. If a CT scan is not available, then presumptive diagnosis and TB treatment are recommended. Cerebrospinal fluid (CSF) should demonstrate an elevation in white cells (predominantly lymphocytes), elevated protein, and low glucose. AFB are visible in only a minority of cases. In HIV-infected patients, meningeal symptoms may be absent and CSF may be completely normal.\(^{48,49}\) LP is important to rule out other forms of meningitis, including bacterial and cryptococcal. Adjuvant corticosteroids started at the time of diagnosis and given for two months improve survival (but not disability) in HIV-negative patients, and further investigation is needed to prove their benefit in HIV-infected patients.\(^{50}\)

**SPECIAL CONSIDERATIONS FOR TREATMENT OF TB IN HIV-INFECTED ADULT PATIENTS**

The comanagement of TB and HIV is challenging for both the patient and the clinician, and can make the selection of drugs for concurrent therapy difficult. First, patients may be reluctant and/or unprepared to undergo immediate therapy for two newly diagnosed diseases that are highly stigmatized and require the ingestion of multiple daily pills for extended durations. Second, clinicians and other providers are overburdened with the provision of routine HIV and TB care in resource-limited settings, where the diagnosis of TB is slow, requires multiple visits to establish, and is often not confirmed due to the lack of sensitive and rapid point-of-care diagnostics. Finally, medication selection is complicated by overlapping toxicities and significant drug-drug interactions that negatively impact the serum levels of key drugs used for the treatment of both diseases.

The treatment goals for TB and HIV disease are identical; in both cases, the intent is to prevent mortality, avoid the emergence of drug resistance, and limit morbidity and further transmission, thus allowing patients to return to their normal lives.
Standard TB Therapy and Monitoring

TB treatment regimens are based on the WHO disease stage of the patient at the time of diagnosis (see Table 2) and the likelihood of resistance (see Tables 3 and 4). Patients are categorized and registered as either “new,” “retreatment,” or “other” (e.g., chronic). The standard regimen for treatment of a new TB case consists of four first-line drugs: isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). Streptomycin (S) is normally used only for retreatment cases. For new TB cases, the intensive phase of therapy consists of two months of daily four-drug therapy (2HRZE). The continuation phase in most settings consists of four months H plus R (4HR), or in some settings six months of H plus E (6HE). The standard six-month regimen that contains rifampicin throughout the entire treatment course has been shown to have better outcomes and significantly reduce the risk of recurrence at 12 months post-therapy.
rifabutin (RFB) is an alternative rifamycin with equal efficacy to rifampicin, as shown in clinical trials involving both HIV-positive and negative patients. The advantage of RFB is that it does not significantly lower key ARV drug serum levels and therefore may be used with protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The disadvantages of RFB are its cost and limited availability. RFB doses are generally decreased when co-administered with PIs and increased when co-administered with efavirenz (EFV). RFB can lead to significant toxicities, including uveitis, gastrointestinal upset, neutropenia, and thrombocytopenia. The use of RFB with azole antifungals and clarithromycin will lead to higher RFB plasma levels and risk of associated toxicities.

**TB in HIV-Infected Patients Not Receiving ART**

Among the four drugs recommended for treatment of new cases of TB (isoniazid, rifampicin,
enzyme system, which rapidly metabolizes and thereby reduces the serum levels of certain ARVs (i.e., NNRTIs and PIs). Concurrently, these same ARVs can also negatively impact the serum levels of rifampicin.

pyrazinamide, and ethambutol), rifampicin is the key drug that allows for the relatively short-course (six-month) treatment regimen currently used by most national TB control programs. Unfortunately, rifampicin induces the liver’s cytochrome P450 3A

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>TB Patient Diagnostic Category</th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Relapses</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>Treatment after default</td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
</tr>
<tr>
<td></td>
<td>Optional</td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
</tr>
<tr>
<td>II</td>
<td>Treatment failure of category I</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>In settings where:</td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
</tr>
<tr>
<td></td>
<td>Representative DRS data show low rates of MDR-TB, or individualized DST shows drug-susceptible disease</td>
<td>Optional</td>
<td>Optional</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
</tr>
<tr>
<td></td>
<td>In settings with:</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>■ poor program performance</td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
</tr>
<tr>
<td></td>
<td>■ absence of representative DRS data or case-specific (individual) DST</td>
<td>Optional</td>
<td>Optional</td>
</tr>
<tr>
<td></td>
<td>■ insufficient resources to implement category IV treatment</td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
</tr>
<tr>
<td>II</td>
<td>Treatment failure of category I</td>
<td>Specially designed standardized or individualized regimens with the use of second-line drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In settings with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ adequate program performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ representative DRS data showing high rates of MDR-TB and/or capacity for DST of cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ availability of second-line drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Still smear-positive or culture-positive after supervised retreatment regimen (formerly called chronic TB case); proven or suspected MDR-TB cases</td>
<td>Specially designed standardized or individualized regimens with the use of second-line drugs</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Recommended Treatment Regimens for Previously Treated TB Patients

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>TB Patient Diagnostic Category</th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2HRZES/1HRZE</td>
<td>5HRE</td>
</tr>
</tbody>
</table>

Numbers preceding regimens indicate the length of treatment in months. Subscripts following regimens indicate the frequency of administration per week. When no subscripts are given, the regimen is daily.

Drug susceptibility testing is recommended for patients who are contacts of known MDR-TB cases.

DRS = drug resistance surveillance; DST = drug susceptibility testing; E = ethambutol; H = isoniazid; MDR-TB = multidrug-resistant tuberculosis; R = rifampicin; Z = pyrazinamide

Source: Adapted from WHO

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A diagnosis of TB requires initiation of multi-drug therapy without delay and before the start of ART. Although precise data are still lacking about the timing of dual therapy, there is general guidance on when to start ART in relation to the start of TB therapy, based on CD4 cell count (see Table 5). The key message is that TB therapy should be initiated and tolerated before adding ART.

**TB in HIV-Infected Patients Receiving ART**

Due to the limited number of TB drugs available and the clear superiority of rifamycin-based regimens to treat TB, including HIV-associated TB, it is generally recommended that the ARV regimen be adjusted to accommodate the required TB regimen. This may require the switch from a PI-based regimen to an EFV or triple-nucleoside regimen, according to national program recommendations (see Table 6).

ART has been shown to reduce TB incidence by some 80% in high-TB-burden settings, especially among those with WHO HIV-associated clinical stage III or IV disease and those with CD4 counts of less than 200 cells/mm$^3$. Nonetheless, coinfected patients receiving ART remain at increased risk of developing TB, especially during the first three to six months after ART initiation. Therefore, development of TB while on ART does not necessarily reflect ART failure. If TB (pulmonary WHO stage III TB or extrapulmonary WHO stage IV TB) is diagnosed within six months of ART initiation, it is not necessarily representative of ART failure and does not necessitate switching to a second-line ARV regimen (see Table 7). Development of TB in the first six months after ART initiation could also represent the “unmasking” variant of TB that indicates IRIS.

For those who develop TB after six months on ART, current recommendations are to treat TB and select an ARV regimen compatible with the rifampicin-based TB regimen, according to routine standards (see Table 6). This approach is acceptable only if the clinician is convinced that there is no evidence of ART failure based on clinical, virologic, or CD4 criteria. In settings where CD4 counts are not available, the development of disseminated or severe extrapulmonary forms of TB should be considered as a sign of ART failure requiring adjustments to the ART regimen. If there is a good response to initiation of TB therapy, then a decision to switch to a second-line ART regimen may be deferred until the end of TB treatment.

### Table 5. Relationship of CD4 Count to Timing of ART in TB Patients on Therapy

<table>
<thead>
<tr>
<th>CD4 Cell Count (cells/mm$^3$)</th>
<th>ART Recommendation</th>
<th>Timing of ART after Initiation of TB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>Give ART (see options in Table 6)</td>
<td>Between 2 and 8 weeks (as soon as TB therapy is tolerated)</td>
</tr>
<tr>
<td>200 to 350</td>
<td>Give ART</td>
<td>After 8 weeks</td>
</tr>
<tr>
<td>&gt;350</td>
<td>Defer ART (unless other non-TB stage III or IV conditions are present, then may give ART)</td>
<td>Reevaluate patient (a) after 8 weeks and (b) at end of TB therapy</td>
</tr>
<tr>
<td>Not available/unknown</td>
<td>Give ART (unless patient has mild TB disease forms, then may defer)</td>
<td>Between 2 and 8 weeks</td>
</tr>
</tbody>
</table>

*Source: Adapted from WHO*
**Table 6. Preferred First-Line Antiretroviral Regimens for Use with a Rifampicin-Based Anti-TB Therapy**

<table>
<thead>
<tr>
<th>ARV Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td></td>
</tr>
<tr>
<td>2 NRTIs + EFV</td>
<td></td>
</tr>
</tbody>
</table>
| ■ EFV 600 mg daily (increased EFV dosing not currently recommended for any weight group) | ■ EFV serum levels reduced by rifampicin  
■ EFV dosage adjustment not currently recommended by WHO  
■ EFV should not be used during the first trimester of pregnancy or in women of childbearing age without effective contraception  
■ If patient has severe anemia, do not use AZT and treat anemia; can use d4T/ABC/TDF + 3TC + EFV |
| **Alternate 1**      |                                                                          |
| 2 NRTIs + NVP        |                                                                          |
| ■ Standard NVP dosing recommended                              | ■ NVP serum levels reduced by rifampicin  
■ NVP-induced hepatotoxicity more common with higher CD4 counts or for patients without a known CD4 count  
■ Rifampicin may potentiate NVP-induced hepatotoxicity; therefore, monitor ALT at weeks 4, 8, and 12  
■ Seek alternate ARV regimen for women with CD4 counts of 250–350 who need ART and are also taking rifampicin  
■ Use with caution in patients with chronic hepatitis B and/or hepatitis C infection |
| **Alternate 2**      |                                                                          |
| 3 NRTIs              |                                                                          |
| ■ AZT + 3TC + ABC    | ■ Safe to use with rifampicin  
■ AZT + 3TC + ABC safe for use in pregnancy  
■ Safe to use where liver toxicity is a major concern |
| or                   |                                                                          |
| ■ AZT + 3TC + TDF    |                                                                          |
| ■ Standard dosing recommended                                   |                                                                          |

**TB in the Setting of First-Line ART Failure**

Construction of a second-line ART regimen that can be used in TB patients taking rifampicin therapy is complicated by the interactions between PIs and rifampicin. Since only certain boosted PI regimens can be used, specialized expertise should be sought, including special clinical and laboratory monitoring. There are limited data available for these recommendations.

**Pregnancy and Breastfeeding**

Anti-TB drugs for the treatment of patients with WHO categories I and III TB are considered safe for use in pregnant women. Data on the use of pyrazinamide during pregnancy are inconclusive. However, streptomycin (used in category II TB) is contraindicated during pregnancy due to ototoxic effects on the fetus. Breastfeeding can be continued during TB treatment, as very low concentrations of most TB drugs are found in breast milk. As noted already, EFV should not be used in the first trimester of pregnancy or in women of childbearing age who are not using effective contraception (see Table 8).
While no standard definition exists, TB-IRIS is a clinical complication that can present, depending on the variant, as a fever or general clinical worsening or new presentation of TB signs and symptoms (e.g., increased cough and/or dyspnea, new or worsening peripheral or mediastinal adenopathy, pleural effusion or pulmonary infiltrate, abscess formation, or increased intracranial pressure). It may occur within days to months of ART initiation and must be differentiated from drug toxicities and clinical deterioration due to ART treatment failure or failure to respond to TB therapy (due to drug resistance, nonadherence, or drug malabsorption). While treatment of TB-IRIS generally focuses on supportive care and initiation or continuation of TB therapy, if sufficiently severe (i.e., there is respiratory compromise), high-dose steroid therapy for several weeks’ duration may be beneficial. Significantly, there have been no randomized or systematically conducted studies to assess steroid therapy, and the potential additive

### Table 7. Patient Who Develops TB within First 6 Months of Starting a First- or Second-Line ART Regimen

<table>
<thead>
<tr>
<th>ART Regimen at Time of TB Diagnosis</th>
<th>Treatment Options for ART Given New TB Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two NRTIs + EFV</td>
<td>Continue with two NRTIs + EFV</td>
</tr>
<tr>
<td>Two NRTIs + NVP</td>
<td>▪ Substitute EFV for NVP or</td>
</tr>
<tr>
<td></td>
<td>▪ Change to triple NRTI regimen or</td>
</tr>
<tr>
<td></td>
<td>▪ Continue with two NRTIs + NVP</td>
</tr>
<tr>
<td>Triple NRTI regimen</td>
<td>Continue triple NRTI regimen</td>
</tr>
<tr>
<td>Second-line ART</td>
<td>Substitute to or continue (if already taking) a</td>
</tr>
<tr>
<td>Two NRTIs + PI</td>
<td>boosted PI regimen in consultation with an ART</td>
</tr>
</tbody>
</table>

* Once rifampicin-based TB therapy is completed, may switch back to NVP. Lead-in dosing for NVP is not required.  
* EFV should not be used during the first trimester of pregnancy or in women of childbearing years without effective contraception.  
* Monitoring of ALT required when NVP or boosted PIs are used with rifampicin (and/or pyrazinamide), due to risk of hepatotoxicity.  
* Rifampicin is known to reduce NVP levels by up to 58%; however, the clinical impact of these changes remains unclear and is still to be validated.  

ALT = alanine aminotransferase; EFV = efavirenz; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor  

Source: Adapted from WHO  

### Immune Reconstitution Inflammatory Syndrome

IRIS is a general term used to describe the clinical worsening of a patient’s condition after the initiation of ART. It is associated with many opportunistic infections (e.g., cytomegalovirus, Cryptococcus neoformans, Mycobacterium avium complex, Mycobacterium tuberculosis, Toxoplasma gondii). TB-IRIS can present as two variants: (1) unmasking TB or (2) paradoxical worsening of existing disease in a known TB patient. The unmasking variant occurs in a patient in whom TB disease is not evident at the time of ART initiation; its incidence is unknown. TB-IRIS of the paradoxical worsening variant may occur in up to one-third or more of coinfected TB patients started on ART, especially those started on ART in the first two months of TB therapy and those with extrapulmonary and disseminated forms. Initial CD4 count, rapidity of rise in CD4 count, or fall in viral load have not always been identified as risk factors for TB-IRIS. While no standard definition exists, TB-IRIS is a clinical complication that can present, depending on the variant, as a fever or general clinical worsening or new presentation of TB signs and symptoms (e.g., increased cough and/or dyspnea, new or worsening peripheral or mediastinal adenopathy, pleural effusion or pulmonary infiltrate, abscess formation, or increased intracranial pressure). It may occur within days to months of ART initiation and must be differentiated from drug toxicities and clinical deterioration due to ART treatment failure or failure to respond to TB therapy (due to drug resistance, nonadherence, or drug malabsorption). While treatment of TB-IRIS generally focuses on supportive care and initiation or continuation of TB therapy, if sufficiently severe (i.e., there is respiratory compromise), high-dose steroid therapy for several weeks’ duration may be beneficial. Significantly, there have been no randomized or systematically conducted studies to assess steroid therapy, and the potential additive
immunosuppressive effect of steroids on HIV-infected patients must be considered.

It is important to note that clinical worsening may also be associated with the initiation of anti-TB therapy in non-HIV-infected and HIV-infected patients, even in the absence of ART. Clinically, this condition cannot be distinguished from TB-IRIS, and the general approach to assessment and treatment is the same. This type of reaction is generally referred to as a paradoxical reaction to TB therapy.

**Isoniazid Preventive Therapy**

Isoniazid preventive therapy (IPT), also commonly referred to as treatment of LTBI, is promoted by WHO for HIV-infected patients who have no evidence of active TB disease. The role of IPT is to reduce TB reactivation among those persons “latently” infected with MTB. Clinical studies have shown a clear benefit of IPT among HIV-infected patients with a positive tuberculin skin test (TST) using purified protein derivative (PPD). No clear benefit has been shown for those with either a negative TST or evidence of anergy (i.e., a condition in which the body fails to react to an injected allergen or antigen). Since TSTs are not widely available in most high-TB and high-HIV-prevalence settings, documentation of a positive TST result is not considered feasible in these settings prior to provision of IPT. WHO therefore recommends IPT for the following groups of people with HIV infection: healthcare workers, household contacts of TB patients, prisoners, miners, and people living in populations where the prevalence of MTB infection is estimated to be greater than 30%. Another barrier to widespread implementation of IPT in countries with limited health infrastructures is the lack of sensitive diagnostics, specifically culture, to confirm that a patient does not have undetected TB disease.

The efficacy of isoniazid for the treatment of tuberculin-positive HIV-positive individuals has been validated in several randomized controlled studies, with a risk reduction for the development of active disease ranging from 36% to 78%. Based on the Cochrane review (meta-analysis) of 11 clinical preventive therapy trials (using any established anti-TB drug protocol), there was a 60% reduction in TB incidence for individuals with a positive TST receiving isoniazid. A smaller
trend in risk reduction (20%) for TB among skin-test negatives and unknowns was also found in the meta-analysis but did not reach statistical significance. There is conflicting evidence concerning possible mortality benefits from treating LTBI in HIV-infected patients. While the Cochrane analysis did not find a significant reduction in all-cause mortality, it did identify a trend toward lower mortality among those with a positive TST (relative risk 0.80; 95% CI, 0.63-1.02).73

IPT is normally provided by the TB service. Although a 6-month course is commonly recommended, a 9-month course of daily isoniazid is ideal and recommended by both WHO and the Centers for Disease Control and Prevention / American Thoracic Society / Infectious Disease Society of America as the preferred regimen for the treatment of LTBI in HIV-positive patients.51,77

This recommendation is based on cost-benefit considerations and extrapolation from data showing that 12 months of therapy are superior to 6 months in HIV-infected patients with LTBI. Clinical trials data from Africa indicate that the durability of a 6-month course of IPT varies, with a reported range of one to two and a half years.76,78,79 The use of isoniazid post-TB treatment as secondary prophylaxis to prevent recurrent disease has also been studied in small cohorts and shown to be potentially beneficial for this purpose, although it is not currently recommended by WHO.80,81 (Note: Pyridoxine [vitamin B6] at 10-25 mg per day is recommended for use with IPT in the setting of severe disease, alcohol abuse, or any signs of malnutrition.)

**Cotrimoxazole Preventive Therapy**

The use of cotrimoxazole to prevent PCP and bacterial infections in HIV-positive TB patients is well accepted. In Africa, cotrimoxazole preventive therapy (CPT) has been shown to substantially reduce mortality in HIV-positive TB patients, by up to 46%.82 In a coinfected patient with active TB, cotrimoxazole prophylaxis should be initiated irrespective of the individual’s CD4 count. CPT can be discontinued in patients who have had a CD4 count greater than 200 cells/mm3 for at least six months or, in countries with a high incidence of bacterial infections or malaria, with a CD4 count greater than 350 cells/mm3 for over six months.51,83

**Infection Control to Prevent Nosocomial TB Transmission**

Although HIV-infected TB patients appear less likely to spread TB compared with HIV-negative patients,84 both sputum smear-negative and smear-positive patients can transmit MTB infection to others.85 Moreover, health-care workers and HIV-infected populations are at particular risk of nosocomial transmission from an infectious TB case.86-88 The importance of infection control as a primary prevention measure is often underappreciated and its benefit underestimated. There is a clear association between poor infection control practices and nosocomial TB outbreaks in health-care and other congregate settings.87-90 Upon exposure leading to infection, any immunocompromised host may proceed quickly to active disease with symptoms and early death, often within weeks to months of infection.91 Rapid progression may occur in either drug-susceptible or drug-resistant disease.

A written, comprehensive infection control plan that specifically addresses standard operating procedures in clinics and hospitals should therefore be part of all HIV and TB control programs. The goal is to protect health-care workers and any susceptible person who may come into inadvertent, close contact with an undiagnosed, infectious TB case. The effectiveness of such policies is well-documented.92 Any setting in which patients congregate should be considered at risk, such as clinic waiting areas, inpatient wards, and emergency
or triage departments. The standard approach to infection control includes a multitiered system of three essential components:

- **Workplace and administrative (managerial) control measures.** These measures are designed to allow for (1) early detection of respiratory symptoms, (2) appropriate respiratory isolation with access to rapid diagnosis, and (3) commencement of adequate therapy without delay for those with suspected or confirmed disease. Staff training, along with patient and community education, is included in this component. Administrative measures are determined and implemented by institutions as policies and procedures that take into account patient flow and care within a given setting.

- **Environmental control measures.** This component consists of natural ventilation and/or mechanical engineering controls that focus on air mixture and air exchange. Natural ventilation, particularly in some older structures with large open windows, has been demonstrated to allow for sufficient air changes per hour to provide protection to susceptible exposed people. Many modern health facilities, however, are at high risk for nosocomial transmission of TB because of inadequate ventilation, due to small room size, too few and small windows, and lack of sufficient cross-ventilation. Negative-pressure isolation rooms, proper upper room ultraviolet germicidal irradiation, and even ultrafiltration methods are alternatives to natural ventilation, but they require specialized air-circulation and exhaust systems that are expensive and difficult to maintain.

- **Personal respiratory protection with respirators.** This measure depends on the willingness of staff and other at-risk people to wear respirator-type masks and to ensure a proper fit with seal. The standard recommendation is to use a particulate respiratory mask (respirator) of the N-95 type. Surgical masks of any material (cloth, paper, gauze) are not adequate. Patients should also be encouraged to cover their mouths and noses when coughing or sneezing to reduce the amount of expelled organisms. Personal respiratory protection alone is not adequate for infection control against any airborne pathogen, including TB. All three components are required and must be in place as part of a comprehensive infection control plan.

**CONCLUSION**

HIV is fueling the TB epidemic in many parts of the world and especially in Africa. The recognition, diagnosis, and management of HIV-associated TB are evolving and have created new challenges for clinicians, public health workers, and national programs. While progress has been made globally, TB is still the leading cause of death among people living with HIV. For this reason, ongoing efforts to rapidly detect and treat TB in resource-limited settings must be strengthened.
TEN ESSENTIAL ACTIONS FOR EFFECTIVE TB INFECTION CONTROL: SAFETY WITHOUT STIGMA

These ten essential actions are based on current WHO policy and are issued to help facilities implement infection control (IC) interventions while waiting for the soon-to-be-released revised WHO policy on TB IC.

1. Include Patients and Community in Advocacy Campaigns
The community should be well educated about TB infection, prevention, and control. Community members should understand the importance of knowing one’s HIV status, that they may be eligible for IPT, and that they have a right to rapid TB diagnosis and treatment. They should know that TB can be spread by coughing and should expect health-care settings and community services to require those coughing to cover their mouths. Community members should also understand that health-care workers may sometimes wear personal respiratory protection and that they too may be asked to wear a mask to protect others. Safety without stigma should be the goal—a request to wear a mask or provide a sputum sample outside or in a well-ventilated room should not be stigmatizing as it contributes to a safer clinic for everyone. Patient and health care worker safety may require the provision of health care in the community to avoid unnecessary admissions to health-care facilities. Information, education, and communication (IEC) campaigns should include themes such as “Our community is TB-safe” or “Our health facilities are stopping TB.”

2. Develop an Infection Control Plan
All facilities should have an IC plan and a facility person or team responsible for IC. This plan identifies high-risk areas for TB transmission and provides information on TB and HIV rates among health-care workers and patients. The plan also provides area-specific IC recommendations for the facility, including the laboratory, which should have its own specialized standard safety procedures.

3. Ensure Safe Sputum Collection
Collecting and processing sputum is an essential part of the diagnosis of TB. Sputum collection can be potentially hazardous for health-care workers and other patients. As such, health-care workers should explain to patients that safety without stigma is the goal of good TB infection control and that sputum should be collected outside (if feasible) or, if necessary, in specially designed rooms with adequate ventilation.

4. Promote Cough Etiquette and Cough Hygiene
At minimum, every facility should have a poster on TB infection control and cough etiquette in the outpatient department waiting area, admissions area, and casualty department. Patients should be instructed to cover their mouth and nose when coughing with their hands, a cloth (such as a handkerchief), a clean rag, tissues, or paper masks. All facility staff are responsible for safety and should work together to help patients adhere to this practice.
5. **Triage TB Suspects for “Fast-track” or Separation**

All patients should be screened upon arrival for chronic cough (i.e., longer than 2-3 weeks), fever, weight loss, night sweats, hemoptysis, or contact with a person with TB. Health-care workers should explain to all clinic visitors that safety without stigma is the goal and that TB screening is part of quality care. People suspected of having TB should be “fast-tracked” for rapid diagnosis and care services or should be asked to wait near an open window or in a comfortable area separate from the general waiting room (outdoors if possible). Whenever possible, community-based treatment models should be encouraged. For inpatient settings, TB suspects should be placed in a room or area separate from general wards. Patients with known or suspected drug-resistant TB should be separated from general ward patients and from other TB suspects.

6. **Assure Rapid Diagnosis and Initiation of Treatment**

Patients suspected of having TB should move to the front of the queue for all services and should undergo prompt evaluation for TB. Sputum collection should be done away from other people, and sputum specimens are to be sent to a quality-assured laboratory for AFB smear and culture (when possible). Turnaround time for sputum AFB smear results should be no more than 24 hours. A patient-tracking system assures that TB suspects who are AFB smear-negative receive additional services (e.g., chest X-ray and referral visits) or treatment as quickly as possible. DOTS treatment for TB begins immediately after a diagnosis of TB is made, and a plan for assuring adherence to treatment should be developed at that time. All people living with HIV who are not TB suspects should be eligible for IPT.

7. **Improve Room Air Ventilation**

Patient waiting areas should be open and well ventilated. Windows and doors should remain open when possible to maximize cross-ventilation. Appropriately placed, simple fans can improve ventilation. Where weather permits, open-air shelters with a roof to protect patients from sun and rain are recommended. Patients should not wait for services in narrow, poorly ventilated corridors. Hospitals caring for patients with drug-resistant TB should provide separate patient wards or rooms, preferably with good ventilation. TB infection control considerations should be integral to the construction of new facilities as well as the renovation of exiting facilities.

8. **Protect Health-Care Workers**

Health-care workers should know the symptoms of TB and be given a health assessment, including screening for TB and HIV, at least annually. All health-care workers are encouraged to know their HIV status, and those living with HIV should be given the opportunity to minimize their exposure to people with TB (e.g., offered a change of duties). HIV-positive health-care workers should be screened for IPT eligibility as part of their basic HIV care and treatment. Health-care workers working in high-risk settings for transmission of TB (e.g., bronchoscopy suites) should be provided with appropriate personal respiratory protection.
9. **Build Capacity**
Training on TB infection control practices should be incorporated into the broader infection control trainings at hospitals and facilities (e.g., hand washing, other respiratory and bloodborne infection control trainings). Where no such trainings exist, trainings on airborne TB infection control practices should be developed. Infection control requires a system-wide approach, and health-care workers at all levels should receive training and be engaged in improving their own safety, as well as that of their patients.

10. **Monitor Infection Control Practices**
Supervision of infection control practices should be a part of every supervisory visit. This should include a facility tour to check that infection control is being implemented and that all essential supplies for infection control are available. At the very least, facilities should have an infection control plan. Where feasible, monitoring of annual TB cases among health-care workers can provide useful information on transmission of TB in health facilities. Surveillance of TB disease among health-care workers is another means of evaluation. Additional on-site measures include examining medical records of a sample of TB patients to look at (1) time interval from admission to suspicion of TB, (2) time from suspicion of TB to ordering sputum for AFB, (3) time from ordering to collection of sputum, (4) time from collection of sputum to reporting of results, and (5) time from reporting of results to initiation of TB treatment and interviewing patients to discuss understanding of infection control, safety, and stigma.


Source: WHO HIV/AIDS and Stop TB Departments in collaboration with the TB Infection Control Subgroup of the Global TB/HIV Working Group
REFERENCE LIST


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91. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with...


According to the World Health Organization (WHO), the global TB epidemic has leveled off for the first time since it was declared a public-health emergency in 1993. The 2008 WHO Global Tuberculosis Control Report found that the number of new TB cases per capita appears to have been falling globally since 2003, in five of the six WHO regions—all except the European Region, where rates are approximately stable.\(^1\) Despite this stabilizing trend, approximately two billion people, one-third of the world’s total population, are presently infected with TB,\(^2\) and the control of this disease continues to strain public health services, particularly those in developing countries.

A direct consequence of the large numbers of adults infected with TB is an increase in childhood TB. Many factors that affect the spread of adult disease will indirectly fuel disease spread in children. A complex interplay of contributing factors, including immigration, malnutrition, poverty, and overcrowding, as well as other diseases, affects the local epidemiology of pediatric TB. It appears that there are significant differences in TB epidemiology among developed countries, where TB is generally well controlled, and developing countries, where rates of TB in children continue to climb. Infants and young children (less than five years of age) are at particularly high risk for infection and carry the greatest burden of disease. They are more likely than adults to develop disease after infection and are significantly more likely to develop extrapulmonary TB (EPTB) and severe disseminated disease.\(^3\)

Difficulties surrounding confirmation of TB diagnosis in pediatrics, poor documentation of cases, limited human resources, and inadequate follow-up have meant that there is little accurate information regarding childhood TB. This is especially true in many developing countries, where childhood HIV infection is also on the rise. For instance, available data from developing countries indicate that 20% or more of TB cases may occur in children, representing an incident rate in excess of 200 per 100,000.\(^4\)

**HIV and TB Coinfection**

The number of individuals, including infants and children, that are living with HIV has reached massive proportions in parts of sub-Saharan Africa and Asia. There have also been reports of increasing levels of HIV/TB coinfection among children in these settings.\(^5\) It is widely acknowledged that
HIV greatly increases the annual risk of progression from TB infection to active TB and is thought to be one of the principle causes of the resurgence of TB within sub-Saharan Africa. The reported prevalence rates of HIV in children in sub-Saharan Africa with documented TB have ranged from 11% to 64%. There is a paucity of information on how the HIV epidemic has specifically impacted the rates of pediatric TB, but it has undoubtedly contributed to the rapidly increasing rate of TB in children in high-HIV-prevalence countries. Naturally, increased rates of childhood TB reflect increased rates of disease among HIV-positive adults in the community. Although far more information exists concerning HIV/TB coinfection in adults, several studies have reported similar findings in children. In a South African study, 48% of children younger than 12 years of age with culture-proven pulmonary TB (PTB) were also found to be HIV-positive. Yet despite high rates of TB and HIV coinfection, it is still unclear whether HIV-positive children are more susceptible to TB infection, more likely to progress to disease than are HIV-negative children, or both. In sub-Saharan Africa, it has been suggested that HIV infection may be an indirect risk factor for TB in children. This view holds that because TB is the most common opportunistic infection in HIV-positive adults in the developing world, it follows that children in this setting are more likely to be exposed to TB irrespective of their HIV status.

Congenital and neonatal TB appear to be increasing in sub-Saharan Africa as well. This is most likely due to the rising prevalence of TB in young women and mothers. Several studies have reported increased maternal and neonatal mortality among pregnant women with TB/HIV coinfection. In one report from southern Africa, up to 16% of infants born to mothers who had bacteriologically proven TB contracted the disease. Despite this high transmission rate, diagnosis in young infants remains difficult, and treatment is often delayed. This is due both to the difficulties associated with diagnosis of TB in this age group and to the nonspecific manifestations of congenital and neonatal TB, which often mimic other infections. It is therefore important that medical staff working in areas where HIV and TB are endemic, especially those involved in postnatal follow-up of infants, be adequately trained in both TB and HIV and always consider both diagnoses. In older HIV-positive children, TB is also likely to be underdiagnosed or diagnosed very late, and treatment outcomes may be poor as a result.

Children who are HIV-positive and subsequently contract TB have also been shown to have higher mortality rates than those who are HIV-uninfected. In an Ethiopian study, children who were HIV-positive had a sixfold increase in risk of death during an episode of TB compared with an HIV-negative child. In Côte d’Ivoire, Mukadi et al. reported a 50% mortality rate over a six-month treatment period for HIV coinfected children who had CD4 percentages of less than 10%. In HIV-negative children, the mortality rate was 4%. Morbidity and mortality also appear to be age dependent. In a recently published review article focusing on pediatric TB/HIV studies, all analyses reported that children infected with TB at less than 1 year of age had excessively high morbidity and mortality, while those aged 1 to 4 years had considerable mortality and morbidity. Five to 10 years of age appeared to be the so-called safe age, when morbidity and mortality were at their lowest. These findings highlight the need for pediatric TB programs that target younger children and for more sensitive diagnostic tools for use in young populations.
TB in Children and Infants Living with HIV

TB in children is mainly a primary infection, and the clinical picture is dominated by the effect of lymphobronchial disease. Children with HIV infection have a higher frequency of extrapulmonary disease, with miliary or meningeal disease being the most important. Large pleural effusions are less common in young children.

History and Clinical Examination

Since children and infants often show nonspecific symptoms of TB, a detailed history should be taken to determine their risk of contact with a TB-infected adult. For children less than two years of age, the index case is more likely to be a caregiver or member of the household as compared with older children. Therefore, for a child with suspected TB and where there is no known TB contact, questions should be asked to determine whether an adult with symptoms suggestive of TB is present in the household or has had contact with the patient, with subsequent follow-up of the suspected individual (a form of reverse contact tracing).

The clinical presentation of PTB in HIV-positive children and infants is characterized by systemic symptoms of cough, with or without wheezing, fever, and loss of weight or failure to thrive. The clinical presentation of EPTB depends on the site of infection and can include limping (spinal TB), a swollen abdomen (abdominal TB), and swollen lymph nodes with fistula formation. The presentation of meningeal TB is often insidious, with changes in behavior, vomiting, and persistent fever. Because the symptoms of TB are generally nonspecific and mimic other clinical conditions, a high index of suspicion in the attending clinicians is required for the appropriate investigations to be ordered.

A community-based study to assess the value of symptoms in the diagnosis of TB in children reported that three well-defined symptoms (persistent, nonremitting cough of more than two weeks; objective weight loss in the last three months; and fatigue) were useful in identifying TB in HIV-negative children three years of age or older. This group of symptoms performed less well in children younger than three years and was of little diagnostic value in HIV-positive children. In light of the difficulty of diagnosis in young and/or HIV-positive children, clinical evaluation of the child, including growth assessment, is considered to be an important element in the diagnostic workup of children. Failure to thrive or faltering growth is a good indicator of chronic disease and provides supportive evidence of TB infection. However, it must be noted that growth faltering in HIV-positive children can often be due to other HIV-related illnesses. Physical examination of the child will assist in identifying signs of extrapulmonary disease, though a chest examination may not result in any specific findings other than the presence of wheezes and rales (i.e., clicking, bubbling, or rattling sounds in the lung).

Bacteriological Confirmation

A definitive diagnosis of TB is made by the recognition of acid-fast bacilli (AFB) in sputum specimens using either Ziehl-Neelsen (ZN) or auramine fluorescence staining. Since TB in children is usually a primary infection, there is greater involvement of the intrathoracic lymph nodes, especially in younger children; even where sputum is produced, specimens tend to be smear-negative. Younger children, especially those under six to eight years, are rarely able to cough up sputum. Thus, the approach to diagnosis of TB in children differs from that of adults and older children, where the primary focus

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is on smear microscopy, and relies instead on a careful assessment of available evidence of infection and disease. Diagnosis of TB in younger children is further complicated by the fact that they tend to have more extrapulmonary and disseminated TB than adults.18

Whenever possible, bacteriological confirmation should be sought for the diagnosis of TB in children. Because disease in children tends to produce few bacilli, smear examination is often smear-negative. Culture is able to identify additional cases that are smear-negative; however, obtaining culture results can often take a long time (six to eight weeks) and limited availability of culture facilities limits the usefulness of this technique. More widespread availability of liquid culture services with shorter turnaround times for results will make this test more useful for routine diagnosis of TB.

For younger children who are unable to produce sputum, gastric aspirates can be used for the detection and isolation of *Mycobacterium tuberculosis* (MTB). However, the yield for gastric lavage is reported in fewer than 20% of cases for microscopy and up to 50% for culture.20 This technique is also inconvenient and uncomfortable and cannot be performed at lower-level health facilities. The use of sputum induction has been shown to increase the diagnostic yield in both HIV-negative and -positive children.21 Yet this technique requires adequate ventilation and other infection control measures and would therefore have limited use in most clinical settings in developing countries. Other diagnostic techniques, such as bronchoalveolar lavage, have lower yields than culture on gastric lavage and are not recommended for routine diagnosis of TB. Similarily, serological tests and molecular techniques, such as polymerase chain reaction, are not recommended for routine use. These tests have not been adequately assessed, and where assessments have been done, they have not performed optimally.22-24

**Tuberculin Skin Test**
The tuberculin skin test (TST) is used to identify infection with MTB and can therefore be used as supportive evidence. Interpretation of the tuberculin test in children is the same regardless of whether bacillus Calmette-Guérin (BCG) vaccination has been given.20 The tuberculin test (Mantoux/Tine test) is frequently negative in children with HIV infection, malnutrition, and/or severe TB disease, and therefore a negative tuberculin test does not rule out TB.25 In HIV-positive children, the cutoff for a positive test should be 5 or greater, as opposed to 10 in HIV-negative children. In children with advanced HIV infection, any degree of induration is probably significant. The ELISPot (enzyme-linked immunosorbent spot) test, a T-cell-based assay, is a rapid blood test for MTB that has been shown to have higher sensitivity than the tuberculin test in children and is less susceptible to variations resulting from protein-energy malnourishment, low weight for age, or HIV infection.26

**Radiography**
Chest radiography has an important role in the diagnosis of TB in children, with a predominance of enlarged hilar, mediastinal, or carinal adenopathy, with parenchymal lesions or pleural effusion. In addition, the radiograph may also show features arising from the obstructive effects of the enlarged nodes, such as hyperinflation or collapse. Milary lesions, cavitation, and large lymph nodes tend to be more common in HIV-positive children than in HIV-negative children. Other HIV-related conditions, such as lymphoid interstitial pneumonitis, may present with a similar radiographic picture and should be considered in the differential diagnosis.

Given the difficulty with bacteriologic confirmation of TB in children, a pediatric score chart based on duration of illness, nutritional status, history of TB in the family, and TST reactivity was first
developing countries begins with an initial phase consisting of four drugs (two months of rifampicin, isoniazid [INH], pyrazinamide, and ethambutol) followed by a two-drug continuation phase (either four months of rifampicin and INH or six months of INH and ethambutol). In HIV-positive children, PTB and lymph node TB are classified as WHO clinical stage III, and EPTB as WHO clinical stage IV. Therefore, all patients infected with HIV who also have TB should be considered eligible for antiretroviral therapy (ART) if CD4 lymphocyte counts are not available.

When to Begin TB/HIV Co-Treatment

While there is a clear need for TB treatment in HIV-positive children with TB disease, the optimal timing for the initiation of ART for those receiving TB treatment is not known. The decision about when to start ART after starting TB treatment involves a balance between the child’s age and health, the pill burden, potential drug interactions, overlapping toxicities, and the risk of immune reconstitution syndrome versus the risk of further progression of immune suppression (with its associated increase in mortality and morbidity).

Additionally, research has clearly shown that the degree of immunodeficiency in TB/HIV coinfected children is highly correlated with mortality and that earlier initiation of ART is more critical in coinfected children with low levels of CD4 lymphocytes.

**Box 1. Recommended Approach to the Diagnosis of TB in Children (WHO)**

**Steps to Diagnosis**

1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing
4. Bacteriological confirmation (where available)
5. Investigations relevant for suspected PTB and EPTB
6. HIV testing (in high-HIV-prevalence areas)
Thus, WHO recommends that ART should begin as soon as possible (usually between two and eight weeks after the start of TB therapy, when the child has stabilized on this therapy) in children at WHO clinical stage IV, regardless of immunological criteria, and in children with clinical stage III and concurrent severe or advanced immunodeficiency. For children at clinical stage III who have either non-significant or mild immunodeficiency, the clinical response to TB therapy can guide the decision as to whether ART should be initiated urgently or can be delayed. Where CD4 percentage is available, the WHO criteria for ART initiation (Table 1) may be used. Recommendations for the timing of ART following the initiation of TB treatment are presented in Table 2.

### INTERACTIONS OF TB DRUGS AND ANTIRETROVIRALS IN CO-TREATMENT

To date, the first-line treatment recommendation for children with TB and HIV coinfection has been the triple nucleoside reverse transcriptase inhibitor (NRTI) regimen consisting of stavudine (d4T) or zidovudine (AZT) + lamivudine (3TC) + abacavir (ABC). Alternatively, in children over three years of age and/or weighing more than 10 kilograms, a standard first-line regimen of two NRTIs plus efavirenz (EFV) has been recommended. In children under three years of age, EFV is not recommended routinely (pharmacokinetic studies in this age group remain to be completed) and the use of a standard first-line regimen of two NRTIs + nevirapine (NVP, as the non-nucleoside reverse transcriptase inhibitor [NNRTI] component) can be considered. However, because of concern about the potential for subtherapeutic dosing of NNRTIs with concomitant rifampicin, a triple NRTI regimen is the preferred choice in this situation. Some clinical reports indicate adequate virological and immunological responses and acceptable toxicity with standard doses of NVP with concomitant rifampicin. This option may be considered where a triple nucleoside regimen is not feasible. However, because NVP levels are reduced more than EFV levels, a regimen of two NRTIs + NVP should only be considered when no other options are available and when careful clinical and laboratory monitoring can be assured (i.e., clinical monitoring for potential liver toxicity and liver function tests). More data are needed to determine rifampicin and NVP interactions and the exact NVP dosage requirement in children receiving rifampicin. In some areas, substituting rifabutin for rifampicin (rifabutin is a less potent inducer of cytochrome P450 enzyme) may be considered, but this is often not feasible in resource-limited settings due to high drug costs.

Alternatively, a triple nucleoside regimen may be considered. Neither option is ideal, as a study in HIV-positive adults on a regimen of AZT + 3TC + ABC reported lower virological potency than an EFV-based regimen (79% versus 89% efficacy, respectively, at 32 weeks). This may be even more

<table>
<thead>
<tr>
<th>Age</th>
<th>Infants &lt;12 months</th>
<th>12 months through 35 months</th>
<th>36 months through 55 months</th>
<th>5 years or over</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CD4</td>
<td>All</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Absolute CD4*</td>
<td>&lt;750 mm³</td>
<td>&lt;350 mm³</td>
<td>As in adults (&lt;200)</td>
<td></td>
</tr>
</tbody>
</table>

* Absolute CD4 count is naturally less constant and more age-dependent than % CD4; it is therefore not appropriate to define a single threshold.
<table>
<thead>
<tr>
<th>Clinical stage of child with TB (as an event indicating need for ART)</th>
<th>Timing of ART following initiation of TB treatment (rifampicin-containing regimen)*</th>
<th>Recommended ARV regimen†</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO pediatric clinical stage IV&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With clinical management alone:</td>
<td>■ Start ART soon after TB treatment (between 2 and 8 weeks following start of TB treatment)</td>
<td>In children &lt;3 years&lt;sup&gt;c&lt;/sup&gt;:</td>
</tr>
<tr>
<td></td>
<td>■ Start ART soon after TB treatment (between 2 and 8 weeks following start of TB treatment)</td>
<td>■ Triple NRTI first-line regimen (d4T or AZT + 3TC + ABC)</td>
</tr>
<tr>
<td></td>
<td>■ If excellent clinical response to TB treatment in first 2 to 8 weeks of TB therapy, and child is stable on CPT;&lt;sup&gt;a&lt;/sup&gt; it may be reasonable to delay initiation of ART</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Standard first-line regimen of two NRTIs + NVP&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In children &gt;3 years&lt;sup&gt;c&lt;/sup&gt;:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Triple NRTI first-line regimen (d4T or AZT + 3TC + ABC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or</td>
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<tr>
<td></td>
<td></td>
<td>■ Standard first-line regimen of two NRTIs + EFV&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Following completion of TB treatment, it is preferable for the child to remain on the ART regimen if well tolerated</td>
<td></td>
</tr>
<tr>
<td>WHO pediatric clinical stage 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Where CD4 is available:</td>
<td>■ Regimens as recommended above</td>
</tr>
<tr>
<td></td>
<td>■ Evaluate the possibility of delaying initiation of ART depending on assessment of clinical status and CD4 counts, and clinical and immunological response to TB therapy:</td>
<td>Where ART can be delayed until after completion of TB treatment, initiation with a standard two NRTIs + NNRTI first-line regimen is recommended</td>
</tr>
<tr>
<td></td>
<td>■ Severe and advanced immunodeficiency:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Initiate ART soon after TB treatment (between 2 and 8 weeks following start of TB treatment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Mild or no immunodeficiency:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Initiation of ART may be delayed until after the completion of TB therapy; closely monitor response to TB therapy and reassess need for ART after TB therapy; if no improvement, consider starting ART</td>
<td></td>
</tr>
</tbody>
</table>

ARV = antiretroviral; CPT = cotrimoxazole preventive therapy; NVP = nevirapine; NRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleotide reverse transcriptase inhibitor; d4T = stavudine; AZT = zidovudine; 3TC = lamivudine; ABC = abacavir; EFV = efavirenz

<sup>a</sup> Administration of CPT is important in children with TB/HIV coinfection.

<sup>b</sup> All children with pediatric clinical stage IV disease should be initiated on ART regardless of CD4 criteria.

<sup>c</sup> Careful clinical monitoring with laboratory support, if available, is recommended where NVP is administered concurrently with rifampicin.

<sup>d</sup> Because of lack of data, the ranking of preferred or alternative ARV regimens is not possible.

<sup>e</sup> EFV is not currently recommended for children <3 years of age, and should not be given to postpubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not using adequate contraception.

<sup>f</sup> CD4 criteria for severe immunodeficiency in children (by age): <25% or <1,500 cells/mm<sup>3</sup> (≤11 months); <20% or <750 cells/mm<sup>3</sup> (12 months to 35 months); <15% or <350 cells/mm<sup>3</sup> (35 months to 59 months); <15% or <200 cells/mm<sup>3</sup> (≤5 years); advanced immunodeficiency is assumed to be up to 4% above the age-specific CD4 threshold for severe immunodeficiency or 200–349 cells/mm<sup>3</sup> for children >5 years of age.

<sup>g</sup> CD4 criteria for mild or nonsignificant immunodeficiency is assumed at age-specific CD4 levels above those defining advanced immunodeficiency.

Source: Adapted from WHO.<sup>29</sup>
Severely immunocompromised children may present with rarer opportunistic infections, including *Pneumocystis carinii* pneumonia.

When children on appropriate treatment continue to do badly or have a poor response, it is always necessary to rule out immune reconstitution TB and to investigate for poor adherence. Additionally, incorrect diagnoses and treatment may also result in deteriorating clinical conditions. Most children who receive treatment for PTB are smear-negative cases. In the absence of easy diagnostic options, an important reason for a poor response to TB treatment is that the child does not truly have PTB. The atypical presentation and overwhelming difficulties in diagnosing PTB in children mean that it may be confused with other causes of HIV-related lung disease. If children do not improve on TB treatment, consider other diagnoses (e.g., lymphocytic interstitial pneumonia [LIP] or cardiac disease).

Although few studies are currently available describing the absorption of anti-TB agents in children with TB and HIV infection, this has been described in adults. Malabsorption of anti-TB drugs should be considered as a possible cause of treatment failure or as a sign of the acquisition of drug resistance, particularly if gastrointestinal symptoms or chronic diarrhea is present.

**Cotrimoxazole Prophylaxis**

While all HIV-exposed infants and children should benefit from cotrimoxazole (CTX) prophylaxis, this intervention is particularly important in children coinfected with TB and HIV. Studies of adults coinfected with HIV and TB have demonstrated better survival rates in patients who received CTX than in patients who received no prophylaxis. A large, randomized, controlled trial of HIV-positive children in Zambia showed significant reductions in mortality and hospital admissions among those receiving CTX. WHO recommends that all children under five years who are coinfected with TB and HIV should be maintained on CTX irrespective of immune recovery in response to ART.

**Monitoring Response to TB Therapy**

A positive clinical response to TB treatment should be observed within the first two to three weeks of receiving anti-TB therapy. This includes apyrexia (absence or intermission of fever), improved respiratory distress, fewer chest signs, and weight gain (or stabilized weight). Children coinfected with HIV and TB are far more susceptible to other respiratory diseases and more likely to die despite TB treatment. Mixed respiratory infections are a particular feature of HIV-positive children, and it is common for children with TB to develop bacterial pneumonia as a complication. In children with moderate immunosuppression, organisms responsible for these secondary infections are most often the same organisms found in HIV-uninfected children and should be treated with the appropriate first-line antibiotic therapy.

Drug-resistant TB

The emergence and discovery of drug-resistant TB is of great importance worldwide, as it impacts TB control in the general population and requires more expensive and difficult diagnosis and treatment. In general, the incidence and types of resistant organisms encountered in children will reflect the organisms circulating in the community. In children, drug resistance is usually primary resistance, as children are less likely to have been unsuccessfully treated in the past. In most children, definite confirmation of drug-resistant TB will not be possible, due to higher relevant in infants and young children, where baseline viremia is often much higher than that found in untreated adults. Other concerns for triple NRTI regimens are cost, limited data in patients with TB, and the need to monitor for hypersensitive reactions due to ABC.
rates of sputum-negative TB cases and difficulties obtaining sputum specimens. Often the diagnosis of drug-resistant TB is made on the basis of confirmation of drug resistance in the index (usually adult) case. However, children in high-TB-prevalence settings may have multiple exposures, so that even if close contacts have drug-sensitive disease, the possibility of resistant disease in the child still exists. The recent increase in reports of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB have caused a great deal of concern and further support the need for routine surveillance of drug resistance patterns to enable countries to adapt treatment options as needed.

**Antiretroviral Treatment Failure and TB Treatment**

When there are signs of treatment failure of the first-line regimen, switching to a second-line regimen can be considered after the child has received more than 24 weeks of ART and has not responded to anti-TB treatment. Single protease inhibitors (PIs) or PIs given with low-dose ritonavir boosting are not recommended to be administered with rifampicin because of the decrease in PI drug levels. Therefore, in children who are receiving a second-line regimen with ritonavir-boosted PIs and who are diagnosed with TB, the choice of antiretroviral (ARV) regimens is extremely difficult. Although there are limited data, some experts recommend lopinavir-ritonavir (LPVr) administration with additional ritonavir dosing to provide standard therapeutic doses. The use of other boosted PI combinations, including saquinavir with higher-dose (i.e., full-dose) ritonavir boosting and nelfinavir, is discouraged until further data become available.

**Immune Reconstitution Inflammatory Syndrome and TB**

Immune reconstitution inflammatory syndrome (IRIS) is well described in adults on ART and is commonly reported in association with mycobacterial infections. IRIS in children has been reported but is less well described. Although IRIS is not specific to HIV infection, it is broadly defined as the apparent clinical deterioration or presentation of opportunistic infections in HIV-positive individuals, usually within three months after starting ART. Immune reconstitution may arise in two different settings: unmasking of preexisting disease in a patient with previously undiagnosed infection, or worsening of previously recognized disease in a patient being treated for an opportunistic infection. This may occur anywhere from one week to six months after initiation of treatment. Symptoms and signs of immune reconstitution PTB include worsening respiratory symptoms, such as cough; high fevers; lymphadenopathy; and worsening of chest radiographic findings.

The diagnosis of a paradoxical reaction is by exclusion and can only be presumed once a thorough evaluation has been made to exclude other etiologies. The optimal time for initiating ART and minimizing the risk of IRIS in patients receiving anti-TB treatment remains unknown. Delaying ART to reduce the risk of IRIS in severely symptomatic TB coinfected children with advanced HIV disease is not presently recommended because the risk of mortality is high. Risk factors associated with paradoxical reactions in children appear to be similar to those in adults and include starting ART within two months of TB treatment, disseminated and extra-pulmonary TB, and rapid ART-mediated CD4 count increase and viral load decrease, especially in cases of more advanced disease. These reactions are generally self-limiting and last 10 to 40 days, although some reactions may be severe and require a short course of treatment with glucocorticoids. Only in extremely severe (rare) cases is the stopping of ART necessary in the management of IRIS.
Preventing the Spread of TB

The source case for TB in children is usually an adult with whom the child has been in close contact. Therefore, establishment of contact screening in cases of infectious TB is one strategy that will enable the early identification and treatment of childhood infection and disease and therefore reduce the morbidity and mortality associated with childhood TB. Several studies have also shown that, contrary to the widespread belief that children are not a source of infection, children with TB can transmit infection to adults.41

Infants and young children under five years of age are at increased risk of developing TB following exposure to infection, with disease developing within two years. The risk of TB disease has been shown to depend on the degree of smear-positivity of the source cases as well as the length of contact and is higher for female contacts (usually the mother or caregiver).42 It is therefore recommended that household contacts of smear-positive cases be screened for symptoms of disease (including clinical assessment, TST, and chest X-ray [CXR] if available) and that children less than five years of age be offered isoniazid preventive therapy (IPT).43 Asymptomatic children and those with no evidence of TB on chest radiograph should be offered 5 mg/kg of INH for six months.

The TST should be used to identify cases of TB infection and should be considered positive if the induration is 10 mm or more in an HIV-negative child who has received BCG vaccination. However, in children with HIV infection, an induration of 5 mm or more should be considered positive, and INH should be offered to children over five years of age.44 (Note: Despite the low sensitivity of TST in HIV-positive children, WHO still recommends the use of TST for screening and diagnosis.)

Prior to providing IPT, the child should be assessed clinically and with chest radiograph in order to exclude TB disease. All children who

Figure 1. Approach to contact management when chest X-ray and tuberculin skin test are not readily available

Source: Ministry of Health Zambia.45

IPT = isoniazid preventive therapy.

a Isoniazid 5 mg/kg daily for 6 months.

b Unless the child is HIV-positive (in which case isoniazid 5 mg/kg daily for 6 months is indicated).
PREVENTION AND MANAGEMENT OF TUBERCULOSIS

are contacts of a smear-positive case and who are symptomatic should be evaluated to exclude TB and should be treated with a full course of IPT, regardless of the result of the tuberculin test. The recommended algorithms for cases in which CXR and TST are or are not readily available are shown in Figures 1 and 2.

If TB is diagnosed in a pregnant woman shortly before delivery, the infant and (when possible) the placenta should be investigated for TB, and the infant treated if infection is detected. If the mother has been on anti-TB treatment for several weeks before delivery, infection of the infant is less likely. Breastfed infants of smear-positive cases are at an increased risk of developing TB and should receive six months of INH followed by BCG vaccination; it is not necessary to stop breastfeeding. An alternative is to give three months of INH and then perform a TST. If the test is negative, stop the INH and give BCG. If the skin test is positive, continue INH for another three months, then stop INH and give BCG.

EPTB IN HIV-POSITIVE CHILDREN

EPTB can occur at any age, but young children are particularly susceptible. Up to 25% of TB cases may present with EPTB. Children less than two years of age are at risk of disseminated disease causing miliary TB or tuberculous meningitis (TBM). Many patients with EPTB also have coexistent PTB.

Figure 2. Approach to contact management when chest X-ray and tuberculin skin test are readily available

Source: Ministry of Health Zambia.

![Diagram of TB test possible scenarios]

- **TB Test Possible**
  - **Tuberculin POSITIVE**
    - Child well: Isoniazid 6 months
    - Child not well: Detailed history and examination for TB (X-ray if possible)
    - Possible or probable TB: Full treatment for TB
  - **Tuberculin NEGATIVE**
    - Child well: Preventive isoniazid 2 months
    - Child not well: Repeat tuberculin test
    - Tuberculin positive: Complete 6 months isoniazid
    - Tuberculin negative and well: Stop isoniazid
Tuberculous Lymphadenopathy
Regardless of HIV status, the lymph nodes most commonly involved in EPTB are the cervical nodes. The usual course of lymph node disease is shown in Figure 3.
- If a patient has EPTB, look for PTB.
- If the patient has had a productive cough for more than two or three weeks, send sputum samples for AFB testing. If the test is negative, perform CXR.
- In severely immunocompromised patients, tuberculous lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis.

Diagnosis of tuberculous lymphadenopathy is possible even without laboratory facilities for histology or TB culture (see Figure 4). Diagnostic sensitivity of tuberculous lymphadenopathy by aspirate and smear for AFB is 70%. Diagnostic sensitivity increases to 80% if the lymph node is excised, the cut surface looked at, and a smear for AFB performed. The histological appearance of tuberculous lymph nodes from HIV-positive patients depends on the degree of immunosuppression, as shown in Table 3.

Although lymphadenopathy due to HIV infection is itself relatively common in children with HIV infection and does not always indicate serious underlying pathology, the following features indicate a need for further investigation:
- Large lymph nodes (greater than 4 cm in diameter) or rapidly growing lymph nodes
- Asymmetrical lymphadenopathy
- Tender/painful lymph nodes not associated with local infection
- Matted/fluctuant lymph nodes
- Obvious constitutional features (e.g., fever, night sweats, weight loss)
- Hilar or mediastinal lymphadenopathy on CXR

Miliary or Disseminated TB
Miliary TB results from widespread blood-borne dissemination of TB bacilli, either due to a recent primary infection or the erosion of a tuberculous lesion into a blood vessel. Patients present with constitutional features. Miliary TB is often an underdiagnosed cause of end-stage wasting in HIV-positive individuals. A high index of suspicion is necessary.

CXR shows diffuse, uniformly distributed, small miliary shadows (miliary literally means “like small millet seeds”). The CXR can appear normal in advanced cases because of severe immunosuppression and therefore inability to mount an inflammatory response. The typical diffuse CXR abnormalities can be confused with those of LIP.

Table 3. Histological Appearance of Tuberculous Lymph Nodes according to Degree of Immunosuppression in HIV-Positive Patients

<table>
<thead>
<tr>
<th>Immunosuppression in HIV-Positive Patients</th>
<th>Histological appearance of lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Degree of immunocompromise</strong></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Caseating lesions with few or no AFB</td>
</tr>
<tr>
<td>Severe</td>
<td>Little cellular reaction with many AFB</td>
</tr>
</tbody>
</table>

Source: WHO.43
There is clinical overlap because LIP presents with a broad range of clinical and radiographic features, which vary depending on the stage of HIV disease.

**Tuberculous Serous Effusions**

Inflammatory tuberculous effusions may occur in any of the serous cavities of the body (i.e., pleural, pericardial, or peritoneal cavities). They are more common in school-aged children with or without HIV infection. Serous effusions are often indicative of primary disease or reinfection.

**Pleural Effusion**

With a pleural effusion, children present with constitutional symptoms and local features...
including chest pain, breathlessness, tracheal and mediastinal shift away from the side of the effusion, decreased chest movement, and/or dull percussion note and decreased breath sounds on the side of the effusion. When available, CXR shows unilateral, uniform white opacity, often with a concave upper border. If available, ultrasound can confirm the presence of fluid in the pleural space in case of doubt. Diagnostic pleural aspiration is recommended if a patient has a pleural effusion. The fluid is usually straw-colored. Occasionally the fluid is blood stained. The presence of pus on aspiration indicates an empyema (purulent effusion).

**Pericardial Effusion**

The diagnosis of pericardial effusion usually rests on suggestive constitutional and cardiovascular features (mainly shortness of breath, difficulty feeding, abdominal swelling, and failure to thrive). CXR may be helpful and shows a large globular heart, usually clear lung fields, and pleural fluid. Electrocardiogram may be helpful if qualified staff are available to interpret the results. Definitive diagnosis is based on echocardiography, which shows pericardial fluid with or without strands between the visceral and parietal pericardium. It is important to exclude uremia and Kaposi’s sarcoma.

Treatment with steroids and anti-TB drugs, without pericardiocentesis, usually results in satisfactory resolution of tuberculous pericardial effusion. In populations with high TB/HIV prevalence, TB is the most likely treatable cause of pericardial effusion. It may be safer for the patient to start presumptive anti-TB treatment than to undergo diagnostic pericardiocentesis.

**Ascites**

Ascites are abnormal accumulations of serous fluid in the spaces between tissues and organs in the cavity of the abdomen that may result from peritoneal TB. Children present with constitutional features and ascites. Marked wasting is common. Signs of other causes of ascites, such as nephritic syndrome (peripheral and periorbital edema) or portal hypertension (marked splenomegaly), are usually absent. There may be palpable abdominal masses (mesenteric lymph nodes).

Where available, CXR should be done to look for associated PTB and a diagnostic ascitic tap performed. The aspirated exudate is usually straw-colored, but occasionally turbid or blood stained. Ultrasound, if available, may show enlarged mesenteric or retroperitoneal lymph nodes. Blind percutaneous needle biopsy of the peritoneum has a low pick-up rate and a high complication rate.

**Tuberculous Meningitis**

Children with TBM usually present with constitutional features and chronic meningitis. There is gradual onset and progression of headache and decreased consciousness. Examination in children seldom reveals neck stiffness and a positive Kernig sign (i.e., pain and resistance on attempting to extend the leg at the knee, with the thigh flexed at the hip). Cranial nerve palsies may result from exudate around the base of the brain. Tuberculomas and vascular occlusion may cause focal neurological deficits and seizures. Obstructive hydrocephalus may develop. Spinal meningeal involvement causes paraplegia (spastic or flaccid).

The diagnosis usually rests on clinical grounds and cerebrospinal fluid (CSF) examination. In most cases of clinically suspected TBM, lumbar puncture is safe. When performing lumbar punctures, it is important to note the following:

- Lumbar puncture is hazardous if the patient has a focal neurological deficit (i.e., cerebral space-occupying lesion) or if fundoscopy shows papilledema (i.e., raised intracranial pressure).
• Lumbar puncture is important for differentiating purulent bacterial meningitis from TBM. Where available, cryptococcal meningitis can be excluded by CSF microscopy (India ink stain) and fungal culture.
• In some countries, cultural beliefs may prevent patients from consenting to lumbar punctures. Under these conditions, health workers should be trained to have a high index of suspicion and a relatively low threshold for empiric TB treatment. Failure to treat appropriately at an early stage is likely to result in profound, permanent neurological damage.

Other Forms of EPTB
Other forms of EPTB are less common. There is no information as to whether they occur any more frequently in HIV-positive children than in HIV-negative children.

RECOMMENDATIONS FOR INTEGRATION OF TB AND HIV CARE FOR PEDIATRIC PATIENTS
The following discussion is based on the recommendations contained in the Zambian TB/HIV Guidelines.46

Key priorities for TB control programs seeking to better integrate TB and HIV care for pediatric patients include prevention of HIV infection through strengthened prevention of mother-to-child transmission (PMTCT) programs; early identification of HIV-infected infants; and early TB identification, care, and prevention. The following is a brief summary of how both TB and HIV care activities can be linked in order to ensure timely detection, treatment, and follow-up of coinfected patients.

TB services can be linked to HIV care and treatment through the following:

- Routine HIV diagnostic counseling and testing (DCT) for all TB patients
- HIV prevention counseling for all patients, which includes easy referrals and linkages to other related services (e.g., PMTCT, maternal and child health services)
- Rapid entry into HIV/AIDS care and treatment programs for TB patients who are infected with HIV—should be done as soon as possible, regardless of the patient’s clinical status (WHO staging) or immune function (CD4 percentage/absolute count)

HIV counseling and testing services (e.g., voluntary counseling and testing, PMTCT) can be linked to TB services through the addition of active symptom screening for TB as a routine component of HIV testing.

HIV care and treatment services can be linked to TB services through the following:

- HIV care and treatment programs should incorporate routine, active screening for TB in all HIV-positive children at all visits. However, more structured, directed screening should be performed (1) at enrollment of all children, especially those who are severely immunocompromised; (2) for those with a recent positive adult contact; and (3) for any child failing to respond positively to ART or who is deteriorating after an initial response. This structured screening should include close monitoring of weight gain and a regular chest exam (particularly for those presenting with failure to thrive, a chronic cough, fever, or weight loss). An easy-to-use checklist (see Figure 5) can be adapted for use in screening children. CXR, where available, is useful but cannot be used to rule out TB infection.
- Patients on concomitant anti-TB therapy and ART should be seen twice weekly until stable
 Community- and home-based prevention and care programs should coordinate and collaborate to maximize the effectiveness, efficiency, and benefits for clients who are coinfected or who are at risk of being coinfected.

**CONCLUSION**

The diagnosis and management of TB in HIV-positive children remains a challenge. Distinguishing between primary TB infection, relapse, or untreated and/or partially treated or drug-resistant subclinical infection is clinically difficult, particularly in areas of high TB prevalence where reinfection rates are high. The optimal timing of ART initiation for children receiving anti-TB treatment has not yet been determined. However, delaying ART initiation to reduce the risk of IRIS in severely symptomatic and/or clinically advanced TB coinfected children is not advisable, because the risk of mortality is high.

Initiation of ART within eight weeks of TB treatment, disseminated and extrapulmonary TB, rapid CD4 count increase (in response to ART), and rapid viral load decrease have all been associated with an increased risk of IRIS. Despite
adequate screening, subclinical infection may be easily overlooked in severely immunocompromised children. Traditional TB diagnostic tools are often insensitive in HIV-positive children and may lead to over- and underdiagnosis and treatment; further research is needed in this area. Avoiding unnecessary TB treatment is important in the context of ART, as the simultaneous administration of ARV and anti-TB drugs is associated with decreased tolerance and adherence, increased drug toxicity, and subtherapeutic ART levels. Integration of TB and HIV services is needed to ensure comprehensive identification and management of coinfected children. Additional research is needed into easier-to-use, point-of-care TB diagnostics, as well as ARVs that cause fewer drug interactions and are therefore better suited for use in children, in order to alleviate the burden of both these diseases in resourcelimited settings.
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Approaches to Prevention and Management of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

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WORLDWIDE, TUBERCULOSIS (TB) is second only to HIV/AIDS as a cause of death from a communicable disease. Two billion people, approximately one-third of the world’s population, are infected with Mycobacterium tuberculosis and have latent TB infection or active disease. In 2006 alone, 9.2 million people were newly infected, and 1.7 million people died of TB infection. In the same year, the World Health Organization (WHO) estimated that 90% of individuals living with TB infection and disease live in developing countries. Although the global incidence rate of TB appears to be declining in many parts of the world, the recent increases in the total number of cases in Eastern Europe, parts of Southeast Asia, and Africa are sufficient enough in number to cause a global increase in TB cases. In Eastern Europe, the increases are attributed to breakdowns in national health-care systems during the economic crises at the end of the communist era, while in Africa, dramatic increases in TB have resulted from the catastrophic scale of the AIDS epidemic in several countries.

Added to the rising burden of TB and HIV is the increasing recognition of the insidious and now growing epidemic of drug-resistant TB in many parts of the world. Although the large majority of TB cases worldwide are susceptible to available effective anti-TB therapy, drug-resistant TB has now emerged as a major and emergent threat worldwide (Figure 1). Drug-resistant TB is defined by resistance to various anti-TB drugs and characterized as resistance to single or multiple agents:

- **Any drug-resistant TB** describes TB with resistance to one of multiple drugs.
- **Multidrug-resistant TB** (MDR-TB) is defined as having resistance to the two most potent anti-TB drugs, isoniazid and rifampin.
- **Extensively drug-resistant TB** (XDR-TB) is newly defined as having multidrug resistance (resistance to isoniazid and rifampin) as well as resistance to at least two additional second-line medications, a fluoroquinolone and one or more injectable agents (amikacin, kanamycin, or capreomycin).

Drug-resistant M. tuberculosis is further characterized by its genesis into acquired or primary resistance.

- **Acquired resistance** is the result of inadequate treatment completion with consequent selection of resistant organisms, also referred to as the amplification of resistance.
Primary or initial resistance is the result of the transmission of TB strains that have already acquired resistance. In this instance, patients may start therapy with the disadvantage of being unable to benefit from the most potent therapeutic regimens.

Acquired resistance resulting from inadequate therapy has been the most common cause of TB drug resistance worldwide, and its presence is taken as a measure of the effectiveness of TB treatment programs.

Although previously often thought of as resulting only from patient adherence failure, the genesis of acquired TB drug resistance is more complex and results from several factors, either singly or in combination, as outlined in Box 1.

Resistant isolates emerge under pressure from (inadequate) drug therapy. Classically, acquired resistance is believed to occur under selective drug pressure as a single mutation or an accumulation of mutations, the latter also known as the amplification of resistance. These mutations either alter the target protein of the antituberculous agent or attenuate the effect of the antituberculous agent by overproducing the target protein.\textsuperscript{10,11} Horizontal or plasmid-mediated transmission of resistance has not been demonstrated in \textit{M. tuberculosis}.

The genetic barrier of a particular drug to resistance is based on the efficacy of the drug and the probability of mutations. For instance, in susceptible \textit{M. tuberculosis}, the average rate of mutations leading to isoniazid resistance is $2.3 \times 10^5$ mutations/bacterium/generation, with an estimated mutation prevalence of $1 \times 10^6$ bacilli in an environment without drug pressure. For resistance to rifampin, the mutation rate is $2.5 \times 10^{10}$ mutations/bacterium/generation, with an estimated mutation prevalence of $1 \times 10^8$. The chances of resistance to isoniazid and rifampin together (MDR-TB) occurring in nature are the product of the individual mutation prevalences—$1 \times 10^4$—and therefore extremely low. Anti-TB agents have differing barriers to resistance: less effective drugs such as capreomycin, cycloserine, ethionamide, thiacetzone, and viomycin have a higher mutation incidence (of $10^3$) and therefore a higher propensity for
Box 1. Factors Contributing to Development of Drug-Resistant TB  

**Patient and Provider Factors:**
- Patient’s nonadherence (lack of education, lack of transportation, substance use disorder)
- Prescribing error (insufficient number of agents, suboptimal dosing)
- Inadvertent use of nonviable medications (treatment of resistant organisms)
- Malabsorption
- Drug interactions

**Health System Factors:**
- Poorly functioning DOTS program
- Medication inaccessibility (stock-outs) or poor-quality medications
- Insufficient providers / distant health-care facilities
- Lack of culture and drug susceptibility testing (including second-line drugs)

resistance, while drugs such as isoniazid, ethambutol, kanamycin, para-aminosalicylic acid (PAS), and streptomycin have a lower mutation rate ($10^4$) and therefore a higher barrier to resistance.  

Many examples of acquired drug resistance have been reported from both high-income and resource-limited settings. Most recently, in a study from South Korea, among 250 patients with TB (excluding HIV-positive patients), MDR-TB was noted in 10% of new cases and 65% of previously treated patients, while XDR-TB was noted in none of the new cases and 16% of previously treated patients, suggesting that the XDR-TB in South Korea is mainly acquired in the setting of inadequate therapy.

A prime example of the amplification of acquired resistance was recently demonstrated in South Africa. Utilizing molecular genotyping and resistance testing, analysis of MDR-TB isolates from 1994 to 2002 revealed the most common genotype, F15/LAM4/KZN, and demonstrated stepwise accumulation of drug resistance to ethionamide, capreomycin, kanamycin, and lastly fluoroquinolones from 1994 to 2000, to become extensively drug resistant. Streptomycin resistance in the F15/LAM4/KZN genotype in 1994, coupled with the practice in South Africa (following WHO guidelines) of adding streptomycin alone to four-drug regimens in patients with interrupted or failing therapy, suggests that this strategy may have aided in the development of XDR-TB in South Africa. Surveillance, nationally and internationally, to monitor trends in drug resistance is recommended to avoid recurrence of this potential iatrogenic phenomenon.

Primary drug resistance, long thought to be less common than acquired resistance, appears to be increasing dramatically in settings of high HIV prevalence. Under these circumstances, unsuccessful treatment for TB is associated not only with individual patient treatment failure and the selection of resistant organisms, but also with the transmission of these resistant organisms to others and the further spread of TB resistance. Such a scenario likely accounts for the recently described epidemic of XDR-TB among HIV and TB coinfected patients in rural South Africa, where 55% of patients with XDR-TB had not previously received antituberculous therapy and therefore had been infected with an isolate that had already accumulated mutations and amplified resistance.

The history of TB drug resistance begins with the development of the first effective antituberculous drug. The discovery of streptomycin in 1945 for the treatment of TB heralded the era of effective TB chemotherapy. However, in 1947, resistance to streptomycin was first reported and its clinical significance was quickly appreciated. The finding of streptomycin resistance among relapsed patients ultimately led to multidrug regimens as standard chemotherapy. Not until the early 1990s, when outbreaks of MDR-TB occurred in New York City, Florida, Madrid, and Argentina, did drug-resistant TB begin receiving attention. These outbreaks of MDR-TB occurred in the setting of a burgeoning

HIV epidemic. Those who were coinfected with HIV and TB experienced very high mortality rates.\textsuperscript{20} Since that time, the global presence of drug-resistant TB has escalated. In 2000, the estimated number of worldwide cases of MDR-TB was 272,906; in 2004, the estimated burden of MDR-TB was 424,203 cases, or 4.3% of all new and previously treated cases.\textsuperscript{2} In 1994, WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) began standardized surveillance of drug resistance and published the first results in 1997. This initial global survey included results from only 35 countries and reported the median rate of MDR-TB among all TB isolates as 1%.\textsuperscript{3} The next survey, published in 2000, included 72 regions and revealed a stable median MDR-TB rate of 1% in all new cases, though extremes were noted in certain regions such as Estonia, where a 14% prevalence of MDR-TB was reported among new cases.\textsuperscript{4} In previously treated cases, the median rate of MDR-TB was 9.3% but ranged up to 48% in areas such as Iran.\textsuperscript{24} India’s southern state of Tamil Nadu, Mozambique, and Zejiang province in China were also considered to have significant MDR-TB burdens. In 2004, WHO reported a stable median MDR-TB rate among new cases of 1.1%, with 10 countries showing rates greater than 6.5%, including Ecuador, China, Latvia, the Russian Federation, Kazakhstan, and Israel; the latter two had the highest rates, at 14.2% each. The median MDR-TB rate among previously treated cases was reported as 9%, with extremes up to 58% and 56% in Oman and Kazakhstan, respectively.\textsuperscript{5} In early 2008, WHO published the most recent survey of drug resistance. Among new cases of TB globally, the proportion of MDR-TB cases rose to 2.9%, reaching a high of 19.4% in Moldova and 22.3% in Azerbaijan. Notably, 14 of the 20 regions with the highest MDR-TB rates are located in the former Soviet Union, and another 4 are in China. Among previously treated cases, the mean MDR-TB rate was 15.3%, with a 17.2% rate in Gujurat state in India, and a high of 55.8% in Azerbaijan and 60% in Uzbekistan.\textsuperscript{24} For the first time, the report also collected information on XDR-TB; over four years, Tomsk Oblast in the Russian Federation and Estonia reported, respectively, 6.6% and 23.7% rates of XDR-TB among their MDR-TB cases. Over six years of routine surveillance from 2000 to 2006, the United States reported 17 cases, or 1.9% of its MDR-TB cases, with available second-line drug (SLD) susceptibility testing results. Over a four-year period, Barcelona, Spain, and the Czech Republic reported 8.1% (3 cases) and 20% (5 cases), respectively, of XDR-TB among MDR-TB cases. In countries that conducted surveys, Rwanda and Tanzania reported 0%; Baku, Azerbaijan, reported 12.8% (55 cases); and Donetsk Oblast in Ukraine reported 15% (3 cases) of XDR-TB among cases of MDR-TB.\textsuperscript{6}

Although WHO has monitored global rates of drug resistance, surveillance has been limited in the areas of the world with the greatest TB burdens and almost nonexistent in African countries, largely due to the lack of infrastructure, particularly laboratory support. Only two countries in Africa have performed serial surveys of resistance, Mozambique and Botswana. Mozambique reported an increase in drug resistance of 3% from 2002 to 2003, in an analysis of HIV patients with newly diagnosed TB. In this study, MDR-TB comprised 5.8% of new cases and 15.8% of previously treated cases.\textsuperscript{37} In Botswana, the prevalence of MDR-TB has been low, although an increasing trend from 0.2% in 1995 to 0.8% in 2002 has been seen.\textsuperscript{26} In South Africa, national surveillance of TB and drug resistance has been too infrequent. The last national surveillance was conducted in 2001–2002, revealing an MDR-TB prevalence of 1.6% among new patients and 6.6% among patients previously treated.\textsuperscript{1} Recent data suggest that this rate likely has risen dramatically since then, but information is available only from isolated areas.\textsuperscript{18,29}
TUGELA FERRY AND THE DISCOVERY OF XDR-TB

SouTh AfRica represents a striking example of the HIV epidemic in sub-Saharan Africa and the interaction of the HIV and TB epidemics. In South Africa, 18.8% of all adults were infected with HIV in 2005. In 1990, 80,400 new cases of TB were reported to WHO, while in 2005, 15 years later, the number had risen more than fivefold, to 270,000. Of new adult TB cases, 58% are HIV positive nationally, though in some areas rates of greater than 90% have been reported. Although antiretroviral roll-out has provided therapy for HIV/AIDS for more than 300,000 people, only one-third of those who require antiretroviral therapy (ART) are currently receiving it. In 2005, the estimated TB incidence was 600 cases per 100,000 population, only 54% of new smear-positive TB cases were cured, 15% completed treatment (but were not cured), 11% defaulted, and 7.4% died during treatment—results that are well below internationally recommended performance levels.

Tugela Ferry is located within the 2,000-square-kilometer rural Msinga subdistrict of KwaZulu-Natal province in South Africa. The subdistrict’s quarter-million population is comprised largely of traditional Zulu residents with high rates of poverty and unemployment. This area was plagued by increasing rates of TB, in the setting of a highly HIV-prevalent population. Prior to the era when ART became available, the mortality in this region among TB/HIV coinfected patients was estimated to be 40%.

In 2003, researchers from Yale University School of Medicine partnered with physicians at Church of Scotland Hospital, the 355-bed provincial district hospital of Tugela Ferry, and Philanjalo, a local nongovernmental organization (NGO), to develop a program to integrate therapy for HIV/AIDS and TB. This program utilized voluntary community health workers, treatment literacy training for all patients prior to initiating antiretrovirals, and household/family support for the initiation and monitoring of TB therapy with isoniazid, rifampin, ethambutol, and pyrazinamide. All TB patients were offered voluntary HIV counseling and testing, and those who tested positive were started on ART with a once-a-day regimen of didanosine, lamivudine, and efavirenz, administered concomitantly with TB therapy. In 2005–2006, mortality rates with the new program decreased to approximately 12%, but the majority of those who died were noted to have had TB with an unexpectedly high level of drug resistance. Laboratory testing revealed resistance to all drugs tested: isoniazid, rifampin, ethambutol, streptomycin, ciprofloxacin, and kanamycin. Of the 14 patients who died, 10 were found to have XDR-TB.

The researchers and physicians subsequently launched a more intensive surveillance effort in Tugela Ferry. Of more than 1,500 patients, 544 (35%) had culture-positive TB. Among those 544 patients, 41% were found to have MDR-TB, and 10% (or 53 patients) were found to have XDR-TB. Among those 53 patients, mortality was 98%, with a median survival of 16 days after sputum collection. Therefore, most patients died prior to obtaining the results of the culture. This was the first and largest global cluster of XDR-TB ever recorded. It was reported in August 2006 at the International AIDS Conference and published shortly thereafter.
globally in most parts of the world: XDR-TB comprised 15% of the MDR-TB cases in South Korea6 in 2004 and 10.9% of MDR-TB in Iran from 2003 to 2005. In Latvia, the percentage of XDR-TB of total MDR-TB cases rose from 19% in 2000 to 21% in 2002.6 A Russian Federation TB reference center reported XDR-TB in 1.4% of new TB cases and 35.9% of retreatment cases in 2006.33

The XDR-TB pandemic has continued to expand. As of February 2008, 45 countries have reported at least one case of XDR-TB (Figure 1).9

As of February 2008, more than 350 cases of XDR-TB have been reported from the district hospital in Tugela Ferry. More than 50 other hospitals and clinics in the KwaZulu-Natal province, and the 8 other provinces of South Africa, have also reported cases of XDR-TB.28,34 Although not the result of a national surveillance sample, a retrospective review of laboratory data from all provinces of South Africa from 2004 to 2007 reported 996 cases of XDR-TB.26

While the emergence of the HIV/AIDS epidemic has had a significant role in increasing worldwide TB incidence, particularly in developing nations, the exact nature of the relationship between HIV and drug-resistant TB is still unclear. HIV infection may increase susceptibility to TB infection and does both increase reactivation of latent infection and facilitate rapid progression to active disease. HIV infection is the strongest risk factor for the development of TB infection and complicates TB diagnosis. Rapid progression to active disease combined with increased susceptibility to infection among HIV patients is one possible model to explain the increasing global spread of TB in the setting of HIV/AIDS.35 However, multiple studies show conflicting data as to the association of HIV with drug-resistant TB.36 In the Tugela Ferry XDR-TB outbreak, 100% of patients tested for HIV were positive.18 In the last national survey in South Africa in 2001–2002, there was no relationship between HIV status and drug resistance.5 Although the majority of cases thus far reported have been associated with HIV-positive patients, XDR-TB disease has now been reported in HIV-negative individuals in South Africa27 and in Korea.38 Two recent studies have demonstrated that HIV is an independent risk factor for drug-resistant TB. Data from Donetsk Oblast in Ukraine in 2006 demonstrate that HIV coinfection is associated
Health-care providers must keep in mind that the epidemiology of drug-resistant TB, especially XDR-TB, in high-HIV-prevalence areas is rapidly evolving, and that the risk factors above are not completely validated or sufficiently accurate to predict the presence or absence of drug resistance. In the initial Tugela Ferry XDR-TB cluster,18 the majority (55%) of the patients with XDR-TB had not previously received any antituberculous agents. A recent evaluation of 170 patients with drug-susceptible and drug-resistant TB demonstrated that while hospitalization within the prior two years and antituberculous therapy within the prior year were significant risk factors for XDR-TB, only 38% and 28%, respectively, of the patients meeting these criteria actually had XDR-TB.40 The unreliability of clinical suspicion makes the selection of an anti-TB regimen for treatment of patients with XDR-TB a complex dilemma for providers.

**MANAGEMENT OF MDR- AND XDR-TB**

**Diagnosis**

The diagnosis of drug-resistant TB is difficult; the medical history, routine physical examination, and X-ray studies are not sufficiently sensitive or specific to distinguish between drug-susceptible and drug-resistant TB. Tuberculin skin test (TST) results are not altered with drug-resistant TB, nor does the presence or absence of acid-fast bacilli (AFB) on sputum-smear microscopy distinguish between drug-susceptible and drug-resistant TB.

However, some historical features in patients with suspected TB are suggestive of increased likelihood of drug resistance (see Box 2). Clinical suspicion is often the main tool available at the time a patient with drug-resistant TB appears for evaluation.

**Box 2. Individual Risk Factors for Drug-Resistant TB**

- History of previous therapy, especially within the last year
- History of recurrence after previous successful treatment
- Hospitalization in an institution with a known MDR/XDR-TB cluster, particularly within the last two years
- History of nonadherence
- Residence in a prison, drug treatment facility, or shelter
- History of kanamycin resistance
- Exposure to or household contact with a known MDR/XDR-TB patient
- Residence in an area with a high prevalence of drug resistance
- History of medications concurrent with TB therapy that may have decreased the efficacy of the anti-TB medications (i.e., drug interactions with antiretroviral therapy)
- History of malabsorption
- Previous participation in a program that was operated poorly
- HIV infection
Diagnosis of drug-resistant TB requires microbiologic studies including culture and drug susceptibility testing (DST). Newer technologies, including molecular tests, are being developed, as described below, but are not readily available in resource-limited settings. The absence of microbiological facilities, including capacity for SLD susceptibility testing, has severely hampered the diagnosis and appropriate treatment of drug-resistant TB. Even when available, current culture preparation and DST require prolonged periods of time and result in delays in appropriate therapy and the continued transmission of resistant organisms. Growth on solid culture can take up to six to eight weeks, while liquid culture requires up to three to four weeks. DST takes up to another six weeks after *M. tuberculosis* is identified by culture. The current preferred choice for DST is the 1% proportion method, evaluating bacterial growth on agar plates infused with known concentrations of antituberculous drugs. Resistance is considered present if 1% of the bacterial concentration is resistant to the critical concentration of the antituberculous drug. Unlike for first-line agents, the critical concentrations for SLDs are often similar to the minimal inhibitory concentration (MIC), making DST for drug-resistant TB more complex. Furthermore, correlation of in vitro testing with clinical outcomes is not optimal, and DST methodology is not standardized. Ideally, all patients with TB, especially those with the risk factors noted in Box 2, should have sputum or other body fluids tested for susceptibility to isoniazid, rifampin, ethambutol, and streptomycin, with the addition of SLD testing. If DST is not possible routinely, as is the case in most resource-limited settings, clinical decision making is hindered and the opportunity for successful treatment outcomes is limited. The lack of laboratory capability for culture and DST has contributed to the growth of MDR- and XDR-TB—patients with drug-resistant TB are initiated on inappropriate and ineffective therapy, which potentiates the spread and increases the risk of toxicities from inappropriate medications. In most regions, as in southern Africa, and in accordance with WHO guidelines, culture is not routinely recommended and is reserved for cases of treatment failure or relapse, or for cases of smear-negative TB and failure to respond to conventional antibiotics. In practical terms, it is often the failure to convert to smear negativity after two months of therapy, or persistence of fever weeks after starting an antituberculous regimen, or clinical or radiological deterioration despite therapy, that leads to the concern about drug resistance. Without DST data, clinicians are forced to rely on algorithms and/or experience to initiate therapy, which has been a failed strategy.

**Newer DST Methods**

Several methods have been increasingly used to replace the lengthy process required by culture on solid media with subsequent DST by the agar proportional method. Automated liquid cultures such as the Bactec 460 and MBBacT are dependent on carbon dioxide production, while the MGIT (Mycobacteria Growth Indicator Tube) depends on oxygen consumption; both types decrease the time to positive culture to two to three weeks. While trials with the MGIT system are under way in several resource-limited settings, the costs of the complicated culture vials (US$2–US$8 per vial) and large incubators needed for backup solid-media culture, and the potentially high rate of contamination of liquid cultures, limit the applicability of this technology for most resource-limited settings.

The Microscopic Observation Drug Susceptibility (MODS) assay is another recent addition. It is inexpensive and simple to conduct, with results available within a median time period of seven days, ideal for resource-limited settings. The MODS assay depends on the characteristic serpentine cording of *M. tuberculosis* and the use of an inverted microscope.
to evaluate for growth and cording, with simultaneous wells supplemented by various concentrations of antituberculous drugs. This assay has shown excellent correlation with traditional Lowenstein-Jensen culture and automated MBbAcT culture systems, and has been validated in highly endemic TB regions. Trials in highly prevalent HIV areas are under way. One major limitation of this assay is that it does not currently include susceptibility testing for SLD.

Molecular assays such as nucleic acid amplification tests (NAATs) are currently the best-studied application for the identification of *M. tuberculosis* and drug resistance. The most common assays include polymerase chain reaction (PCR), transcription amplification (GenProbe), and strand displacement amplification; all show high specificity, though sensitivity is slightly lower than that of culture. Loop-mediated isothermal amplification (LAMP) is being developed for improved case detection and would potentially require little molecular training for staff, though it does still require specimen processing, albeit via simplified methods. Trials in resource-limited settings show highly variable results, however, and the costs and expertise required to run these assays and to maintain the equipment are currently beyond the capacity of laboratories in most resource-limited settings.

A barrier to molecular tools for diagnosing TB has been specimen processing and DNA extraction. One promising new tool involves real-time PCR (GeneXpert) on clinical specimens; it automates the entire process and requires little from lab personnel and little laboratory infrastructure. It is currently being developed to identify the presence of *M. tuberculosis* as well as molecular beacons for rifampin resistance with a turnaround time of less than two hours.

With regard to DST, there are other new technologies that may be very helpful and in certain instances could lead to more rapid initiation of treatment with SLDs. These include line probe assays for the gene mutations in the rpoB sequence supporting rifampin resistance as well as phage-based assays such as FASTPlaque, which assesses rifampin resistance within days. The phage-based FASTPlaque has been developed into a commercial kit and is in trials, though it does require new technical skills for laboratory workers. The Hain and Innogenetics assays both utilize standard PCR on smear-positive sputum with amplicon hybridization to oligonucleotide probes on nitrocellulose strips, promising results within 24 hours, and have shown good results in early studies, though up to 10%–15% show indeterminate responses, requiring retesting. A pilot study of this assay in 536 patients showed 99% sensitivity and 100% specificity in smear-positive cases, and 14 out of 15 smear-negative culture-positive specimens were also correctly identified. The costs associated with this assay may be less than with traditional culture and DST; a larger demonstration project is under way.

While these assays would require substantial training of laboratory workers, the real-time PCR (GenXpert) mentioned above has also shown promising results for rapid identification of rifampin resistance with little required infrastructure, ideal for resource-limited settings.

**Therapy**

Patients with drug-resistant TB are at increased risk of treatment failure—therapy is less potent, more complex, more toxic, more prolonged, and more expensive compared to treatment with first-line drugs. All these factors contribute to decreased completion rates, decreased cure rates, and increased mortality. Treatment can be successful if a plan of care with sufficient infrastructure and individual patient commitment is established.

The cornerstone of TB treatment has been DOTS—initially an acronym for directly observed therapy and short course chemotherapy—which has evolved to encompass the main public health...
strategy for TB control. Implementation of DOTS showed significant improvement in TB control in several countries, though resistance also increased. A DOTS-plus strategy was introduced in 1998, focused on improving resources for MDR-TB and deriving individual treatment regimens from DST or empiric therapy based on local epidemiology. This strategy has been successful, with cure rates approaching 70% in selected resource-limited settings, though highly HIV-prevalent areas have had less success. The Stop TB Strategy established in 2000 has broadened the scope of the approach to managing TB to include health-system strengthening, strategies for MDR-TB and HIV/TB coinfection, patient and community empowerment, and promotion of research into newer diagnostics, drugs, and vaccines.

There are no randomized controlled trial data on which to base treatment guidelines for drug-resistant TB; these are primarily the result of case series and expert consensus. Experience with MDR-TB is limited in certain areas, and expert consultation is usually recommended. The choice of regimen is ideally based on DST; however, this is not always possible. Hospitalization has traditionally been preferred for the initiation of therapy so that the infectious person is removed from the community, adverse effects can be addressed immediately, treatment can be supervised, and the patient can be educated with regard to the importance of treatment. However, in light of recent findings suggesting the nosocomial spread of XDR-TB, this approach is currently being debated and some advocate for outpatient therapy. An outpatient course of therapy hinges on the clinical stability of the patient; some patients require hospitalization at least for initiation of therapy. The decision for inpatient treatment is made after an individual case-by-case discussion between providers and patients, based on risks and benefits.

There have been few trials evaluating the feasibility and safety of this strategy. In Peru, 75 patients with MDR-TB were treated in the ambulatory setting, with 66 completing therapy and 83% considered probable cures. Only 1 patient among 65 patients tested was positive for HIV in this study. Another study of 48 XDR-TB patients from Peru demonstrated that cure rates of 60.4% were possible with aggressive monitoring, though none of these patients were HIV positive. Another recent study in rural Guangxi province in China reported improved cure and completion rates among

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**Box 3. Principles for Choosing and Administering a Regimen for MDR/XDR-TB**

- Minimum of four drugs, preferably five or more
- Include any first-line agents to which the patient’s isolate is susceptible
- Include an injectable if possible
- Include a fluoroquinolone if possible
- Bactericidal drugs are preferable to bacteriostatic agents
- Make use of the higher end of the recommended dosing, as tolerated
- Each dose of medication should be administered under DOTS (directly observed therapy short course)
- Patients should also receive 150 mg pyridoxine (B6) daily as part of the regimen
- Once drug susceptibility testing results are available, treatment regimens should be adjusted to consist of preferably five drugs sensitive to the patient’s isolate
- Medications should be administered six days per week, commonly twice per day to decrease side effects
- The injectable medication should be administered for at least six months after sputum conversion
- Continuation phase should continue for 18–24 months after sputum conversion
- A patient-centered approach is essential to avoid default and improve outcomes
- Documentation of all therapy is critical
should be performed as soon as a problem is identified. Close monitoring and support is also important for psychological tolerance of medications.

Hospitalization for the initial phase may also be important to address substance abuse or psychiatric comorbidities, if present. However, the likely nosocomial spread of XDR-TB may incline providers against prolonged hospitalization.

Empiric therapy of drug-resistant TB should begin with six or seven new drugs, including at least two that are bactericidal (Table 1).

Treatment is likely the last chance for cure and should be approached this way with the patient. Education of the patient decreases the likelihood of default. Medications likely to cause gastrointestinal distress should be taken at bedtime. Interventions such as antiemetics for nausea, loperamide for diarrhea, and electrolyte repletion for patients with significant gastrointestinal losses should be monitored and anticipated, and any dose adjustments should be performed as soon as a problem is identified. Close monitoring and support is also important for psychological tolerance of medications. Hospitalization for the initial phase may also be important to address substance abuse or psychiatric comorbidities, if present. However, the likely nosocomial spread of XDR-TB may incline providers against prolonged hospitalization.

Empiric therapy of drug-resistant TB should begin with six or seven new drugs, including at least two that are bactericidal (Table 1).

With XDR-TB, aiming for five drugs may be more desirable but less feasible. It is important to be familiar with the patient’s previous medications as well as local resistance patterns. An empiric regimen (Box 4) should include enough medications such that if some need to be discontinued due to toxicities or tolerability issues, an adequate regimen will still be in place. Once the results of susceptibility testing are known, the most toxic or weakest drugs can be removed.

### Box 4. Suggested Regimens

For isolates with resistance to isoniazid and rifampin (MDR):
- Pyrazinamide–ethambutol–fluoroquinolone–streptomycin–ethionamide
- Streptomycin (or other injectable) should be continued for at least 6–12 months and until sputum conversion; remaining regimen should be continued for at least 18 months

For isolates with resistance to isoniazid, rifampin, ethambutol, and pyrazinamide (MDR):
- Fluoroquinolone–injectable (kanamycin/amikacin/capreomycin)–2 of the following: ethionamide/cycloserine/para-aminosalicylic acid (PAS)
- The injectable may be discontinued after 6–12 months or sputum conversion; remaining regimen should be continued for at least 18 months after sputum conversion

Isolates with resistance to isoniazid, rifampin, fluoroquinolones, injectables (XDR)*
Standardized regimens or guidelines do not exist for the treatment of XDR-TB. A regimen must be constructed utilizing the principles described above. Some possibilities include the following:
- Capreomycin–PAS–cycloserine (or terizidone)–ethambutol and/or pyrazinamide (if susceptible)–thiacetazone (if HIV negative) or third-line agents
- Pyrazinamide–PAS–capreomycin–ethionamide–ethambutol–terizidone**
- Pyrazinamide–PAS–capreomycin–ethionamide–terizidone**
- Pyrazinamide–capreomycin–ethionamide–terizidone–clarithromycin–amoxicillin/clavulanate**

*Not based on data or guidelines
**Regimens used at TB reference hospital in South Africa

smear-positive and smear-negative patients, and decreased default rates among patients treated at a decentralized township hospital in comparison to traditional county dispensaries, though HIV status was not reported. This type of ambulatory strategy has yet to be implemented among patients with HIV, who may experience more adverse effects and drug interactions and require concomitant HIV therapy and closer monitoring.

The key principles for choosing a regimen and treating patients with MDR-TB therapy are listed in Box 3.
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Metabolism</th>
<th>Dose</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Line Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid (H, INH)</td>
<td>Isonicotinic acid hydrazide</td>
<td>Bactericidal; inhibits cell wall mycolic acid synthesis</td>
<td>Hepatic acetylated (individual slow vs. fast acetylator predicts half-life)</td>
<td>5 mg/kg, 300 mg daily</td>
<td>Hepatitis&lt;br&gt;Peripheral neuropathy (prevented with 25 mg or 50 mg pyridoxine daily)&lt;br&gt;Uncommon: gynecomastia, psychosis, seizure</td>
</tr>
<tr>
<td>Rifampin (R) Rifabutin Rifapentine</td>
<td>Rifamycins</td>
<td>Bactericidal; binds to D subunit of RNA polymerase</td>
<td>Hepatic</td>
<td>8–12 mg/kg, 300–600 mg daily</td>
<td>Hepatitis&lt;br&gt;Orange body fluids&lt;br&gt;Class cross-resistance&lt;br&gt;Rifabutin is a less potent inducer of CYP450, and, therefore, drug interactions less concern&lt;br&gt;Rifapentine should not be used in patients with HIV infection or unknown HIV status, cavitary disease, or positive sputums at end of initiation phase&lt;br&gt;Decreases efficacy of oral contraceptives; consider increased estrogen dose</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>Nicotinamide</td>
<td>Bacteriostatic; mechanism unclear, disruption of membrane</td>
<td>Hepatic; renal excretion</td>
<td>25 mg/kg, 1 g daily</td>
<td>Hepatitis&lt;br&gt;Hyperuricemia</td>
</tr>
<tr>
<td>Ethambutol (E, EMB)</td>
<td>Ethylidimino</td>
<td>Bacteriostatic; inhibition of cell wall synthesis</td>
<td>Renal excretion</td>
<td>15 mg/kg, 800 mg daily</td>
<td>Uncommon: retrobulbar neuritis in renal failure&lt;br&gt;Some experts recommend 25 mg/kg initially, decreasing to 15 mg/kg once culture negative</td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>Aminoglycoside</td>
<td>Bactericidal; binds to 16sRNA, inhibits translation</td>
<td>Renal excretion</td>
<td>15 mg/kg, 1 g intramuscularly daily</td>
<td>Ototoxicity, potentiated by renal failure, loop diuretics&lt;br&gt;Nephrotoxicity&lt;br&gt;Peripheral neuropathy&lt;br&gt;Pain at injection site&lt;br&gt;Vestibular toxicity&lt;br&gt;Contraindicated in pregnancy</td>
</tr>
</tbody>
</table>
### Table 1. Antituberculous Agents (cont.)

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Metabolism</th>
<th>Dose</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second-Line Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin (CPX)</td>
<td>Fluoroquinolones</td>
<td>Renal excretion</td>
<td>CPX 1500 mg daily</td>
<td>GI upset</td>
<td>Class cross-resistance</td>
</tr>
<tr>
<td>Ofloxacin (OFX)</td>
<td></td>
<td></td>
<td>OFX 800 mg daily</td>
<td>Mild psychosis</td>
<td>Decreased absorption with milk, antacids, divalent cations</td>
</tr>
<tr>
<td>Levofloxacin (LFX)</td>
<td></td>
<td></td>
<td>LFX 750 mg daily</td>
<td>Seizure (mainly in elderly)</td>
<td>Gatifloxacin may prolong QT interval and dysglycemia</td>
</tr>
<tr>
<td>Moxifloxacin (MFX)</td>
<td></td>
<td></td>
<td>MFX 400 mg daily</td>
<td></td>
<td>Greatest long-term data with levofloxacin</td>
</tr>
<tr>
<td>Gatifloxacin (GFX)</td>
<td></td>
<td></td>
<td>GFX 400 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin (K)</td>
<td>Aminoglycoside</td>
<td>Renal excretion</td>
<td>15 mg/kg, 1 g daily</td>
<td>Ototoxicity, potentiated by renal failure, loop</td>
<td>Contraindicated in pregnancy</td>
</tr>
<tr>
<td></td>
<td>Bactericidal; binds to 16srRNA,</td>
<td></td>
<td></td>
<td>diuretics Nephrotoxicity Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inhibits translation</td>
<td></td>
<td></td>
<td>Pain at injection site Vestibular toxicity</td>
<td></td>
</tr>
<tr>
<td>Amikacin (AMK)</td>
<td>Aminoglycoside</td>
<td>Renal excretion</td>
<td>15–20 mg/kg, 1 g</td>
<td>Ototoxicity, potentiated by renal failure, loop</td>
<td>Class cross-resistance</td>
</tr>
<tr>
<td></td>
<td>Bactericidal; binds to 16srRNA,</td>
<td></td>
<td>intramuscularly daily</td>
<td>diuretics Nephrotoxicity Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inhibits translation</td>
<td></td>
<td></td>
<td>Pain at injection site Vestibular toxicity</td>
<td></td>
</tr>
<tr>
<td>Capreomycin (CM)</td>
<td>Cyclic polypeptide</td>
<td>Renal excretion</td>
<td>15–20 mg/kg, 1 g</td>
<td>Nephrotoxicity OtotoxicityPeripheral neuropathy</td>
<td>No cross-resistance with aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>Bactericidal; inhibits tRNA and</td>
<td></td>
<td>intramuscularly daily</td>
<td>Pain at injection site Vestibular toxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>protein synthesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide (ETO)</td>
<td>Thiamides</td>
<td>Hepatic metabolism,</td>
<td>15–20 mg/kg, 750 mg</td>
<td>High-frequency GI distress Metallic taste Hypothyroidism, especially with</td>
<td>Seizures with cycloserine</td>
</tr>
<tr>
<td>Prothionamide (PTO)</td>
<td></td>
<td>renal excretion</td>
<td>daily</td>
<td>PAS</td>
<td></td>
</tr>
<tr>
<td>Class</td>
<td>Mechanism</td>
<td>Dose</td>
<td>Side effects</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------</td>
<td>--------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Second-Line Agents (cont.)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloserine (CS)</td>
<td>Alanine analogue, disrupts cell wall proteoglycan synthesis</td>
<td>Renal excretion</td>
<td>Neurologic/psychiatric: irritability, aggression, headaches, tremors Uncommon: psychosis, neuropathy, seizures esp. with alcohol and INH</td>
<td>Add 50 mg pyridoxine for every 250 mg CS to attenuate central nervous system (CNS) side effects May increase phenytoin levels</td>
<td></td>
</tr>
<tr>
<td>Terizidone (Trd)</td>
<td>Contains cycloserine, similarly efficacious</td>
<td>15–20 mg/kg daily</td>
<td>GI distress, headache seizures, dysarthria</td>
<td>Vitamin B6 should be given to attenuate CNS side effects</td>
<td></td>
</tr>
<tr>
<td>Paraaminosalicylic acid (PAS)</td>
<td>Salicylic acid, inhibits folic acid metabolism</td>
<td>200–300 mg/kg, 2–4 doses, 12 g daily</td>
<td>Hypothyroidism, especially with ETO Uncommon: hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Third-Line Agents (little available information)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiacetazone (THZ)</td>
<td>Weakly bactericidal; inhibits mycolic acid synthesis</td>
<td>2.5 mg/kg, 150 mg daily</td>
<td>GI distress vertigo conjunctivitis, hypersensitivity reactions including Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS) especially in HIV infection</td>
<td>Cross-resistance with INH and ETO; avoid in hepatic, renal impairment; avoid in HIV patients</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>Not established</td>
<td>Renal excretion 30%</td>
<td>Unknown for MTB</td>
<td>Lowers seizure threshold, myelosuppression if duration &gt; 2 weeks, peripheral neuropathy Serotonin syndrome</td>
<td></td>
</tr>
<tr>
<td>Clofazimine (CFZ)</td>
<td>Bacteriostatic; binds to DNA, inhibits growth</td>
<td>GI excretion</td>
<td>GI distress, reddish brown discoloration of skin, slowly resolves after discontinuation of drug</td>
<td>Concentrates in lung, liver, spleen Interacts with aluminum, magnesium, phenytoin Contraindicated in pregnancy and breastfeeding</td>
<td></td>
</tr>
</tbody>
</table>
For ethionamide/protonamide, cycloserine, and PAS, split daily dosing has traditionally been used, primarily to decrease toxicity. For aminoglycosides, if susceptible, streptomycin is the preferred agent. Kanamycin or amikacin is considered the next step; they are similarly efficacious but demonstrate cross-resistance. If streptomycin and kanamycin are not options based on DST, or if renal insufficiency is present, capreomycin is the agent of choice. Viomycin behaves similarly to capreomycin and will show cross-resistance with it. Between ethionamide/protonamide and PAS, the former is usually chosen for its lower cost and demonstrated efficacy, while the latter is chosen due to an enteric-coated formulation that is well tolerated. Given the high incidence of GI side effects with both of these agents, often one is used with cycloserine instead of together, unless both are necessary based on DST results. B6 should be given with cycloserine and terizidone to attenuate the central nervous system (CNS) side effects of these agents. Thiocetazone’s use is limited by potentially severe skin reactions, including Stevens-Johnson syndrome. This has been particularly noted in HIV patients, and the drug should be avoided in these patients.

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/Clavulanate</td>
<td>β-lactamase</td>
<td>Bacteriostatic</td>
<td>Not established for MTB</td>
<td>Rash, GI distress</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caution in hepatic impairment Lower efficacy of oral contraceptives</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Macrolide</td>
<td>Binds to 50S subunit of rRNA</td>
<td>Hepatic</td>
<td>GI distress, headache, Rare hepatic failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Halve dose for CrCl&lt;30</td>
</tr>
<tr>
<td>Viomycin (V)</td>
<td>Polypeptide</td>
<td>Inhibits translation and protein synthesis</td>
<td></td>
<td>Cross-resistance with capreomycin</td>
</tr>
</tbody>
</table>
In the setting of extrapulmonary TB, the design of a therapeutic regimen is based on similar principles as above. In the setting of CNS TB, drug penetration needs to be considered. The aminoglycosides and capreomycin penetrate in the setting of meningeal inflammation, while ethambutol and PAS demonstrate poor penetration.\textsuperscript{14}

Surgery has been a useful adjunct to medical therapy of drug-resistant TB. Indications for resection include high-level resistance (four or more drugs), multiple relapses despite appropriate therapy, persistently positive sputum for AFB after four to six months of therapy, and localized disease. Surgical intervention is not feasible with extensive bilateral

Many patients treated for drug-resistant TB may require nutritional supplements. For patients requiring divalent cation mineral replacements, these should be administered separately from fluoroquinolones to avoid poor absorption. No therapeutically reliable regimens exist for XDR-TB. When suspected, the greatest number of second-line agents possible is appropriate until DST results are available. Clofazimine, linezolid, amoxicillin-clavulanic acid, and clarithromycin have been utilized in specialized centers as “third-line” agents.\textsuperscript{55,59} However, limited information is available about their efficacy in the treatment of MDR- or XDR-TB.\textsuperscript{13,14}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Change Required?</th>
<th>Dose and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>N</td>
<td>300 mg once daily</td>
</tr>
<tr>
<td>Rifampin</td>
<td>N</td>
<td>600 mg once daily</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Y</td>
<td>15–25 mg/kg per dose three times per week</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Y</td>
<td>25–35 mg/kg per dose three times per week</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Y</td>
<td>12–15 mg/kg per dose two or three times per week</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>N</td>
<td>400 mg once daily</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>Y</td>
<td>400 mg three times per week</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Y</td>
<td>750–1000 mg per dose three times per week</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Y</td>
<td>600–800 mg per dose three times per week</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Y</td>
<td>1000–1500 mg per dose three times per week</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Y</td>
<td>12–15 mg/kg per dose two or three times per week</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Y</td>
<td>12–15 mg/kg per dose two or three times per week</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Y</td>
<td>12–15 mg/kg per dose two or three times per week</td>
</tr>
<tr>
<td>Ethio/Protonamide</td>
<td>N</td>
<td>250–500 mg per dose daily</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Y</td>
<td>250 mg once daily or 500 mg per dose three times per week</td>
</tr>
<tr>
<td>PAS</td>
<td>N</td>
<td>4 g per dose, twice daily</td>
</tr>
<tr>
<td>Terizidone</td>
<td>Unknown</td>
<td>Unavailable</td>
</tr>
</tbody>
</table>

TABLE 2. Dosing in Patients with Renal Insufficiency (CrCl<30 or on Hemodialysis)\textsuperscript{14}
disease, but may be utilized to improve chances of survival by “debulking” a particularly burdensome area of tuberculous disease. Ideal conditions for surgical intervention include sputum conversion on appropriate treatment, usually occurring with eight months (median two months) of treatment. Some experts recommend a more aggressive surgical intervention earlier in the treatment course, especially with more drug resistance, and providers should be familiar with the local surgical expertise for adjunctive treatment of drug-resistant TB.

Other assessments include serum albumin, imaging with chest X-ray (CXR) or computerized tomography (CT), pulmonary function tests (PFTs), and blood gas (PaCO₂ > 6 kPA generally precludes surgery). Treatment outcomes with surgical interventions have not been rigorously studied, though perioperative mortality rates of 3%-4% and cure rates up to 90% have been reported in patients with MDR-TB. Risk factors for treatment failure include the presence of cavities beyond the area of surgical resection, low body mass index (BMI), quinolone resistance, and primary resistance despite no history of antituberculous therapy. After resection, medical therapy should continue for 18–24 months.

Access to SLDs is essential and often problematic. To address this issue, the WHO Green Light Committee was established in association with the Global Fund to Fight AIDS, Tuberculosis and Malaria and has made significant advances in the past few years. As of the end of 2007, patients in 51 countries were approved for SLDs, and aggressive plans for expansion were under way but still only some 30,000 patients had been approved for treatment, a small number in comparison to the need.

**Monitoring**

Monitoring of patients on therapy should occur frequently (see Table 3), at least monthly while receiving an injectable agent. Once therapy with the injectable has been completed and the patient is taking only oral medications, visits with the clinician may take place less frequently (every two to three months).

**SPECIAL CONSIDERATIONS**

**Pregnancy**

Pregnancy is not a contraindication to treatment of active TB; in fact, the severity of the illness may threaten both the fetus and the mother, and treatment is obligatory. Due to the severity of adverse effects of certain antituberculous agents, pregnancy tests should be conducted in all women of childbearing age presenting with suspected TB, and those not pregnant should strongly consider birth control to avoid potentially severe teratogenic effects. Providers should be aware of the interaction of rifampin with oral contraceptives. Depo-Provera injections can be provided during the MDR/XDR-TB treatment course, but all women should be counseled for condom use to prevent against sexually transmitted infections and HIV. In pregnant women with drug-resistant TB and limited treatment options, the risk of teratogenicity must be balanced with the possibility of disease progression without treatment. Generally, aminoglycosides (streptomycin, kanamycin) should be avoided in pregnant patients due to ototoxicity and potential deafness in the fetus. However, if an injectable is needed, capreomycin may have less ototoxicity and may be an alternative. Ethionamide generally induces nausea and vomiting in pregnancy and has been shown to be teratogenic in animal studies and should be avoided in pregnancy if possible.

For women who are breastfeeding, all tuberculous agents may be found in small concentrations in breast milk. The effect of this in newborns has not been well studied. While it is ideal for mother and child to remain together, the child may transiently need care from others if a mother...
is smear positive. Breastfeeding is encouraged only once the mother has become smear negative. Mother-child interactions should take place outdoors, where temperatures allow, or in well-ventilated areas, or, if possible, an N95 respirator should be worn. If resources exist, infant formula may be provided until the mother completes therapy.
Pediatric Infection
Drug-resistant TB in children almost always occurs as a result of primary transmission. It is therefore imperative to identify the contacts and potential exposures of the child when designing a regimen. This is particularly true in children in whom sputum cultures are less obtainable, extrapulmonary disease is more frequent, and culture-negative or paucibacillary disease is more common. Despite this, every attempt to obtain culture and DST should be made to avoid exposure to and toxicities of potentially unnecessary medications. Detailed discussions are required between clinicians and families when designing a regimen, given the paucity of data on treatment of drug-resistant TB in children. Dosing should be calculated based on weight for all drugs. The use of fluoroquinolones in children has been out of favor, given concerns for hindering cartilage development; however, some data exist for their use in children with cystic fibrosis. The benefits of using quinolones to treat drug-resistant TB likely outweigh the risks. Ethionamide/protonamide, cycloserine, and PAS have been successfully used and tolerated in children. Weighing to determine medication dosing and to measure response to therapy is essential; all drug dosages should be adjusted as weight increases.

OUTCOMES
In studies of treatment of MDR-TB, success—as defined by completion of an extended course of therapy and/or cure—has been as high as 60%–70%. In Latvia, using a DOTS-plus strategy, of 204 patients with MDR-TB, 62% achieved “cure,” defined as those who completed treatment and were culture negative for the last 12 months. However, less than 1% had HIV disease. Frequency of cure decreased with history of previous treatment. Of those with new TB, 89% were cured. Of those with a history of previous treatment for TB, 64% achieved cure, while those with previous treatment for MDR-TB had only a 43% cure rate.

In a retrospective review of 205 patients treated for MDR-TB from 1994 to 1998 at a U.S. TB specialty center, 75% were reported to have long-term success, while 12% died. A study of 48 XDR-TB patients from Peru, all of whom were HIV uninfected, demonstrated cures in 60.4% of patients. Death occurred in 22.9%, treatment failure in 10.4%, and default in 6.2%. Notably, therapy with an injectable agent was continued for a median of 15.4 months. A recent study from South Korea in HIV-uninfected patients demonstrated poor outcomes associated with XDR-TB. Of 43 patients with XDR-TB, only 55% experienced treatment success, while 14% died. Of note in this study, approximately 40% of XDR-TB patients had only two to three susceptible drugs and so received isoniazid and rifampin to complete a five-drug regimen. XDR-TB patients also more frequently underwent surgical intervention (48%). Independent risk factors for poor outcome included low albumin, and borderline factors included underlying comorbidity and the presence of bilateral pulmonary cavities.

Coinfection with HIV is associated with significantly poorer outcome. Recently, 65 patients from New York City with XDR-TB were reported; 24 of 65 had primary XDR-TB, while 41 had acquired XDR-TB. Of these, 33.8% completed therapy. As expected, mortality was highest in HIV-coinfected patients; 75% of the HIV-coinfected patients died, while only 30% of the non-HIV patients died during therapy.

A study of TB patients in Tugela Ferry showed 6-month mortality rates among patients with non-MDR-TB of 32%, MDR-TB 69%, and XDR-TB 79%, while at 12 months mortality rates were 42%, 73%, and 85%, respectively. Notably, HIV serological status was not associated with survival (P=.21). However, this likely reflected low power to detect a
Clarithromycin is being utilized in treating XDR-TB and has interactions with the antiretroviral protease inhibitor atazanavir.\textsuperscript{67} Clarithromycin’s metabolism is inhibited, causing an increase in the area under the curve (AUC), requiring a 50% dose reduction.

Coinfected patients are known to have a higher rate of adverse reactions to both antituberculous and antiretroviral medications.\textsuperscript{58} Patients with drug-resistant TB and HIV need extensive social support and economic relief, given their initial isolation, the extended duration of therapy, the higher frequency of adverse effects, the high risk of treatment failure and death, and social stigma. Staff must be trained and supported to ensure that patients are treated humanely and not penalized because of their illness. Social welfare benefits and social support can assist in allaying the concerns patients have for their families, encourage them to seek care earlier in the course of disease,\textsuperscript{68} and avert default.

Care of coinfected patients requires both coordination between HIV and TB clinicians and a new structure for delivering care. Traditionally, services for TB and HIV patients have been distinct, and patients have faced the additional burden of receiving care in separate facilities. Collaboration of care has been proposed for years to improve diagnosis, treatment, and outcomes for patients with both TB and HIV disease, and has become part of international strategy and planning to improve clinical outcomes.\textsuperscript{69-74} Concerns have been raised that integration of care will result in increased TB transmission to vulnerable HIV-positive patients. However, proper attention to infection-control measures is absolutely necessary to minimize this risk (see following section, “Prevention of MDR- and XDR-TB”), and early diagnosis and treatment in the setting of a comprehensive approach to coinfected patients may justify the potential risk of transmission.

At the King George V TB referral hospital in South Africa, 62 patients from throughout KwaZulu-Natal province (including Tugela Ferry) were treated for XDR-TB with regimens including amoxicillin-clavulanate, clarithromycin, and clofazimine (although there is currently no clear evidence of the effectiveness of these drugs against TB), with a 52% survival rate at six months.\textsuperscript{59} It should be noted, however, that the patient population at King George V Hospital may be biased toward survival since many die before reaching this TB referral facility. Among the 51 out of 62 patients tested, 76% were HIV positive and 56% of these were being concurrently treated with antiretrovirals. Five of 20 deaths were attributed to medication effect, specifically hypokalemia secondary to capreomycin.\textsuperscript{59}

**DRUG-RESISTANT TB AND HIV/AIDS**

The use of antiretroviral therapy (ART) in HIV patients with TB improves survival from TB and delays progression to AIDS. However, significant drug interactions and adverse effects can occur in coinfected patients, which threaten the treatment of both diseases. Best known are the interactions of rifampin with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs).\textsuperscript{58} Another interaction involves didanosine (ddI), a common antiretroviral agent in resource-limited settings, and fluoroquinolones. Nonenteric-coated didanosine contains aluminum- and magnesium-based antacids and should be given at least six hours prior to or two hours after fluoroquinolone is administered.\textsuperscript{13}

There are presently no data regarding antiretrovirals and second-line TB medications.
PREVENTION OF MDR- AND XDR-TB

The Stop TB and HIV departments of WHO developed an XDR-TB Task Force in late 2006 to review the discovery of widespread XDR-TB and make recommendations for action. The recommendations recognize the need for more than the DOTS strategy and include improved laboratory capacity (such as technologies to rapidly identify resistance and to increase access to SLD testing), programmatic restructuring to reflect HIV/TB comanagement, increased advocacy to promote international efforts, mobilization of resources, and research and development for drug-resistant TB, as well as increased attention to reducing the transmission of drug-resistant TB. New antituberculous medications are critically needed and long overdue, but, apart from fluoroquinolones, are unlikely to be widely available within five years. Critical in the prevention arena is the development and implementation of policies and practices designed to reduce the transmission of drug-resistant TB in both health-care and community settings.

Infection Control

Airborne infection control is a major and necessary part of the management of MDR- and XDR-TB. Despite this, insufficient attention has been paid to this strategy. Policies and procedures to reduce the aerosolization of infected airborne particles and to reduce exposure to these are essential and have been recommended but are infrequently implemented. The recently described cluster of XDR-TB in South Africa has been associated with nosocomial transmission and has raised awareness of the importance of airborne infection control to reduce the spread of both drug-susceptible and drug-resistant TB.

Airborne infection control can be organized into three broad areas of policy and practice: administrative, environmental, and personal. Administrative measures include the development and deployment of policies and protocols to address infection control, staff education, increased communication among hospital departments, decreasing reliance on hospital care by decreasing hospital admissions and reducing length of stay in hospital, utilization of rapid laboratory diagnosis of TB, rapid identification of drug resistance, and strategies for the isolation of TB patients suspected or proven to have drug-resistant TB. However, isolation of TB suspects and patients who are coughing and producing infectious aerosols is particularly difficult in most facilities in the developing world, as most are characterized by large, open, and overcrowded wards. Moving patients out of the hospital and into the community for continuation of care has been proposed to decrease nosocomial transmission.

Among environmental measures, increased natural ventilation has been highlighted as an inexpensive and easy method to decrease transmission in warm climates. Natural ventilation relies on air flow through open windows and doors and may be facilitated by ceiling fans, while mechanical ventilation is found more in developed nations and is usually based upon the creation of negative-pressure facilities. Research on natural ventilation in Peru has demonstrated that simply opening doors and windows significantly affects air exchange and the risk of transmission from an infectious patient. These studies, which used the quintessential model for airborne infection transmission, the Wells Riley TB equation model, showed that the transmission risk in the hospital wards was 11% with all windows and doors open, compared to 39% with mechanical ventilation. High-efficiency particulate (HEPA) filters and ultraviolet light, considered mycobactericidal, are other respiratory-pathogen-specific techniques utilized in health-care facilities and laboratories to reduce transmission. Isolation in smaller groups of 5 or 10 patients rather than large open wards has also been proposed to decrease nosocomial spread of TB.
Personal transmission-reduction measures include the use of protective equipment such as respirator masks for staff and cough hygiene for patients, both of which can be of utmost importance in reducing transmission to vulnerable patients and particularly to health-care workers. Within the spectrum of personal protection, provider-initiated HIV testing and counseling of patients is considered essential to identify susceptible patients, potentially isolate them on this basis, and provide ART and cotrimoxazole.76,77

The issue of transmission to health-care workers is of particular importance and sensitivity and requires special attention. The scarcity of health-care workers in most resource-limited settings further complicates the provision of care and treatment. In the Tugela Ferry cluster,19 two staff members were among those who acquired XDR-TB. Since 2005, eight health-care workers at this rural provincial district hospital have died of drug-resistant TB.80 Voluntary HIV counseling and testing should be made freely available to health-care workers and strongly encouraged; if individuals test positive, there should be opportunities for reassignment to hospital units with less risk of TB exposure.76 A recently proposed model suggests that this intervention alone would decrease XDR-TB infections among health-care workers by one-third.79 Another intervention for health-care workers who are found to be HIV-positive is the initiation of ART at higher CD4 lymphocyte counts than those recommended by national guidelines.79

These strategies all make good sense and their rapid institution is critical, but their effect on transmission risk reduction is difficult to document. However, a recent study employing mathematical

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**Figure 2. Efficacy of infection-control measures in various combinations in reducing XDR-TB transmission**78

5 pt = isolating patients in groups of five patients; LOS = reducing average length of stay to 5 days; Mask = both staff N95 respirators and patient masks, with adherence enforcement; MODS = Microscopic Observed Drug Susceptibility assay; VCT = voluntary counseling and testing for HIV in admitted patients, with subsequent antiretroviral therapy for those who qualify; vent = improvements in natural ventilation

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modeling has provided strong support for their effectiveness. This report estimates that 1,300 cases of XDR-TB will occur from 2007 to 2012 in Tugela Ferry in the absence of interventions to reduce nosocomial transmission. Individual measures in the administrative, environmental, and personal categories all can reduce risk, but at a modest level. However, by combining available airborne infection control strategies, a significant proportion of anticipated cases (48%, or 625 cases) could be averted (see Figure 2).79 The most effective combination of measures included use of respirator masks by staff, reduction of hospital admission and length of stay, increased natural ventilation, rapid drug resistance testing, isolation of patients into smaller groups of five, and inpatient and staff HIV testing and provision of antiretrovirals.

With regard to the isolation of patients, there are some who advocate for involuntary detention as a means to control transmission.68 However, a careful analysis of this issue, taking into account both individual human rights and public health concerns, does not favor confinement as a major intervention. For the vast majority of patients, involuntary detention is not necessary. Most patients accept isolation and long-term inpatient stays as a means of decreasing transmission, monitoring side effects, and increasing overall chances of survival.81 Key to this approach is education of the patient and the patient’s family to improve cooperation and decrease defaulting. Though confinement may be necessary for the occasional patient, in general this approach is unwar- ranted and only serves to stigmatize drug-resistant TB at a time when clinicians hope that TB suspects will seek care as early as possible. Indeed, a compassionate and humane approach should be required for these patients, most of whom have primary infection and poor survival prospects.81 Furthermore, a recent model of infection-control measures suggests that involuntary detention as a sole intervention, without the provision of adequate isolation facilities, would actually serve to increase the number of cases of XDR-TB by 3% over the next five years due to the promotion of nosocomial spread.79 Strengthening of outpatient and community-based care and reducing reliance on prolonged inpatient care is a more satisfactory approach to this treatment issue.

**Provision of ART**

In the setting of coinfection with HIV and infection with, or risk for, drug-resistant TB, antiretrovirals are essential. Their use decreases viral loads, increases CD4 counts, and potentially reduces susceptibility to and improves survival in cases of drug-resistant TB. It is imperative that all TB patients undergo HIV testing and, if positive, initiate appropriate ART; this is particularly true in endemic regions where TB may be transmitted among HIV patients during encounters with the health-care system. Despite a national policy for testing all TB patients, the rates of testing have been low in most countries.82 If CD4 counts are available, they may be utilized to decide when to initiate therapy; however, when to start ART in relation to antituberculous medications remains controversial.83 One strategy to improve survival is to offer antiretrovirals earlier than national guidelines suggest; however, studies are needed to confirm the efficacy of this strategy.

Additionally, multiple studies have shown a mortality benefit in coinfected patients by administering cotrimoxazole to prevent concurrent *Pneumocystis jirovecii* infection as well as other bacterial infections.83 Despite general awareness of the benefit, this protective measure has not been widely implemented.

**Latent TB and Contact Tracing**

In areas of low TB prevalence, all HIV patients should undergo purified protein derivative (PPD) testing. Although a high proportion may be anergic, a positive test will allow for the treatment of latent
WHO THREE I’S FOR HIV/TB: INTENSIFIED CASE FINDING, INFECTION CONTROL FOR TB, AND ISONIAZID PREVENTIVE THERAPY
WHO HIV and TB Departments

Globally, WHO reported around 700,000 TB cases among people living with HIV in 2006. An estimated 230,000 people living with HIV will die as a result of TB in 2008—roughly 630 people every day—despite the fact that TB is curable. Sub-Saharan Africa is home to 85% of the people living with TB and HIV, with a disproportionately heavy burden in some countries. South Africa, for example, has 0.7% of the world’s population but accounts for 28% of the world’s HIV-positive TB cases and 33% of cases in the African region.

The majority of TB cases are curable, but drug-resistant TB has recently emerged as a significant public health threat—particularly for countries with a high HIV prevalence. Both MDR- and XDR-TB have been identified in all regions of the world. Given the underlying HIV epidemic, drug-resistant TB could have a significant negative impact in Africa and requires urgent action, including an increased focus on preventing, diagnosing and treating TB.

As resource-limited countries rapidly expand their HIV/AIDS treatment and care programs, important opportunities are emerging to better deal with the dual scourge of HIV/TB coinfection. Both HIV and TB are treatable and preventable, yet despite this, TB remains a major public health threat for people living with HIV. Indeed, TB is the most frequent life-threatening opportunistic disease, even in those receiving ART, and shamefully it remains a leading cause of death for people living with HIV.

Key points to consider include:
- People living with HIV are at increased risk of acquiring TB in the community or the health-care setting—**better infection control (IC) can reduce these risks**.
- Once infected with TB, HIV accelerates the appearance of TB disease—**this evolution to disease can be greatly reduced by isoniazid preventive therapy (IPT), a simple, safe, and cost-effective intervention**.
- Any delay in diagnosing established TB disease and starting appropriate therapy can lead to negative health outcomes including death—**intensified case finding (ICF) can identify cases early and improve treatment outcomes**.

Prevention and treatment of TB in people living with HIV is an urgent priority for both HIV/AIDS and TB programs. WHO therefore recently reviewed policy and practice in these three key domains, referred to as the “Three I’s for HIV/TB”: IPT, ICF, and IC. These interventions are key public health strategies to decrease the impact of TB on people living with HIV. In April 2008, the WHO HIV/AIDS and Stop TB Departments, in collaboration with other key partners, convened a meeting of international stakeholders to develop guidance for accelerating Three I’s implementation for people living with HIV. In April 2008, the WHO HIV/AIDS and Stop TB Departments, in collaboration with other key partners, convened a meeting of international stakeholders to develop guidance for accelerating Three I’s implementation for people living with HIV. In April 2008, the WHO HIV/AIDS and Stop TB Departments, in collaboration with other key partners, convened a meeting of international stakeholders to develop guidance for accelerating Three I’s implementation for people living with HIV. Several conclusions and concrete actions came out of this meeting, including:
- TB is a major public health threat for people living with HIV and threatens the significant gains made in recent years in HIV care and ART scale-up.
• There is an urgent need to strengthen the Three I’s supply chain, particularly potential isoniazid/cotrimoxazole coformulations and/or copackaging.

• Advocacy “push” and “pull”—top-down and bottom-up approaches will be necessary to ensure implementation progress. Advocacy should focus on the importance of the Three Is and the need to create community demand for TB screening, IPT and IC as positive actions to fight TB.

• Monitoring and evaluation is critical to monitor progress in scaling up the Three I’s to people living with HIV and their communities.

• Resource mobilization is essential for success and political commitment and resources for Three I’s implementation will need to be mobilized.

There is an urgent need to strengthen public health laboratory capacity and referral systems for the timely diagnosis of TB.

People living with HIV, health-care workers, and the community have a right to a safe clinical environment, which means immediate implementation of WHO-recommended TB infection control measures.

The Three I’s should be a central part of HIV care and treatment and are critical for the continued success of ART scale-up. Everyone accessing services in a higher HIV and TB prevalence area should be screened for TB and either diagnosed with TB or placed on IPT. Infection control is a key part of the screening process.

Implementation of the Three I’s should be owned by HIV programs and seen as being as indispensable as patient monitoring or cotrimoxazole prophylaxis.

There is an urgent need to strengthen the public health laboratory capacity and referral systems for the timely diagnosis of TB.

Resource mobilization is essential for success and political commitment and resources for Three I’s implementation will need to be mobilized.

infection, if appropriate, and close monitoring for active disease. For those primarily exposed to a patient with known MDR- or XDR-TB and newly diagnosed latent infection, there are few pharmacological options. Currently there are few data to support chemoprophylaxis or treatment of latent infection in contacts of patients with drug-resistant TB. The best-studied regimens have been isoniazid and rifampin, which will not be helpful in MDR- or XDR-TB infection. WHO does not support the use of SLDs for chemoprophylaxis of contacts, though certain agencies have recommended the use of pyrazinamide and either ethambutol or quinolone for the contacts of patients with MDR-TB. One small study of chemoprophylaxis in children who are contacts of MDR-TB patients has demonstrated benefit. Given the paucity of data, the potential toxicities of first- and second-line drugs, and the possibility of infection with strains other than those carried by the index patient, especially in endemic areas, contacts of MDR and XDR TB patients currently should be monitored closely for development of TB disease for at least two years. In those contacts with HIV infection, exposure to a person with known MDR- or XDR-TB may be an impetus to start ART. Knowing the TB drug susceptibilities of the index case is critical, if this information is available. If symptoms develop, a regimen for the treatment of MDR-TB should be chosen.

Surveillance of Drug Resistance

Laboratory capacity to improve the diagnosis of active TB and TB drug resistance in individual patients is essential, as discussed earlier in this chapter. Resources in the form of both facilities and human infrastructure are needed, though not likely
to be available for all patients. Regardless, ensuring a system for the surveillance of drug resistance is necessary to monitor trends in drug resistance and permit more rapid deployment of resources, particularly directed toward "hot spots" or sentinel events. Sturm et al have demonstrated that increasing drug resistance in South Africa has been building for years, but the absence of a proper surveillance system, adequately linked to local control programs, has led to a dangerous, costly, and tragic delay in the detection of XDR-TB. It is imperative that drug-resistance surveillance measures, including SLD susceptibility testing, be widely implemented in national TB programs.

CONCLUSION: THE WAY FORWARD

MDR- and XDR-TB uncover past and current neglect and deficiencies in TB knowledge, strategies, and programs, and illustrate the global nature of TB drug resistance. Fueled by the weakness and disruption of TB control programs and the explosive growth of HIV/AIDS, the presence of TB drug resistance, particularly in MDR and XDR forms, threatens the gains made in the past decades in the treatment of both TB and HIV, including the historic roll-out of ART in resource-limited countries. Challenges in epidemiological characterization, program development, and epidemic control strategies as well as in the prevention, diagnosis, and treatment of individual patients are great.

Effective short-term and longer-term solutions are critically needed to improve treatment completion and success and reduce the transmission of drug resistance to populations at risk. Short-term goals include dramatic increases in resources for struggling TB control programs, more rapid drug development and new drug testing, wider availability of existing and newer TB diagnostics and DST, and improvements in infection-control measures in health-care facilities and community settings. The demonstration of effectiveness and rapid implementation of such strategies is essential. Within this context, the protection of health-care workers is a top priority. Community-based treatment in areas of high TB and HIV prevalence needs further development, with a demonstration of effectiveness in the setting of drug resistance and HIV/AIDS; trials to optimize treatment for MDR/XDR-TB and universal access to ART are essential goals. Longer-term goals include the expansion of the TB therapeutic armamentarium, an effective TB-protective vaccine, and, ultimately, elimination of the social and economic conditions and disparities that breed TB, HIV, and TB drug resistance.
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Expanding the Role of Nurses in TB Prevention, Care, and Treatment

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The International Council of Nurses (ICN) Code of Ethics for Nurses identifies four fundamental responsibilities of the nurse: to promote health, to prevent illness, to restore health, and to alleviate suffering. These inherent nursing roles must be fostered to allow effective and full functioning of the nursing workforce as it tackles the global TB pandemic. Nurses and other professionals are challenged to deal with the burden of TB-related disease and disability, and with proper investment in their training and support they can become key partners in the global fight against TB.

TB ranks third among infectious diseases as a leading cause of death, suffering, and disability, and its global incidence is growing at approximately 0.4% per year, with faster increases in sub-Saharan Africa and the former Soviet Union. Every year, there are an estimated 8.2 million new TB cases worldwide (incidence rate of 136/100,000) and 1.82 million deaths from TB, of which 226,000 (12%) are attributable to HIV. The increase of multidrug-resistant TB (MDR-TB), and, more recently, the emergence of extensively drug-resistant TB (XDR-TB), poses additional challenges for global TB control.

The United Nations Millennium Development Goal (MDG) for TB is to halt and begin to reverse incidence of the disease by 2015. The World Health Organization (WHO) Stop TB department target is a 70% case detection rate with successful treatment of 85% of those detected. Nurses are critical if global initiatives such as TB control programs are to be successful. There is consensus, however, that health systems globally are facing a shortage of nurses in general and TB nurses in particular, leading to fragile health systems. With such a shortage, it is difficult to imagine how nursing services can contribute effectively to global Stop TB targets and the TB-related MDGs. To add to these challenges, nurses in many high-TB-burden countries are restricted by nursing practice acts that limit their scope of practice and restrict their clinical roles and responsibilities.

TB nurses and other frontline health-care workers in a variety of health-care settings perform the bulk of the work in TB care and control. However, the lack of well-trained personnel and poor capacity at the management level are major constraints in TB control and care. The absence of nursing representation in policy and strategic decision making...
is another constraint in enhancing the quality and quantity of human resources for TB control, particularly in the high-TB-burden countries.

Despite these constraints, there is growing recognition of the crucial role played by nurses in TB control and care. For example, nursing roles in the WHO DOTS (directly observed therapy short course) strategy cover the entire spectrum of activities, including advocating for political commitment, case detection, administering and monitoring drug regimens, ensuring a regular supply of medicines, and standardizing recording and reporting systems.

Failure in any of these activities is likely to contribute to treatment failure and to the development of drug resistance. Nurses working in primary health-care settings are often the first to identify and manage suspected TB cases; this early identification is essential to ensuring a high level of case detection and is a cornerstone of TB control. Strengthening initiatives should not just target nurses working in specialist TB services, but the generalist nurses as well. In the era of HIV/AIDS, TB is often a coinfection, and overall nursing competence in detection, control, and care is crucial. In addition, further competencies are required in dealing with MDR- and XDR-TB.

The aim of this chapter is to set out the issues, challenges, and strategies for scaling up the contribution of nursing to TB prevention, detection, care, and treatment. The chapter will argue that scaling up nursing roles in TB prevention, detection, care, and treatment, as well as involvement in key policy and decision making, is the cornerstone of effective national TB programs.

CONTINUUM OF CARE

Holistic and patient-centered care requires a continuum of seamless services that address patients’ needs based on the stage of the disease and the setting in which care is provided.

Refocusing Prevention, Detection, Care, and Treatment

Too often, health systems focus on curative services at the cost of prevention and care. Within these systems, nurses are often hampered in their efforts to align TB prevention, detection, care, and treatment into a continuum of care. This continuum refers to a seamless approach to care with prevention of TB a top priority and early detection, care, and treatment for people living with TB stretching from the home to acute care and outpatient settings. The continuum of care should include access to quality TB treatment, with adherence as a key element of treatment success and prevention of drug resistance. Care must be holistic and address the psychosocial aspects and needs of TB patients and their families.

Nurses are aware that treatment helps limit the spread of TB, as people undergoing treatment are less infectious. TB patients who are in contact with nurses and other health professionals and who are receiving follow-up care and treatment are also more likely to take responsibility for adhering to a treatment regimen. Access to TB treatment brings patients in contact with health facilities and health-care providers and provides opportunities for education on prevention and completion of the full course of treatment to achieve a cure. In order to ensure a continuum of care, nurses must play a key role in lobbying to change distorted priorities that focus only on treatment and neglect prevention and care. Nursing leadership and involvement at the policy level is crucial for aligning the tenets of TB prevention, detection, care, and treatment into national TB programs.

Enhancing Nursing Competence

Nurses are responsible for educating and supporting patients with TB, detecting medication side effects, educating and supporting patients at home through follow-up clinics, and, where
appropriate, running telephone help lines. Nurses are also responsible for screening those who have been in close contact with patients with infectious TB and perhaps running clinics for patients taking prophylactic TB treatment. Because of their frontline presence in all health-care facilities and their diversity of skills, nurses are the natural ally in the fight against TB. However, nurses in many countries lack adequate training in TB detection and management. Nursing education programs generally lack depth and breadth in their TB coverage, leaving graduates ill prepared to deal with the complexities of the disease and its management. Education systems often develop curricula that disregard national development plans or health needs, thus failing to provide trained professionals with the locally required skills.7

There is also a general lack of understanding among nurses of the guidelines and targets of national TB programs, which can often lead to inappropriate treatment and follow-up protocols. Yet nurses working in primary health care are often the only health professionals available for TB prevention, detection, care, and treatment, and a competent nursing workforce is crucial for the success of TB programs. In addition, nurses’ scope of practice tends to be restrictive and dependent on their relationship to physicians. The lack of adequate training in management of TB and limited scope of practice represent a missed opportunity in nursing’s ability to make a difference in the fight against TB globally.

Training nurses in TB prevention and care at the basic and more advanced levels is an effective way of improving competence and is much needed. Evidence shows that educational outreach has improved TB case detection by nurse practitioners working in South African primary care clinics.8 That is why ICN, in partnership with Eli Lilly, is conducting TB and MDR-TB training-of-trainers (TOT) programs that target high-TB-burden countries. The ICN initiative aims to improve nursing competence in TB prevention, detection, care, and treatment. It has so far been implemented in Malawi, the Philippines, Russia, South Africa, and Swaziland, and more than 100 nurses have successfully completed their training. Preliminary follow-up data show that participants in the TOT program introduce changes in their practice and improve care outcomes. For example, nurses who participated in the TOT program in Malawi have reduced the turnaround time for sputum results from two weeks to two days. Nurses in all participating countries have trained other health-care workers, thus ensuring the sustainability and impact of the program.

A win-win situation for nursing and for health systems in general is to enhance nursing competence by integrating TB into the basic nursing curriculum and providing continuing education programs. Resources must be made available in order to develop nursing competencies and allow nurses to become accountable for their work across the continuum of care.7 National nurses associations, nursing regulatory bodies, and schools of nursing are challenged to work closely with their national TB programs to ensure continuous nursing competence and an expanded scope of practice in TB prevention and care.

HIGHLIGHTS OF NURSING ROLES IN TB

Improving Adherence to TB Treatment
TB therapeutic regimens recommended by WHO have been shown to be highly effective in both preventing and treating TB.10 However, poor adherence to anti-TB medication represents a major barrier to global TB control,11 with nonadherence to treatment regimens being a persistent challenge to nurses and other health professionals. Nurses are aware of the consequences of nonadherence and
its high cost to the patient, the community, and the health-care system. In addition, nurses are all too familiar with the frustration of the treatment failures, poor health outcomes, and patient dissatisfaction that accompany nonadherence.

Nurses at different levels have the responsibility to shape a health system that provides quality care and better treatment outcomes. The five major barriers to adherence often cited are lack of awareness and knowledge about adherence, lack of clinical tools to help health professionals in evaluating and “treating” adherence, lack of behavioral tools to help patients develop or change their habits, lack of appropriate provision of care for chronic conditions, and dysfunctional communication or relations between patients and health professionals.

ICN estimates that there are about 13 million nurses worldwide. With proper understanding of the dynamics of adherence, and techniques for assessing and monitoring the problems of nonadherence, these millions of nurses can be a formidable force in improving adherence and care outcomes for TB patients. Nursing interventions to scale up adherence must be based on innovative approaches that involve nurse prescribing, patient participation in self-care, and continuous assessment and monitoring of treatment regimens. Such approaches should foster therapeutic partnerships between patients and nurses that are respectful of the beliefs and choices of the patients in determining when and how treatment regimens are to be followed.

Because much of the treatment for TB takes place in the home and community setting, nurses provide a link to the formal health-care and support system through home visits, telephone calls, and other reminders that facilitate adherence. Through sustained contact, nurses can form a therapeutic alliance with patients and their families and provide ongoing support for taking the recommended medications. Some techniques of monitoring adherence include directly observed therapy (DOT), pill counting, thoughtful and nonjudgmental interviews, and reviewing medication cabinets.

Nursing strategies to improve adherence include:
- assessing the extent of adherence using non-threatening questions;
- asking about side effects of medication and the effect on patients’ quality of life;
- educating patients on the illness, the importance of adherence, how the treatment will help, and possible side effects and how to deal with them;
- suggesting cues and reminders such as a detailed schedule, integrating medication times with daily habits, using medication boxes, and timers, alarms, beepers, and so on;
- rewarding and reinforcing adherence behavior, such as through charts and graphics that show the impact of medication on clinical markers of disease (e.g., sputum conversion from positive to negative, clinical improvement, weight gain);
- encouraging patients to cultivate therapeutic relationships with health professionals; and
- talking with peer groups and family members.

Ensuring that TB treatment regimens are followed and administering medications and other treatments are some of nurses’ key roles. Nurses have diverse skills that must be tapped in improving adherence and care outcomes. Continuing education programs can improve the competence and awareness of nurses and other health professionals about the importance of adherence in achieving a cure and preventing MDR- and XDR-TB.

**Training and Supervision of DOT Supporters**

DOT, the approach recommended by WHO as an integral part of the DOTS strategy, requires that an observer watch the patient swallow his or her medicines. Success of TB treatment depends on regularly following the prescribed treatment regimen. Nurses
have a major responsibility in ensuring that patients complete TB treatment to improve cure rates. There is evidence that achieving the WHO target of a 70% case detection rate and successful treatment of 85% of those detected depends on, among other things, the presence of a committed frontline health workforce. These frontline health workers are generally nurses with varying degrees of expertise in TB care.

The DOTS approach involves a comprehensive set of services delivered by a multidisciplinary team. These services include setting clinic appointments that are suitable for the patient, assessing voluntary DOT supporters, and reducing barriers to adherence to treatment. For example, a South African nurse who participated in the ICN TB/MDR-TB TOT program in 2005 assists her community in adhering to TB treatment by raising funds to support patients’ travel to health-care facilities. A Philippine nurse who also participated in the TOT program organized a DOT Club, composed of cured patients and treatment partners, to act as peer educators for TB patients.

The DOT supporter can be a health worker or a trained and supervised member of the community. For example, in South Africa, local pharmacists and shopkeepers are trained as DOT supporters, and in Malawi, community volunteers are trained to be guardians for TB patients. Nurses provide training and supervision of DOT supporters, who then volunteer to perform direct observation. DOT supporters often use a log system to document the adherence of their patients, and this information is used by nurses to monitor the success of the program.

**Task Shifting and Expanding the Scope of Practice**

Nursing’s role in improving access to TB treatment must be based upon the realities at the front lines of care. These realities require innovative approaches that allow a broader scope for nurses, including diagnostic and prescriptive roles. The public-health approach to TB treatment should be based on simplified clinical decision making, standardized first- and second-line anti-TB regimens, a limited set of laboratory and radiological options, and a limited set of therapeutic options. Nurses can be equipped to provide these services in most resource-constrained clinical settings.

The delivery of effective and sustainable TB care depends on a large number of well-trained health-care personnel, and nurses are only one part of a well-functioning health-care system. Experience in many countries has shown that nonspecialist doctors, clinical officers, and nurses can effectively deliver HIV-related clinical services, including antiretroviral therapy (ART). This experience with HIV/AIDS can be transferred to TB care and treatment. Through a public-health approach, tasks such as basic diagnostics and prescribing can be shifted from more specialized to less specialized health-care workers (e.g., from specialized physicians to general physicians and/or clinical officers, from physicians to nurses, and from nurses to non-nursing counselors).

Using the task-shifting approach, nurses can manage a large proportion of TB cases at the primary health-care level, with the referral of complicated cases to more specialized levels of care. In some settings, physicians may be reluctant to task shift, especially if there is underemployment or if doctors do not have experience in sharing certain tasks for greater efficiency and quality of care. Nevertheless, task shifting is a critically important strategy to ensure the success of the public-health approach to TB care, detection, and treatment.

Effective clinical mentoring can be provided through skilled on-site input from senior nurses or TB specialist nurses. This input can be provided through case consultation or case review, or consultation by phone, radio, or e-mail, and can support providers who are inexperienced in TB care in making sound health-care decisions and appropriate referrals.
While the concept of task shifting can be contentious, the goal is to expand the scope of nursing practice and to tap into nursing’s great potential to strengthen TB prevention, detection, care, and treatment.

**Strengthening Advocacy, Communication, and Social Mobilization**
Stemming the tide of the global TB pandemic will require community and resource mobilization that encompasses all sectors and professional organizations. One of the main barriers to TB care and treatment is the lack of resources, including human resources. Nurses are ideally placed to serve as advocates for the mobilization of resources, in order to influence policy changes and sustain political and financial commitment to TB programs. Communication between nurses and people with TB, as well as with communities, is vital in improving knowledge of TB control activities. Social mobilization is crucial to galvanize support for the campaign to stop TB.14

Increasing community involvement in TB projects, including DOTS, should be clearly placed on the nursing agenda. Events such as World TB Day can be used to further community sensitization and mobilization. TB patients and those cured of the disease must be involved in creating a positive environment for TB education and advocacy. Using TB champions, such as iconic and respected community members, is vital in raising the profile of TB prevention and care and in the destigmatization of the disease. Communication with other professional and community associations will create a collective ownership of the TB agenda and help create a sustainable environment for infection control and treatment support.

**Measuring Outcomes**
Outcome measurement is often a weakness of health systems, due in part to a lack of accurate data or a lack of training in the use of data. Standardized recording and reporting systems are an integral part of the DOTS strategy. Standardized recording, including information on patient outcomes, is vital for monitoring such issues as treatment completion, default rates, treatment failure, and cure rates at the facility level. Nurses in TB care often cite a number of problems related to standardized recording and reporting systems and inconsistencies between different health facilities. For example, nurses note that completion of TB treatment does not equate with cure until this is confirmed by clinical and laboratory tests, yet some facilities confuse completion and cure rates, which is misleading.

Establishing a reliable monitoring and evaluation system with regular communication between the peripheral and central levels of the health system is vital. Recording and reporting, while taking much of nurses’ valuable time away from direct patient care, are nonetheless essential for collecting the quality data needed to measure outcomes of care and monitor programmatic success. Accurate recording and reporting are also vital in monitoring default rates and in improving adherence to TB drug regimens. Using benchmarks, nurses are able to monitor the effectiveness and outcomes of TB programs. The nursing process and the DOTS strategy provide systematic approaches to providing patient-centered care and to measuring outcomes of care. Nurses need support in data entry and analysis to be able to utilize the information they gather for program review and quality improvement.

**CHALLENGES AND STRATEGIES IN EXPANDING THE NURSING ROLE**
A number of constraints challenge nurses’ ability to provide quality services in TB care. Some of the challenges arise from within the profession itself, while others are external. Innovative approaches are needed to tackle these challenges.
Human Resource Planning and Shortfalls

Human resources are the most important input of health programs and are essential to disease control. Developing human resources capacity, including nursing capacity, is the cornerstone of TB control and care. Key elements of human resources capacity building for TB control and care must be addressed at different levels (e.g., government, institutional, and individual).

The major constraints to DOTS expansion reported by national TB program managers from the 22 high-burden countries were lack of qualified staff at different levels, insufficient preparation for decentralization, noncompliance of the private sector with DOTS, inadequate health infrastructure, and weak political commitment. Inadequate human resources ranks first among the top five constraints to achieving global TB control targets in 17 of the 22 high-burden countries. Reasons cited for shortcomings in this area included lack of skilled and/or motivated staff; inadequate distribution of staff; poor retention; deficiencies of staff at the central level; inadequate planning, provision, and technical support for staff at district or provincial levels following decentralization; and staff with inadequate qualifications. Suggested strategies for increasing human resources are improving productivity, quality, and motivation, given spare capacity; mobilizing community resources and nongovernmental organizations (NGOs); addressing migration issues in both sending and receiving countries; and increasing the stock of health personnel.

Nurse leaders must be aware that human resources for TB control must be taken from within the overall context of human resources for health. It is important to position TB control activities within the current health system functions while taking into consideration the social, political, and economic environment. This will facilitate identification of opportunities for collaboration with other programs (such as HIV/AIDS programs) and of champions and decision makers for targeted advocacy. Advocacy is also needed to change technical and donor agencies’ ideas and policies regarding human resources and the processes involved. For example, an emergency program for human resources in Malawi supported by donor agencies successfully implemented recruitment and retention strategies, including substantial increases in the salaries of nurses and other health professionals. The approach appears to have resulted in a reduction of the outflow of staff from the public sector.

WHO argues that health worker density, in terms of numbers and quality, is positively associated with access to a package of essential health interventions, including the scaling up of interventions for HIV/AIDS and TB. Current global shortages of nurses and other health professionals are major challenges to TB programs and other initiatives to improve population health. For example, a nurse in a Malawi hospital works a 12-hour shift and cares for up to 100 patients with HIV/AIDS, TB, and other diseases by herself. In order to fully implement the DOTS strategy, health systems must deploy nurses and other health professionals with appropriate competencies in appropriate numbers. This strategy must consider the training and skills requirements of various health professionals, their working conditions, geographic distribution, performance monitoring and supervision, and the development of a career structure. Overextended health systems and national TB programs are reaching a breaking point due to the acute shortages of nurses and other health-care providers. Increasing the numbers and competence of health-care workers for TB control programs must be seen within the perspective of the broader health-care system.
Training and Supervision

Training and supervision of nurses and other personnel are the key to the success of TB programs. As the bulk of TB cases are likely to be first detected by nurses, training in TB and in the elements of the DOTS strategy is essential to the success of the program. TB should be integrated into the nursing curriculum, followed by hands-on clinical experience in TB centers.

Supportive supervision is also a critical component of capacity building in TB care. Regular supervision and follow-up after training ensures that nurses can implement the lessons learned during initial training sessions. Supportive supervision should focus on the conditions required for proper functioning of the clinic and clinical care team. Supportive supervision aims at improving the quality of TB care and treatment service delivery through observation, discussion, direct problem solving, mentoring, and learning from the clinical and management situations observed. These activities will help ensure that key requirements for TB care, therapy, and prevention, as well as an appropriate process for case management, are in place.

Nursing has a long history of using mentorship to transmit skills, knowledge, and attitudes. Clinical mentorship is a system of practical training and consultation that fosters ongoing professional development to provide sustainable, high-quality clinical care outcomes. Clinical nurses or other mentors must be experienced, practicing clinicians in their own right, with strong teaching skills. Mentoring should be seen as part of the continuum of education required to create competent nurses. Mentoring is an integral part of the continuing education process taking place at the facilities where health-care workers manage patients. It should be based on principles of adult learning and employ participatory approaches rather than didactic lectures.

The way the clinic service is organized and functions affects the ability of individual healthcare workers to implement clinical care protocols. Ample opportunities exist during clinical mentoring to incorporate supportive supervision activities, including discussing issues such as patient flow, workload, organization of care and treatment services, triage, and recording and reporting practices. Clinical mentors must keep in mind that the basic aim of mentoring is to promote a nurturing relationship with the learner and to improve competency rather than to audit the clinical environment. Current dire staff shortages in many countries often make it difficult to provide training, supervision, and mentorship, even for junior nursing staff. Often there are only one or two staff members in a facility, with little or no access to continuing education. Expanding nurses’ roles will require ongoing educational programs that utilize supportive supervision and mentorship.

Nursing Involvement in Health Policy

The current health-care environment is characterized by economic constraints and increased demand for health services, in terms of both quality and quantity, including TB-related services. While nurses are the backbone of TB programs globally, they are absent from policymaking in many countries. The absence of nursing input in policy and strategic decision making is a constraint to enhancing the quality and quantity of human resources for TB control and care. The ICN Policy on Participation of Nurses in Health Services Decision Making and Policy Development affirms the following:

Nurses have an important contribution to make in health services planning and decision-making, and in development of appropriate and effective health policy. They can and should contribute to public policy pertaining to the determinants of health. In addition, nurses
are involved in strategic planning, budgeting, efficient resource planning and utilization, and the planning, management and evaluation of programs and services.

Because of their close interaction with patients and their families in all settings, nurses help interpret people’s needs and expectations for health care. They are involved in decision making at the clinical practice level as well as in management. They use the results of research and trials to contribute to decisions on quality and cost-effectiveness in health-care delivery. They conduct nursing and health research that contributes evidence to inform policy development. Because nurses are often coordinators of care provided by others, they contribute their knowledge and experience to strategic planning and the efficient utilization of resources. For these reasons, nursing must be represented at the policy level in order to articulate a nursing perspective in the goals and strategies for TB control.

Nurses’ intimate knowledge of the reality “in the trenches,” and their background in clinical care and management, makes them a vital resource for enriching the policymaking process. Capable and competent nurses with preparation in management and leadership are suitable candidates for involvement in policymaking bodies. One approach to promote such leadership is ICN’s Leadership for Change (LFC) program, established to develop nurses as effective leaders and managers in a constantly changing health environment. The LFC methodology and key strategic goals are designed to assist nurses at a country or organizational level to participate in health policy development and decision making.24

Nurses and professional nursing organizations are well placed to use a number of strategies to contribute to effective policy development, including monitoring the utilization of nurses in the workforce, incorporating new models and management strategies, marketing a positive image of nursing to key management and policy stakeholders, disseminating relevant knowledge and research, and developing and maintaining appropriate networks to enable collaborative working relationships with governmental and nongovernmental organizations.

Nursing’s continued absence from policymaking is a critical factor hampering the profession’s contribution to effective TB control programs.

**Logistics and Management Support**

Nursing’s ability to maximize its contribution to TB control and care is largely dependent on management and logistics support. The efforts to promote TB prevention, detection, care, and treatment require that health-care providers, time, equipment, materials, and drugs be brought together to achieve stated objectives. The implementation of the DOTS strategy and the achievement of its objectives depend upon the knowledge and skills of health professionals using all necessary resources.

In many countries, and particularly high-TB-burden countries, nurses face constraints in logistics and management support. Nurses too often lack equipment, such as masks and gloves, to protect themselves and their patients from infections. At times, inadequate stocks of anti-TB drugs result in interruptions of treatment, putting patients at risk of death or of developing drug-resistant TB. Too often nurses do not have access to transport services to conduct outreach services or to transport sputum specimens. The experience of a nurse in Swaziland who participated in the ICN TB and MDR-TB TOT project demonstrates these typical challenges. The nurse shared her frustration at the difficulty in getting sputum specimens to a nearby laboratory. She indicated that the driver was refusing to carry specimens to the laboratory for fear of becoming infected in the process. After trying a number of approaches, the nurse decided to pack
the sputum, but she would not tell the driver what was in the package. In this way, she was able to find a short-term solution to the lack of logistics support, but the problem remains unresolved.

Often management and health professionals lack regular communication and a forum to discuss problems and find solutions. This can often lead to an “us versus them” perspective, with each group seeing the other as the reason for the therapeutic failure. The answers to logistics and management challenges could be found if health professionals were fully involved in policymaking and decision making.

In an effort to tackle the root causes of management issues, the ICN TB and MDR-TB TOT project is linking with the International Hospital Federation (IHF), which provides TB training for managers of health facilities. The ICN/IHF joint training plan aims to bring together nurses and managers for back-to-back training that includes discussions of issues of common concern to both groups. In this way, nurses can openly discuss the management and logistics problems hampering their efforts, while managers can offer their perspectives and input. The ultimate goal is to find solutions that will improve the quality and effectiveness of TB services.

**Safe Work Environments**

Nursing personnel comprise the majority of healthcare workers in most countries and have a frontline caring role that brings them in close contact with patients; this increases their potential risk of being exposed to TB. Although the risk is relatively small, it is often compounded by staff reductions and shortages in the wake of health service restructuring, lack of basic personal protective equipment or cleaning materials, and the rise in the number of people with TB. In some instances, the growing prevalence of MDR- and XDR-TB has heightened the perception of occupational risk of exposure to TB. This possible increased risk must be addressed in a timely manner with appropriate information, infection control guidelines, and protective equipment.

Adherence to standard precautions and infection control guidelines is effective in the prevention of airborne infections. However, it is clear that preventive measures are difficult to practice if protective supplies such as masks and other equipment are in short supply, which is the case in many high-TB-burden countries. Protection and occupational safety of nurses and other health professionals continues to be a neglected area.

Poor working conditions, where nurses are overburdened with multiple tasks and heavy patient loads, represent a major barrier preventing nurses from maximizing their contribution to TB prevention, detection, care, and treatment. Some anecdotal evidence even suggests that difficult working conditions and dissatisfaction with the work environment are pushing nurses to depletion, burnout, and migration. The few health workers left behind take up the extra workload to make up the staffing shortfall, and it is difficult for nurses to provide high standards of care under these difficult conditions. Unsafe working conditions and heavy workloads due to staff shortages compromise nursing effectiveness and potential. Maximizing nurses’ contributions requires management and logistics support to create safe work environments and appropriate staffing levels and workloads.

**THE OVERLAPPING TB AND HIV PANDEMICS**

HIV is fueling the TB pandemic in regions with a high prevalence of HIV, and TB is one of the most common causes of morbidity and mortality in HIV-positive adults. In some high-burden countries, more than 70% of TB patients are coinfected with HIV. Rose Dlamini, a nurse on the TB ward
at Raleigh Fitkin Memorial Hospital in Swaziland, described the situation as follows:

In Swaziland, HIV/AIDS and TB are joined at the hip; it is natural that the same treatment problems occur with both. It’s a challenge, ensuring HIV-positive people stick to a regimen of antiretroviral treatment. If they fall off treatment, it may not work for them any more. It is the same with TB.

TB and HIV infection coexist in populations worldwide, and HIV and TB programs need to collaborate to reduce the overall disease burden and relieve suffering. The spread of the HIV pandemic throughout sub-Saharan Africa in the past decades has been accompanied by up to a fourfold increase in the number of TB cases registered by national TB programs.

The incidence of TB is also increasing in other high-HIV-prevalence countries, where populations with HIV infection and TB overlap significantly. Persons with undiagnosed, untreated, and potentially contagious TB are often seen in HIV care settings. However, there are still very few TB services that provide appropriate routine HIV counseling and testing services. This suggests that TB control and the DOTS strategy will not make much headway in HIV-prevalent settings unless HIV control is also achieved.

In many settings, TB services are the best initial entry points for patients in immediate need of antiretrovirals (ARVs). TB is a common, treatable HIV-related disease and a leading killer of people living with HIV. As a consequence of the overlapping nature of TB and HIV, there is a strong need for close collaboration between AIDS and TB programs. Implementation of the WHO-recommended DOTS strategy for TB control and improving care for people with HIV and TB should be an integral part of this collaboration.

A major constraint to scaling up initiatives to combat TB and HIV is the shortage of nurses and other health personnel who are skilled in treating both diseases. For example, in order to roll out ART nationally, Mozambique would need eight health workers per 1,000 patients receiving treatment. Yet currently there are only 0.36 full-time equivalent health workers per 1,000 people, making it difficult for Mozambique to tackle the HIV epidemic without additional human resources.

Two Diseases, One Patient: Synergy between TB and HIV/AIDS Control Programs to Deliver TB and HIV Activities

Nurses are challenged by fragmented and vertical approaches to national TB and AIDS control programs that tend to have minimal collaboration. As frontline health-care providers, nurses are often the first to see people living with the deadly duo of TB and HIV. This represents a challenge for nurses and others, but it also provides them with an opportunity to bring to health service delivery a synergy that is guided by the holistic principle of two diseases, one patient. It is encouraging that the expanded scope of the new strategy for TB control in high-HIV-prevalence populations includes interventions against TB, such as TB case finding, treatment, and prevention, and interventions against HIV, including condoms, sexually transmitted infection (STI) treatment, harm reduction for intravenous drug users, and ARVs.

Some of the TB/HIV interventions clearly fall under the responsibility and expertise of the national TB programs (such as DOTS expansion), while others fall under the responsibility and expertise of the national AIDS programs (such as prevention of mother-to-child transmission [PMTCT] of HIV, voluntary counseling and testing [VCT] services, safe blood supply). However, most activities overlap AIDS and TB programs.
programs. These include increased community involvement that benefits TB diagnosis and care as well as HIV/AIDS care and prevention, and isoniazid preventive therapy (IPT), a concern both of TB services (which are likely to supply and monitor the isoniazid) and of VCT / national AIDS control program services (whose clients will benefit).

Many potential synergies exist between HIV and TB service providers at the service delivery level. For example, TB patients often have a high rate of STIs and would therefore benefit from STI screening and treatment. Similarly, HIV-positive VCT clients have a high rate of TB, therefore benefiting from TB screening and treatment, and TB patients have a high rate of HIV, therefore benefiting from VCT and related services.

The overlapping nature of the two diseases demands that HIV prevention and care be a priority concern of TB programs, and that TB care and prevention be a priority concern of national HIV/AIDS control programs. This integration of care is based on the “two diseases, one patient” approach.

Increasing Access to Voluntary HIV Counseling and Testing and TB Testing

WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) have proposed new guidelines on provider-initiated HIV counseling and testing (PICT). As part of the PICT strategy, health-care workers recommend HIV testing to individuals visiting health-care facilities as a standard component of routine medical care. Encouraging and enabling populations to know their HIV status should be a priority of all health-care services, and HIV care programs in particular. Similarly, nurses should be vigilant in detecting the signs and symptoms of TB in all health-care settings and take measures for early detection of TB. Nurses, particularly those in high HIV and TB burden settings, should consider adopting PICT on a voluntary basis to detect TB. However, nurses must caution against compulsory testing of individuals suspected of TB and/or HIV.

As HIV and TB are both stigmatized conditions, stigma, lack of confidentiality, and lack of treatment options can contribute to low uptake of VCT or PICT. Encouraging and enabling community members to know their HIV and TB status can be facilitated by providing accessible, acceptable, and confidential VCT as well as testing for TB. Educating communities and patients to recognize the symptoms of TB and to seek health care and further investigations should be routine in settings providing care for HIV-positive individuals.
ICN PARTNERSHIPS AND INITIATIVES TO BUILD NURSING CAPACITY FOR TB/MDR-TB PREVENTION, DETECTION, CARE, AND TREATMENT IN HIGH-BURDEN COUNTRIES

The challenges nursing faces as it seeks to play a leadership role in the global fight against TB require a concerted approach and resource mobilization. About three million nurses work or are registered in the 22 countries with the highest burden of TB. In most of these countries, nurses are the primary health-care providers and often the only source of TB care. Strengthening nurses’ role in TB care is vital to the success of national TB programs and to the availability of adequate and competent human resources for health care in general and TB care in particular.

Partnerships
In recognition of the important role of nurses, the International Council of Nurses (ICN) has joined forces with other health-care professionals and Eli Lilly to tap the enormous potential of the nursing workforce for the diagnosis, care, treatment, and surveillance of TB and MDR-TB (multidrug-resistant TB). ICN has also forged partnerships with the International Red Cross Federation (IRCF), Partners in Health (PIH), the International Hospital Federation (IHF), the World Medical Association (WMA), the International Union Against Tuberculosis and Lung Disease, the WHO Stop TB Partnership, the U.S. Centers for Disease Control and Prevention (CDC), the Norwegian Association of Heart and Lung Diseases (LHL), the TB Survival Project, and the Tropical Diseases Foundation.

Eli Lilly provided funding to support ICN in developing guidelines for nurses in treating TB and MDR-TB. In addition, ICN developed a training-of-trainers (TOT) program for nurses in high-TB-burden countries in order to mobilize, motivate, and equip them for TB and MDR-TB prevention, detection, care, and treatment. Through this initiative, ICN and nurses on the ground can play a key role in the global fight against TB.

Project Achievements to Date
The ICN TB/MDR-TB project has been implemented in a number of high-TB-burden countries, and a number of teaching and learning resources have been developed. Achievements to date include the following:

Development of TB/MDR-TB Learning Resources
TB Guidelines: ICN developed TB Guidelines for Nurses in the Care and Control of Tuberculosis and Multi-Drug Resistant Tuberculosis as a practical tool for the generalist nurse. The guidelines address issues such as diagnosis, improving adherence to anti-TB treatment, prevention of drug resistance, and follow-up care. They include evidence-based interventions and standards for TB control and care. Currently, the guidelines are available in English and Russian. The guidelines were revised in 2007 and will soon be translated into Spanish, French, Chinese, and Portuguese. The guidelines have been disseminated to all 129 ICN member associations, as well as to many other organizations and individuals, and are included in the content of the
ICN Mobile Library and the Nursing Library for Refugee Health.

**Training Package:** Based on the TB guidelines, ICN developed a training package that includes trainer and participant manuals for the TOT program. The training package uses the TOT approach and prepares participants to train nurses and other health-care workers at their health-care facilities. The training package is currently available in English and Russian and will be translated into Chinese and Portuguese.

**Global TB/MDR-TB Resource Center:** On World TB day 2005, ICN launched a global Web-based TB/MDR-TB Global Resource Center, the first of its kind for nurses. The center contains all ICN guidelines, fact sheets, position statements, and additional learning materials related to TB prevention and care, as well as links to other resources. In addition, the ICN TB Web site offers the opportunity for users to exchange experiences in interactive forums. These public forums allow users to discuss complex issues and ask questions related to treatment regimens, side effects, adherence, and care for TB patients.

**CD-ROM:** A CD-ROM with the ICN TB guidelines and trainer and participant manuals was developed and disseminated. The CD is currently available in English and Russian, as a key resource to help TOT program participants implement training in their health facilities.

**Stigma Tool Kit:** Stigma is a major barrier in the fight against TB and to achieving quality care and treatment adherence and completion. To provide strategies and methods to reduce stigma, ICN has developed a tool kit entitled TB and Stigma: A Double Burden. The tool kit was based on an extensive literature review and was informed by the results of the ICN global survey on TB-related stigma and discrimination. The tool kit will be widely disseminated to nurses and others.

**Fact Sheets:** ICN has developed the following fact sheets:
- TB in the Health Care Settings: Prevention of Occupational Transmission
- TB and HIV/AIDS
- TB/MDR-TB Related Stigmatization and Discrimination

**Awareness Tool Kit on TB and MDR-TB in the Workplace:** In partnership with the Global Health Initiative (GHI) of the World Economic Forum, ICN has also been engaged in developing an awareness tool kit on TB/MDR-TB in the workplace. The ICN fact sheets for nurses on TB-related stigma and discrimination in the workplace are being published as part of this awareness-building tool kit.

**ICN TB Advisory Group:** The ICN TB/MDR-TB Advisory Group was established in 2005 and comprises TB specialist nurses and other experts from ICN partner organizations and national nurses associations. The advisory group provides peer review of ICN TB/MDR-TB-related publications and training materials.

**TOT Program**
The interactive training program is designed as a five-day workshop that addresses TB epidemiology, prevention, diagnosis, therapy, adherence to treatment, care and nursing standards, and the DOTS strategy. In addition, TB-related stigma, ethical aspects, patient education, and counseling of family and community members are addressed. The training also introduces basic principles of adult teaching/learning methods, leadership, and supervision.
After the successful pilot TOT program in South Africa and the Philippines in 2005, the training was rolled out to Malawi, Swaziland, and one region of Russia in 2006. The TOT program is implemented in collaboration with the national nurses association and the national TB program in each country. Each training participant is committed to train at least 10 nurses and 10 allied health personnel. The workshop participants record and report ongoing training activities to the local project coordinator, who is responsible for regular monitoring and evaluation in collaboration with ICN. Currently, training activities are taking place in all five countries.

ICN/Lilly TB Award
To acknowledge the significance of nursing’s contribution and expertise in TB and MDR-TB, ICN and Eli Lilly have teamed up to offer an annual award that recognizes nursing excellence in TB/MDR-TB prevention, care, and treatment. The ICN/Eli Lilly TB Award gives recognition to a nurse or a group of nurses who symbolize nursing excellence in TB prevention, care, and treatment. In 2007, the award was given to five outstanding nurses in the countries where the TOT program has been implemented: Malawi, the Philippines, South Africa, Swaziland, and Russia.

Future Plans
- ICN is moving forward with plans to develop an online learning course based on the TB/MDR-TB training materials and will award international continuing nursing education credits (ICNECs) to those successfully completing the course.
- ICN plans to develop a framework of competencies for generalist nurses in TB/MDR-TB control and care. The competencies are intended to be sufficiently broad to be applied globally, yet specific enough to provide guidance for those countries that have yet to develop competencies for nurses in TB care and control.
- In many countries, the emergence of extensively drug-resistant TB (XDR-TB) poses a serious threat to the population at large and to health-care workers. ICN plans to respond to the crisis by strengthening nursing capacity through information, education, and training, as well as providing educational resources and materials on XDR-TB, such as fact sheets and briefings, which will also be available via the online resource center (http://www.icn.ch/tb/index.html).
- To track the implementation of the TOT program and its intended outcomes, regular monitoring and evaluation are being conducted. Each TOT program participant has established an action plan outlining objectives, planned activities, resources, and a time frame to achieve the goals. The monitoring will determine the extent to which inputs, work plans, other required actions, and targeted outcomes are proceeding according to plan. The monitoring will continue to be led by ICN in collaboration with the national nurses association in each country.
- The TOT program will be rolled out to other high-TB-burden countries in Africa, Eastern Europe, and Asia in 2008 to 2010 and beyond.

For more information on the ICN TB/MDR-TB project, visit http://www.icn.ch/tb/index.html.
REFERENCE LIST


18. Johnson D. Key issues in human resource management in low and middle-income


RAPID DETECTION AND DIAGNOSIS OF TB is a key public-health intervention in both high- and low-resource settings throughout the world. High TB prevalence rates and drug resistance among HIV-positive individuals are of particular concern in many resource-limited settings. The capacity to rapidly detect and control the spread of Mycobacterium tuberculosis (MTB) in these settings, as well as globally, is critically important. In an effort to combat the global spread of TB and drug resistance, the Stop TB Partnership, guided by the World Health Organization (WHO) and many other partnering organizations, has devised a strategy to strengthen TB programs in low- and middle-income countries. A key element of this strategy, as outlined in the Global Plan to Stop TB, 2006-2015, is to “introduce or scale up facilities and technical capacity for mycobacterial culture services and drug susceptibility testing, and the incorporation of new diagnostic tools.”

This chapter provides information on current and developing technologies for TB diagnosis and drug susceptibility testing with respect to infrastructure development and support experience in resource-limited settings. To illustrate these principles, the experience of setting up a TB reference laboratory in Zambia, a high-TB-burden, resource-limited setting, is also discussed.

Laboratory examination of sputum by direct acid-fast smear has been the most rapid and cost-effective method to detect infectious cases of TB in resource-limited settings for approximately 125 years. However, increasing HIV/TB coinfection rates and smear-negative TB case reports have prompted the need for rapid and sensitive diagnostic testing techniques to be performed in laboratories where these services do not currently exist. Most national TB laboratory facilities currently lack adequate infrastructure and human resources to provide a safe work environment for culture and drug susceptibility testing. Therefore, TB programs must expand and improve existing laboratory facilities, implement new technologies, and empower laboratory technicians to sustain and effectively manage diagnostic programs for the new demands of rapidly expanding TB and HIV treatment efforts.

DETECTION OF ACID-FAST BACILLI USING BRIGHT FIELD MICROSCOPY

Bright field microscopy (BFM) has remained the most cost-effective procedure for the screening of acid-fast bacilli (AFB) in sputum. It is an
indispensable tool for rapid detection of infectious cases of presumed TB in high-TB-burden settings. In resource-limited settings, it is common for suspected TB patients to seek medical treatment during the advanced stages of disease, when acid-fast organisms are in large numbers and are detectable by direct BFM. However, AFB in some patients coinfected with TB and HIV are fewer in number and are therefore not as easily detected as in most HIV-negative patients. This difference has major implications for TB diagnosis in those resource-limited settings where a majority of patients presenting are coinfected with TB and HIV.

Once AFB are detected, smear-positive cases managed with six- to eight-month treatment regimens can be expected to convert to smear-negative cases after approximately two to three weeks, assuming anti-TB therapy is successful. Thus, AFB smears should be performed at diagnosis and at two, five, and eight months for each TB case. The ability to document the absence of AFB in the sputum smear, along with improvement of clinical symptoms, serves as a measure of response to therapy.

BFM is labor intensive and tedious because of the large number of TB cases and the number of smears to be examined at 1,000× magnification. In most laboratories using BFM in resource-limited settings, HIV care and treatment services are also performed by the same technicians. Thus, high TB smear volumes, the amount of time needed to confirm a negative smear, and the performance of other HIV laboratory monitoring tests limit the amount of time that can be devoted to smear microscopy. For example, it is not uncommon for a laboratory technician to perform as many as 60 to 100 smears per day, especially in light of guidelines requiring at least two specimens for diagnosis (more recent WHO guidelines allow the use of one positive sputum sample for the diagnosis of TB in HIV-infected patients).

BFM requires smear examination under oil immersion at 1,000× magnification, and the time recommended for examining and reporting a negative smear is approximately five minutes on 100 fields. The quality of smear microscopy is highly dependent on the technician’s level of expertise and diligence in spending the requisite time on each smear. Smear microscopy can assist with disease control by identifying smear-positive patients who are highly infectious, allowing for early treatment initiation and measures to prevent transmission. However, workload volumes and long smear examination times, coupled with the low sensitivity of diagnosing TB in HIV coinfected patients, have highlighted the need for new, improved, and cost-effective diagnostics in resource-limited settings.

**FLUOROCHROME SMEAR MICROSCOPY**

Fluorochrome microscopy (FM) has been used routinely in most TB laboratories in developed countries for at least 30 years. In low-TB-incidence settings, TB clinical specimens tend to have fewer AFB because the patient seeks treatment in the early stages of disease. In resource-limited settings, FM is now being considered a feasible option to detect lower numbers of AFB in the sputum samples of HIV coinfected patients. Using FM, AFB in smears are easily detected because of their typical morphological characteristics fluorescing on a black background when potassium permanganate is used as a counterstain. A larger sample area of the smear is viewed with FM, which uses either 200× or 400× magnification. This represents an advantage over BFM, which is viewed at 1,000× with oil immersion and has a smaller viewing field, thus requiring a longer time for the examination of the recommended 100 fields (the number of fields recommended before a smear is reported as negative).
Another advantage of FM is that smears may be screened at 200× magnification and confirmed at 400× magnification, thus allowing the smear to be read in less time because of the larger visual field. Shorter reading times and sharper visualization give FM the potential to decrease turnaround times for reporting AFB smear results compared with basic fuchsin staining or BFM. A comparison of AFB quantifications of bright field and fluorochrome microscopy is provided in Table 1.

(Note: Smears stained by FM methods can be restained with Ziehl-Neelsen [ZN] staining if there is a need to do so. However, restaining is not recommended except during implementation, when technicians are unsure of AFB morphology. Overstaining of FM smears using ZN should not be performed for rechecking quality assessment because of the difficulty in confirming small numbers of AFB using the ZN method with the less sensitive BFM.)

In an early publication by Smithwick, calculation of the theoretical difference in time required to read an acid-fast negative smear by FM and BFM was reported to be less than 2 minutes using FM and approximately 15 minutes each for BFM. Based on those estimates, the time required for a 50-smear workload would be approximately 1 hour and 28 minutes for FM and 12 hours and 42 minutes using BFM. Although it is unlikely that technicians would devote more than 12 hours to reading 50 smears given several other competing priorities, the potential for increased laboratory capacity realized by using FM rather than BFM is clear. During implementation of FM, it has been helpful to have technologists prepare two smears from a set of sputum samples and stain sets, one with BFM and the other with FM; the technologist should read the smears blinded. This technique allows the trainer to monitor the training process while the technologist can see that FM is faster and more sensitive than BFM for detection of AFB.

While FM can provide increased accuracy in detection of low numbers of organisms in TB specimens as well as enhanced workload capacity, additional factors need to be considered for its use in resource-limited settings, including the high cost of equipment. For instance, upgrading a regular light microscope to a fluorescent microscope can cost approximately US$3,000, whereas a new conventional fluorescent microscope may cost up to US$13,000. Mercury vapor replacement bulbs for FM cost roughly US$150 and last a few hundred hours, whereas microscopes equipped

<table>
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<tr>
<td>Result</td>
<td>BFM (1,000×)</td>
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<tr>
<td>Negative</td>
<td>Zero AFB/100 HPF</td>
</tr>
<tr>
<td>Actual</td>
<td>1–9 AFB/100 HPF</td>
</tr>
<tr>
<td>1+</td>
<td>10–99 AFB/100 HPF</td>
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<tr>
<td>2+</td>
<td>1–10 AFB/F</td>
</tr>
<tr>
<td>3+</td>
<td>&gt;10 AFB/F</td>
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AFB = acid-fast bacilli; BFM = bright field microscopy; F = field; FM = fluorochrome microscopy; HPF = high power field; IUATLD = International Union Against Tuberculosis and Lung Disease; WHO = World Health Organization

Source: Van Deun.18
with light-emitting diode (LED) light sources have the potential to last for 20 years. These novel FM (LED) light sources are currently being field tested in resource-limited settings. Conventional fluorescent microscopes also require a dark room for smear examination. Ideally, an air conditioner is needed to reduce the amount of heat accumulating during microscope use. Timing is also critical because acid-fast organisms lose fluorescence intensity; smears must be read within 24 hours after staining and protected from exposure to light. Additionally, the correct fluorescence filter system must be in place during smear examination. In general, proper training and monitoring should be provided to ensure technical competence.

When implementing FM, it is recommended that equipment procurement and maintenance be standardized at the national level. Selection and standardization of FM microscopes in the TB laboratory network has many advantages, including (1) an expected cost savings for purchasing in volume quantities from the same vendor or manufacturer; (2) standardization of training materials; (3) transferable consumables, such as microscope bulbs and other parts; and (4) potential for standardized preventive maintenance and negotiated microscope service and repair from a common manufacturer.

**SMEAR MICROSCOPY QUALITY CONTROL**

Routine quality control on each batch of staining reagents should be performed using a negative control and low-quantification smears of 1+ or 2+ of MTB as a positive control. Positive patient smears containing cellular debris and mucous are best for positive controls, which should be prepared in large batches, fixed, and stored for use. Ideally, for maximum quality control, a regional or national TB laboratory should prepare AFB control smears and staining reagents. Staining reagents can be prepared in batches, stored in brown bottles away from sunlight, and distributed to local laboratories. Local laboratories should still perform daily positive and negative controls and document the results. To detect potential environmental contamination of rinse water and reagents, negative controls should be carefully examined each time staining is performed.

False-positive and false-negative results, major concerns with FM, can in contrast be minimized with BFM by thorough training of microscopy technicians, good laboratory practices, and clean water (free of environmental AFB) for rinsing and reagent preparation. A Millipore filter container system to remove environmental AFB from reagent and rinse water is highly recommended. Laboratories may not have vacuum lines, but an electrical vacuum pump can be used to prepare sufficient quantities of bacteria-free water.

The importance of monitoring smear microscopy results for quality cannot be overemphasized, regardless of the technique being used. Aside from poor microscope quality, most errors in TB microscopy have been observed to result from deficiencies in quantifying AFB based on the interpretation charts. Errors in microscopy quantification generally indicate that technicians need closer supervision during practical training sessions and guidance in interpreting the number of AFB reported in each microscopic field. As previously mentioned, restaining FM smears with ZN is counterproductive for at least two reasons: (1) no time is saved in the effort to confirm a positive smear (this practice also does not take into consideration undetected negative smears) and (2) when attempting to confirm an actual count or small numbers of AFB (1-9 per 100 fields) by the ZN method, smears are often reported as negative because such low quantities are usually not detected by this less sensitive and time-consuming procedure.

Collecting the best sputum specimens is critical for detecting AFB in smears. Methods are similar in
most standard operating procedure manuals, such as those of WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD).18 (See “Patient Instructions for Sputum Collection” in the chapter by Reid et al in this publication for more information.) However, some HIV-infected patients do not provide a large volume of sample, and the quality of the sample may appear to be suboptimal (i.e., watery and saliva-like). Such specimens should not be discarded based on appearance or the number of white cells seen on smears. On the contrary, the samples should be carefully examined for AFB. Often numerous AFB are seen in the sparse background on the stained smear. The thin smear background with little or no cellular debris is possibly responsible for many smears being reported as negative. The technologist or microscopist working in this era of TB/HIV coinfection will need to adjust expectations, contrary to the descriptions of quality sputum specimens found in textbooks from the era before the high prevalence of HIV and TB.

Quality assurance measures for sputum specimen collection include the use of proper national TB program-quality containers with screw caps for safety and leakproof transport, proper labeling of the collection and transport container, use of a standard requisition/report form, and ensuring that the specimen arrives promptly in the testing laboratory. The turnaround time for AFB smear results should be 24 hours or less to ensure that clinicians receive information promptly to aid diagnosis. Several papers have been published describing concentration methods with bleach to enhance detection of AFB. In general, that procedure has been shown in some studies to enhance AFB detection, but issues regarding optimal turnaround time and extended steps in specimen processing are of concern. Smear-negative specimens from suspects or follow-up treatment cases with clinical symptoms of TB examined by BFM should be considered for referral to a higher laboratory level for examination by FM. For example, in Zambia, several provincial laboratories are equipped with FM capacity. Implementation of FM is now a more feasible consideration because of the possibility of using LED scopes, which are less expensive and do not require dark rooms for examination.

**IMPLEMENTING AN EXTERNAL QUALITY ASSESSMENT PROGRAM**

Beyond internal quality control, which each laboratory site should perform, the national laboratory network needs to conduct external quality assessment (EQA) in one of three ways: on-site evaluation, blinded rechecking, or panel testing.22,23 On-site evaluation or supervision requires the least amount of resource investment and should be conscientiously performed to achieve optimal quality. On-site evaluation can include nominal amounts of panel testing and/or rechecking in various laboratory sites as needed to further improve the laboratory network. Any EQA must be performed by a clinical staff member with experience in AFB smear microscopy to ensure that the best quality is achieved. The national program should designate an EQA manager. Basic considerations for implementing each method are described briefly in Table 2.

The national TB laboratory rechecking program should include realistic performance goals and provide useful and rapid feedback to the network laboratories. The number and types of microscopic errors deemed unacceptable should be determined along with plans for corrective actions and continuous motivation for good performance. Rechecking of AFB smears based on blinded rechecking of a random statistical sample of patient smears has been implemented in Mexico24 and Zambia.25 Implementing rechecking throughout the network at one time is usually not possible to manage because of constraints in human resources, finances, and organization. One or more areas of the network can be evaluated during the year, with efforts focusing on where problems may exist.
<table>
<thead>
<tr>
<th>Method</th>
<th>Purpose</th>
<th>Recommendations</th>
<th>Other considerations</th>
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| On-site evaluation  | Determine if smear reading and result reporting are performed according to standard operating procedures  
Provide feedback, corrective action, and support for problems detected  
Determine available supplies and operating equipment                             | Implement this method first  
Develop a national action plan and national customized checklist  
Determine available human and financial resources  
Schedule visits with each laboratory  
Base frequency of visits on number of laboratories in network and resources  
One or two on-site supervisors are needed in large national networks  
Provide feedback on blinded rechecking results                                 | Evaluations should be performed at least once a year in each laboratory and more frequently when there is high staff turnover  
Evaluations should be performed when problems are detected by rechecking or when on-site training is needed  
Integrate with smear collection for blinded rechecking or perform panel testing as needed  
Using the same on-site supervisors is best for labs and maintains consistency |
| Blinded rechecking  | Provide a measure of routine work performed within a laboratory  
May motivate and improve laboratory performance by providing rapid feedback     | Blinded rechecking is the second most important to implement after on-site evaluation  
Perform in regions of the network at different times rather than attempting to implement in the entire network at once  
Random selection of smears should take place according to national standard procedure  
Blinded reading and data management are critical to program quality  
Trainings on smear storage procedures are necessary                           | Collect smears as part of on-site evaluation  
Adequate supply of slide boxes for smear storage is critical  
Excellent organizational skills are required  
Assess human, financial, and data management resources  
FM rechecking is performed by restaining but not by ZN method                 |
| Panel testing       | Determine competency in staining techniques, reading, and result reporting  
Identify faulty equipment  
Investigate excessive errors in rechecking programs and provide training and corrective actions | Adopt a standard for the network, and then modify as needed  
All TB laboratory staff should demonstrate panel-testing national competency  
Optimal panel testing includes standardized stained and unstained smears  
Use as a pretest and posttest in evaluating training activities              | Preparation is time consuming  
Panel testing is not required on an annual basis unless indicated  
Testing is best performed on-site and under the supervision of the on-site evaluator  
This method does not measure routine lab performance                           |

Source: Adapted from Association of Public Health Laboratories et al.22
TB CULTURE, IDENTIFICATION, AND DRUG SUSCEPTIBILITY TESTING

Liquid culture and drug susceptibility testing have been in place in developed countries for many years. Because of the increasing number of smear-negative cases and the potential for multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of TB among people living with HIV, the need to implement these methods in developing countries is rapidly increasing. Until recently, the use of TB culture in developing countries was generally limited to surveillance studies and treatment failure cases. Now the need for earlier detection of TB in smear-negative cases and for drug resistance testing is prompting many national TB programs to expand laboratory capacity for liquid culture and rapid first-line drug resistance testing.

Historically, the only culture method considered feasible and cost-effective for use in resource-limited settings was conventional culture using in-house preparation of Lowenstein-Jensen solid media. However, using Lowenstein-Jensen media without liquid culture is slow and inadequate for early diagnosis and drug resistance testing. For instance, a rapid liquid culture system, coupled with a rapid TB identification system, can provide TB culture and drug susceptibility test results within 30 days after the sputum specimen has been received by the laboratory, compared to two to three months using Lowenstein-Jensen methodology.26 But this increased efficiency comes at a cost.27-29 Setting up a TB laboratory facility for performing culture can cost up to US$200,000 or more, depending on the volume of cultures to be performed and the geographical region (based on author’s experience).

Necessary equipment includes refrigerated safety-capped centrifuges, class II biosafety cabinets, and automated generators to maintain a constant power supply in areas where the supply of electrical power is erratic. A one-pass air-handling system or negative-pressure room for specimen and culture manipulation should also be available.30,31 It is important to keep in mind that biosafety cabinets in high-volume work areas in windy or dusty climates require certified biannual validation. TB laboratory technologists should be trained in the proper use of the biosafety cabinet and specimen handling during culture processing and other sample manipulations for safety and infection control. Training for these procedures may be obtained from international consultants or by having technologists work in a supranational laboratory for a time, followed by periodic on-site visits and consultant support. A certified biosafety engineer should ensure proper functioning of the cabinets on a periodic basis for the protection of laboratory staff during sample and culture manipulations. Such services are expensive because of the limited number of certified engineers in resource-limited settings. To reduce costs, all safety-cabinet validations within the country should be coordinated on a schedule, so that they can be serviced during one trip and costs can be shared among the laboratories whenever possible.

Support for acquisition and setup of rapid TB culture systems, either automated (Mycobacterial Growth Indicator Tube [MGIT] 960) or manual (Becton Dickinson), can be easily obtained from the vendors.32-34 National standardization of the equipment selected can be beneficial in terms of streamlining reagent acquisition, training, maintenance, and selection of manufacturers or vendors. Equipment that has been shown to function well in high-resource settings may be considered for use in resource-limited settings, but the local and technical environments, which may differ from those for which the equipment was designed, should also be considered and appropriate accommodations made. Some differences for consideration include laboratory technicians’ limited
computer skills, climate differences, availability of reagents and supplies, time to acquire supplies and equipment, availability of air-cooling systems, reliable electrical supply at the facility, water quality, stability of power, disease prevalence, and the ability of the TB/HIV program to sustain the technique without significant donor and consultant support should it diminish in the future.

Any national TB culture laboratory should enroll in an EQA program with a supranational laboratory such as the National Health Laboratory in South Africa, or with a proficiency testing program such as the U.S. Centers for Disease Control and Prevention (CDC) Model Performance Evaluation Program for MTB drug susceptibility testing.

**TB IDENTIFICATION METHODS**

Once mycobacterial cultures show indication of growth, whether on conventional or liquid media, the presence of AFB should be confirmed as quickly as possible with presumptive identification of MTB, then drug resistance testing procedures should be started. In high-TB-burden countries, AFB detected in these cultures are presumed to be MTB. However, rapid identification should be done to avoid reporting nontuberculosis mycobacteria as drug-resistant MTB, which requires different therapy. Identification can be performed using one of several methods, including serpentine cording observed on AFB smear microscopy or growth on media containing paranitrobenzoic acid. Other common methods include conventional biochemical tests for MTB (e.g., niacin, nitrate, catalase testing at 68°C). Conventional biochemical methods, such as niacin, nitrate, and catalase testing, work well on Lowenstein-Jensen cultures but are not ideal for use with rapid liquid culture methods because they require further growth on solid media; in other words, these methods negate the speed advantage of the rapid culture method. When rapid liquid culture methods are used, identification using AccuProbe (Gen-Probe) or another rapid identification method should be implemented, such as the Capilia assay, which is under investigation and detects the secreted protein MPB64 from MTB with the complementary monoclonal antibody. With methods such as AccuProbe or Capilia, the culture can be confirmed as MTB the same (or following) day the culture growth is determined to be acid fast.

The AccuProbe system has been available for several years, and though it may be considered expensive for resource-limited settings, it has the capacity to identify isolates from both liquid and solid culture media. The total number of tests to be performed annually should be considered by the national program when considering options for the purchase of reagents as well as equipment, service, and training. Other species that can be identified by the AccuProbe method in addition to MTB complex include *M. avium intracellulare*, *M. kansasii*, and *M. gordonae*. Laboratories with limited resources may acquire probes for MTB complex only or also include *M. avium intracellulare*, since these are the most common pathogens found in TB/HIV coinfected patients. The AccuProbe method uses small, tabletop items such as a luminometer reader, ultrasonic water bath, and microfuge, which reference laboratories should be able to provide. The combination of a rapid culture method and AccuProbe, Capilia, or other rapid identification tool allows the laboratory to provide identification and drug resistance testing within a week to 10 days of initial culture growth.

Other rapid methods for detection of MTB can be performed directly from respiratory specimens, such as the Amplified *Mycobacterium tuberculosis* Direct (AMTD) test (Gen-Probe) and Genotype MTBDR plus (Hain Life-science) for detection of MTB complex and resistance to rifampicin and/or isoniazid from culture samples or pulmonary
smear-positive patient material. The Genotype MTBDR plus test is based on polymerase chain reaction (PCR) and reverse hybridization (line probe) and is under review to determine its performance in resource-limited settings.\textsuperscript{37} The AMTD test uses the chemiluminescent reader from the AccuProbe system with an amplification step. This method is approved for use with smear-positive and smear-negative respiratory specimens.\textsuperscript{36} The best use for the AMTD test is for the identification of TB in smear-positive clinical specimens, and from the sediment of positive broth cultures demonstrating cellular morphology consistent with TB morphology, such as cording. AMTD tests are costly and may be technically challenging in most limited-resource TB laboratories; thus, they should only be used in laboratories that have PCR expertise to avoid contamination and similar potential amplification issues.\textsuperscript{39} A number of direct specimen methods have been supported for investigation by the Foundation for Innovative New Diagnostics (FIND) for the direct detection of MTB in several specimen sources.\textsuperscript{40} These ventures are exploring rapid detection protocols, ranging from smear microscopy and rapid culture to serological and molecular technologies, which will be appropriate for implementation in resource-limited settings. Nonculture methods, such as reverse dot blot hybridization and blood sample tests such as ELISPOT, QuantiFERON-TB Gold (Cellestis), and T-Spot.TB (Oxford Immunotech) are also being investigated for use in determining the presence of TB infection.\textsuperscript{41-43} These tests detect infection with MTB complex but do not distinguish between latent and active infection. Additionally, they are expensive and require blood collection rather than a skin test, making them potentially impractical for use in some resource-limited settings. The logistics and testing algorithms for implementation of these tests in high-TB-burden public-sector settings are under development.

**DRUG RESISTANCE TESTING**

Efforts to rapidly detect MDR- and XDR-TB are of vital importance globally. Although molecular methods are used to detect drug-resistant genes, rapid liquid drug resistance culture confirmation is still required because of numerous genetic and phenotypic drug resistance mechanisms for anti-TB drugs. Molecular tests to detect drug resistance are being evaluated in both high- and low-resource settings. New developments in this area are of critical importance for the care of TB and HIV in coinfected populations.

Drug resistance testing should be performed as soon as mycobacteria are identified, because cultures are typically performed for patients that appear to be failing treatment.\textsuperscript{44} TB culture is not recommended for decentralization within the laboratory network, and only a few laboratories should have the capacity to perform culture and drug resistance testing; however, test results should be turned around in the shortest time possible to interrupt the spread of TB generally and drug-resistant strains in particular.

Performing drug resistance testing requires meticulous technique in weighing drugs, pipetting, interpreting results, and managing quality control strains. For instance, resistance testing for some anti-TB drugs, such as ethambutol and streptomycin, is less reproducible than for other drugs, such as isoniazid and rifampicin.\textsuperscript{45} Rapid culture identification and drug susceptibility testing has been reported using early morphology cording of TB. Microscopic observation of drug susceptibility assays of MTB, indicated by cord formation, is an inexpensive method proposed for drug resistance testing. This method is performed using liquid media in a microtiter plate format and read on an inverted microscope.\textsuperscript{46-49} (Note: Although this method is not as labor intensive as other culture techniques, strict biocontainment is required since liquid media are used.)
CONCLUSION
Success in the TB laboratory program is tied to the support provided by the Global Fund to Fight AIDS, Tuberculosis and Malaria; the U.S. President’s Emergency Fund for AIDS Relief (PEPFAR); and other partners and donors, with leadership coordination by the national TB program. The renovation of the national laboratory and new regional facilities can provide capacity for culture and drug resistance testing. TB culture is primarily used when a patient appears to be failing treatment or for drug resistance surveys. The burden of smear-negative TB cases among people living with HIV has increased the need for more culture capacity in high-TB-burden settings. While solid culture may appear to be cost-effective, factors such as result turnaround time and national TB control benefits must be given serious consideration in light of the potential for the global spread of MDR- and XDR-TB strains. Effective use of rapid liquid culture coupled with a rapid TB identification system can reduce TB culture and drug resistance testing turnaround times and has the potential to make a significant impact on diagnosis and detection of drug resistance, while improving overall outcomes of TB/HIV care and treatment programs.

The laboratory plays an important role in providing test results for early diagnosis, TB control, and management decisions at regional, national, and global levels. There are many challenges inherent in establishing a sustainable TB reference laboratory program in low-resource, high-TB-burden settings. However, these challenges can be overcome with planning, technical expertise and support, and adequate resources. Although TB remains a significant global threat, this ancient disease will be controlled and eventually eliminated through strong and effective partnerships supporting rapid TB diagnostics, laboratory program infrastructure, and sustainable human resource capacity development.
HE INCIDENCE OF TB IN ZAMBIA is 600 cases per 100,000 population, and the HIV coinfection rate ranges from 50% to 70%. Before 2005, the Zambia TB program was supported by one laboratory with conventional TB culture capacity, the National Chest Diseases Reference Laboratory. Because of the critical need to strengthen and expand TB diagnostic capacity within the country, Zambia’s Ministry of Health requested donor support and technical assistance from PEPFAR to expand the reference laboratory’s capacity in the northern region of the country. The Tropical Disease Research Center (TDRC) TB Regional Reference Laboratory was established to support the National Chest Diseases Reference Laboratory in improving TB diagnostic service turnaround time in the northern region of the country.

Both the National Chest Diseases and TDRC TB Regional Reference Laboratories support the Zambia TB program with FM, rapid identification, culture, and first-line drug susceptibility testing. These laboratories provide EQA support for approximately 160 smear microscopy centers in the TB network. Many challenges were encountered in the process of strengthening the national TB reference laboratory network. Lessons learned that may be particularly relevant to other settings are discussed here.

**Development of Containment Facility Plans for New and Existing TB Laboratory Facilities**

Most containment facility drawings for TB culture facilities were created 10 to 30 years ago. These plans typically included laboratory workbenches positioned in front of windows, a few sinks for staining and hand washing, a limited number of electrical outlets, and walk-in incubators using space heaters and fans (uneven heating environments that did not provide optimal growth conditions for TB cultures). Laboratory space in the National Chest Diseases Reference Laboratory was adequate, but adjustments included adding two class II biosafety cabinets for a safe work environment. A temperature-controlled culture room for two BACTEC MGIT 960 TB culture systems was established. The walk-in incubator room was renovated for storage of four floor model incubators. A temperature-resistant film was placed on the laboratory windows to reduce the amount of heat entering from the outside while still allowing light to enter and protecting the room from excessive heat accumulation during warm weather. Multiple air-conditioning units were placed at strategic points within the laboratory to maintain a temperature-controlled environment for equipment operation. The renovated space now facilitates a safe and efficient laboratory workflow with improved human resources and rapid testing capacity.

Development of a new biocontainment facility for rapid TB culture was easier than renovation of the existing facility, in terms of the planning process, since space limited what could be put in the older facility. The major challenge with the existing facility was scheduling work around renovation activities and protecting cultures from contamination. In both new development and renovations the
amount of time required for completion of the physical work was a challenge. Developing the new facility at TDRC entailed slow work processes as well as nonfunctional support services and discovery of inadequate electrical outlets after occupancy of the facility. Other surprises included low water pressure, facility leakages during the rainy season, and the need to protect equipment from dust contamination during dry and windy seasons. As expected, the hiring of sufficient laboratory personnel and the planning of training activities to improve technical and organizational skills required more time for the new laboratory facility development.

Expansion of Electrical Output to Support Laboratory Equipment
Refrigerators, freezers, class II biosafety cabinets, and automated culture systems require high-voltage electrical output supported by automatic backup generators, power supply regulators, and surge protectors. These are in both the renovated National Chest Diseases Reference Laboratory and the newly established TDRC Regional TB Reference Laboratory.

Clean and Reliable Water Supply
Laboratory water supply (e.g., boreholes as an underground water source) for technical work and safe waste disposal are important additions when expanding technical capacity to support new and developing laboratories in Zambia and in many sub-Saharan African countries. Most laboratories have water supply problems, such as low pressure, which limit the amount of water available. Challenges encountered in Zambia included inadequate numbers of sinks (for staining smears, glassware washing, and hand washing), as well as several other water-related issues.

To ensure a constant water supply, water tanks and pumps and adequate electrical sources to operate the pumps were installed. Distillers and a supply of water filter replacement cartridges are also required for the preparation of reagents and dilution of drugs for susceptibility testing. It is important to design schedules and procedures to ensure that equipment is inspected, serviced, and maintained on a regular basis.

Implementation of New Diagnostic Equipment
The use of new diagnostic equipment to support rapid and sensitive testing requires procurement of the proper reagents. Reagent acquisition requires planning and knowledge of the testing environment, as well as knowledge about how to order and negotiate the best services for the national TB program. Procurement of reagents in resource-limited settings can be especially challenging because of the time it takes to receive supplies and equipment, different procurement procedures for different reagents, and lack of technical laboratory expertise with new equipment and reagent requirements. The implementation of diagnostic equipment designed for high-resource settings requires patience, adaptation, and knowledge of international guidelines and rationale for existing or original protocols, as well as careful planning with the in-country technical experts who will be the end users. This process should be carried out with support from consultants familiar with the use of the equipment in a range of settings. To simplify the implementation process, equipment selection should be standardized across sites whenever geography, physical infrastructure, technical expertise, and clinical needs permit.
Human Resource Capacity Development and Technical Training Support

Aside from physical infrastructure improvements, capacity development and support are the most challenging aspects of laboratory capacity building for TB/HIV programs. Human resources are limited for national programs. Resources may be provided through cooperative agreements and seconding from other donors, allowing TB laboratory technicians to adequately support the national program. Additionally, local TB donors and laboratory partners can work cooperatively with international professional organizations and instrument manufacturers to provide training directly to the national network and take responsibility for diagnostic and treatment support in various regions of the country.

TB Specimen Transport Mechanisms

Regional and national TB laboratories provide diagnostic support for rural, district, and provincial facilities by referral systems. Because full-service TB laboratory support for culture and drug susceptibility testing is limited within a country due to geographical distances, human resources, and infrastructure capacity, it is important to develop a mechanism to provide services across those distances. This can be done by transporting specimens via numerous mechanisms, such as bicycles, motorcycles, private vehicles, and commercial courier systems. Commercial courier transport of diagnostic specimens is the most cost-effective and stable method for providing services in both high- and low-resource settings. For any transport strategy to be effective, there must be adequate planning for implementation and secured financial commitment. Areas that require particular attention include acquisition and management of appropriate sample transport packaging, staff training, sample preparation, and documentation of sample pickup and delivery times to and from the testing sites with ongoing monitoring and evaluation to ensure quality of service.

Internal Quality Control and External Quality Assessment Activities

The internal quality control programs for laboratories in Zambia continue to be strengthened. Challenges for implementing internal quality control include difficulty acquiring reference quality control strains due to cost, material transfer issues, biosafety, and international transport concerns for shipment of mycobacterium species. Participation in international smear microscopy and drug susceptibility testing programs is in progress in both laboratories in Zambia.

Technical Consultation to TB Laboratories in Resource-Limited Settings

Validation procedures for FM, liquid culture, AccuProbe identification, and rapid first-line drug resistance testing are in place at the National Chest Diseases Reference Laboratory and more recently have been implemented at TDRC TB Regional Reference Laboratory. The provision of technical assistance in resource-limited settings can be very rewarding for international consultants because small interventions can make major contributions to the treatment and care of patients coinfected with TB and HIV. Both the implementation of laboratory procedures and the
provision of desired laboratory services for clients in resource-limited settings frequently take longer than anticipated, which requires a significant amount of patience and resilience.

The use of international technical consultants to assist in the implementation of TB diagnostic procedures, such as ZN smear microscopy, EQA, panel testing, and blinded rechecking, can be highly effective. However, several challenges are associated with having an outside professional assist in the setup of these systems, which can lead to frustration on all sides. For instance, most laboratory scientists in resource-limited settings are accustomed to experiencing shortages of needed supplies on a routine basis, which can slow or halt activities. Outside consultants will also need to consider local conditions and limitations when attempting to implement international scientific protocols and technical standard operating procedures. For example, samples used in direct smear microscopy in resource-limited, high-TB-burden settings will differ significantly in comparison to the concentrated samples common in low-prevalence, high-resource settings. Reference manuals and training materials developed jointly with WHO, IUATLD, CDC, and other global laboratory partners are invaluable resources for international laboratory consultants who will work with in-country professionals to adapt procedures to local laboratory management practices and conditions to accomplish the needed tasks.
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Integration of TB and HIV Care in Large, Urban Primary Health Centers: Lessons Learned from Lusaka, Zambia

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Given the global impact of HIV infection on tuberculosis (TB), the World Health Organization (WHO) Stop TB Strategy now includes a focus on TB-HIV collaborative activities. Although the potential benefits of TB-HIV integrated systems have been documented, developing systems to implement such services is an ongoing challenge for TB and HIV programs in high-burden countries. The aim of this chapter is to present initial experiences and early lessons from the integration of TB and HIV programs in Lusaka, Zambia.

Zambia is one of the countries hardest hit by the dual TB-HIV epidemics: the country has the world’s eighth highest TB incidence rate and a national HIV seroprevalence of 17%. Lusaka District encompasses Zambia’s capital city of Lusaka, with a population of approximately two million individuals served by a network of 27 primary care public health centers. Depending on the size of the health center, HIV departments vary in size from 1,000 to 8,000 enrolled patients, and TB departments treat from 200 to 2,100 patients annually. These health centers provide an array of services, among them inpatient and outpatient adult and pediatric medical care, labor and delivery, and maternal and child health, including programs for the prevention of mother-to-child transmission. To date, HIV care and TB care are provided through independent, vertical programs. In this chapter, the term integration refers to enhanced case finding and diagnosis of both TB and HIV by health-care workers within both TB and HIV programs and the strengthening of referral systems between these programs.

Developing Partnerships

In response to the World Health Organization’s call for greater collaboration between HIV and TB programs, the Zambian Ministry of Health (MOH) established the National TB-HIV Coordinating Committee in 2005. This was the first step in initiating national-level action in support of the integration of TB and HIV activities. The formation of this committee was critical in establishing the commitment and leadership of the MOH on this issue and demonstrating the priority status accorded to TB-HIV. Committee membership is composed of the MOH and national and international nongovernmental organizations (NGOs) involved in TB and HIV care in Zambia. Since its inception, the coordinating committee has led the formulation of policies calling
for the training of health-care workers in provider-initiated HIV testing and counseling (PITC), also termed diagnostic counseling and testing (PITC), as standard care in TB programs and the creation of integrated patient care forms and patient management algorithms.

A similar coordinating committee and TB working group were formed at the district level by the Lusaka District Health Management Team. All TB-HIV stakeholders in Lusaka District were invited to meet to harmonize TB-HIV-related activities. Through this mechanism, the Centre for Infectious Disease Research in Zambia (CIDRZ) partnered with the MoH. CIDRZ is a Zambia-based NGO with funding from the U.S. President’s Emergency Plan for AIDS Relief and is affiliated with the University of Alabama at Birmingham. One of its roles is to assist with scale-up of TB-HIV integration activities at the health center level, including design of TB-HIV integration systems, training of health-care workers, systems implementation, monitoring, and evaluation.

SITUATION ANALYSIS AND SITE SELECTION AT THE HEALTH CENTER LEVEL

TB and HIV screening practices and patient flow between departments were analyzed in several health centers. This information was used to develop an integration model that was piloted at one health center. Once the model had been evaluated and modified, it was scaled-up to other health centers (see Figure 1). In preparation for this scale-up, MOH and CIDRZ staff surveyed Lusaka District health centers, prioritizing them for implementation by the following criteria: (1) centers offering both TB and HIV services, (2) centers with adequate staff and counseling rooms to perform PITC, (3) centers with high volumes of TB- and HIV-infected patients, and (4) centers with opportunities to coordinate integration with the opening of new HIV departments. Planning for infrastructure expansion at other sites was initiated concurrently to provide lead time for the completion of needed renovations or construction. Using these criteria, 15 health centers were initially targeted, followed by 7 more that provided TB but not HIV care.

Prior to implementation at each health center, the district TB-HIV focal person facilitated a meeting with health center staff to introduce TB-HIV integration as an MOH initiative. The focal person also introduced representatives from CIDRZ and explained that they would provide technical support for this initiative.

INTEGRATION ACTIVITIES

All integration activities were based upon recommendations in the Interim Policy on Collaborative TB-HIV Activities from WHO’s Stop TB and HIV/AIDS departments. The three goals of the WHO policy are to (1) establish the mechanisms for collaboration, (2) decrease the burden of TB in people living with HIV, and (3) decrease the burden of HIV in patients with TB.

These goals were achieved at the health center level through the following activities:

1. Improved communication and referral links between TB and HIV departments. All TB and HIV patients carry patient care cards with diagnostic and treatment details that are used to improve the sharing of critical patient care information between TB and HIV departments. Clinicians have been trained to check these cards at each visit for updated details of their patients’ treatment. Communication of patient information from HIV departments to TB departments is facilitated by the TB corner referral/drug update form. This form documents referrals to TB departments and suggested TB treatment regimens, as well as
initiation, or changes to ART regimens or initiation of cotrimoxazole preventive therapy.

2. **Establishment of PITC at TB departments.**
   Group education sessions in the TB department waiting area provide information on TB-HIV coinfection, the importance of knowing your status, and HIV prevention. PITC is offered to all patients at their time of enrollment into TB care (see Figure 1, TB Department). For those who initially refuse testing, PITC is reoffered at the end of the intensive phase of TB treatment and again at completion of TB treatment.

3. **Improved screening and diagnosis of TB in HIV departments.**
   Doctors and clinical officers are trained in typical and atypical clinical presentations of TB-HIV coinfection and the use of diagnostic algorithms. Clinicians review symptoms at all visits and are encouraged to screen for TB whenever patients present with symptoms consistent with TB (see Figure 1, HIV Department). Since the TB diagnostic process can occur over multiple visits and involve different clinicians, a TB diagnostic worksheet was developed to assist with continuity of care and improve documentation.
HUMAN RESOURCE DEVELOPMENT

Staff members targeted for training in integrated care included health center management, medical and clinical officers, HIV and TB department nurses, nurse-counselors, peer educators, and pharmacy and laboratory technicians. After discussing staffing requirements for integration, health center staff in charge select those to be trained. Depending on job responsibility, staff receive 2 to 10 hours of training consisting of rationale for integration, TB-HIV epidemiology, clinical diagnosis and management of TB and HIV, and PITC techniques.

Training days are chosen to maximize attendance and minimize the effect on health center operations. Sessions are usually held in the afternoons, when the clinic is less busy. Clinical training is conducted by an internal medicine physician or general practitioner, while PITC, patient flow, and systems training are taught by nurse-counselors.

Training Curriculum and Format of Training Sessions

Days 1 and 2 (half-day sessions)—all staff in attendance

- Rational for integration of TB-HIV care
- Basics of TB-HIV epidemiology
- Management of TB-HIV coinfection

Days 3 and 4 (half-day sessions)—staff are divided into two groups

- Group 1: PITC training for nurse-counselors
- Group 2: Training for clinicians, including nurses, doctors, and clinical officers. Training covers basics of PITC, advanced diagnosis and clinical management, and diagnosis of coinfected patients, including X-ray interpretation and TB-HIV cotreatment.

Standard training materials were prepared using the following guidelines: the WHO TB-HIV: A Clinical Manual, the UNAIDS and WHO Guidance on Provider-Initiated Testing and Counselling in Health Facilities, the Zambian MOH Guidelines for TB-HIV Integration, and the Zambian National Guidelines on Management and Care of Patients with HIV/AIDS. The training materials include didactic PowerPoint presentations and X-ray interpretation, as well as training in correct completion of patient care forms used with the electronic medical records system for all Lusaka HIV departments (e.g., TB diagnostic worksheet, TB corner referral/drug update forms). The sessions are designed to be case based, interactive, and relevant to the day-to-day realities of clinical practice in Lusaka. Pre- and posttest evaluations are used to gauge the level of participant knowledge and effectiveness of training. Nurse-counselors also receive practical training in HIV-testing techniques using rapid test kits.

Implementation of Diagnostic Counseling and Testing

Forms and registers are delivered to health centers on the final day of training. The health centers are then given two days to set up PITC rooms, organize registers and forms, and ensure an adequate supply of test kits. During the first week, CIDRZ staff make daily visits to assist with implementation. Implementation entails working with clinic staff to set up patient systems, including PITC in TB departments, TB screening in HIV departments, and referral systems between departments. This includes real-time implementation of patient education sessions, patient flow, specimen collection, and completion of forms and registers, as well as patient tracking and follow-up. Implementation staff also monitor counseling sessions and patient clinical visits to assess performance and, where appropriate, make suggestions. Supervision of implementation usually lasts one week. During this period, information acquired during training is reinforced and/or clarified, and any misunderstandings are identified and corrected.
It is critical that follow-up activities occur in the weeks after implementation to ensure adherence to new systems and to ensure that appropriate modifications are made to address the unique circumstances of each health center. Initially, follow-up visits occur weekly; once systems are running smoothly, visits are reduced to biweekly. During these visits, TB-HIV integration staff check registers for complete and correct responses, examine TB and HIV department files for appropriate care, documentation, and referral, and discuss any issues or concerns with health center staff. Integration staff review monthly PITC returns with health center staff both during follow-up visits and at quarterly district meetings attended by all TB and HIV clinicians in charge. These quarterly meetings are an opportunity for health center staff to compare results and problem solve issues of concern, especially methods to improve the proportion of TB patients undergoing HIV testing, referral, and completion of HIV department enrollment. If feasible, all activities are led by district staff with the long-term plan to transition program responsibility to the MOH.

MONITORING AND EVALUATION

Systems have been developed to monitor patient flow between TB and HIV departments, assess follow-up, and evaluate program activities. Many of the items measured are based on WHO recommendations for monitoring TB-HIV collaborative activities. PITC registers were created to record test results and the numbers of patients that: (a) receive pretest counseling, (b) accept testing, (c) test positive, (d) are referred to HIV departments, and (e) enroll in HIV care. Additional registers are placed at both TB and HIV departments to record successful referrals between clinics. TB department staff summarize information from these registers on a monthly reporting form, which is forwarded to MOH and CIDRZ and entered into a database.

Monthly summaries are generated from the database and used by implementation team members to monitor and problem solve issues during follow-up visits. Data are disseminated to clinic staff at quarterly meetings and sent to district and provincial health staff.

Register data are supplemented by data from an electronic medical record system used in all Lusaka HIV departments. Patients referred to HIV care from TB departments have unique patient ID numbers identifying them as TB patients. Patient data collected from this system include date of HIV department enrollment, ART start date, and cotrimoxazole preventive therapy (CPT) start date. One limitation is that new TB diagnoses are not routinely captured in the existing electronic system; this feature is being added to the system’s next version.

Figure 2 (next page) shows summary PITC data from the first seven Lusaka health centers to implement PITC. These health centers implemented PITC between December 2005 and March 2007. All patients offered PITC at these health centers prior to April 30, 2007, were included in an observational cohort. This cohort was followed through August 31, 2007, to allow an adequate period of time for HIV department enrollment. A total of 2,053 patients were approached by providers for HIV testing using the PITC strategy. Of patients who did not have prior HIV-positive test results, 1,519 (77%) accepted HIV testing and 1,049 (69%) of these tested HIV positive. At the time of data collection, 591 of 1,006 (59%) TB-HIV co-infected patients with traceable medical record numbers had enrolled into long-term HIV care and treatment. Median CD4 count among those who enrolled was 161 (interquartile range, 84-277), with 88% at either WHO Stage III with a CD4 count of less than 350 cells/mm³ or WHO Stage IV, making them eligible to receive ART according to Zambian national guidelines.
SUCESSES AND CHALLENGES
Implementation of integrated services has resulted in many successes and challenges. These will be discussed as they relate to the following issues: staff response, space and staff capacity, patient acceptance, integration of TB and HIV cotreatment, infection control, TB diagnosis in ART clinics, and communication between TB and ART clinics.

Staff Response
TB-HIV integration has been readily adopted by district TB staff, as they have long recognized that HIV coinfection affects the majority of their patients and leads to poorer clinical outcomes and relapse. Despite prior training in diagnosis and treatment of opportunistic infections, HIV department staff have appreciated further training in TB diagnosis and management. Even though TB is a common finding in HIV departments, its management poses significant challenges, especially in terms of diagnosis and cotreatment with TB and ART regimens.

Space and Staff Capacity for PITC
Many of the smaller health centers were able to provide PITC to all new TB patients as well as to the “backlog” of patients already receiving TB treatment at the time of implementation. However, several of the centers with large patient volumes and limited staff numbers were unable to approach all patients for counseling and testing before they completed TB treatment. This was addressed by the addition of nurse-counselor overtime shifts and the construction of dedicated PITC counseling rooms.

Patient Acceptance
Although acceptance of HIV testing was high (77%), it was below the goal of 100%. Health center staff report that barriers to testing included patients’ inability to cope with two diagnoses,
wanting to consult a spouse, fear of ART and/or cotreatment with TB drugs and ART, HIV stigma, and variations in the quality of counseling. Couples counseling is not available at PITC sites but would be helpful when patients wish to consult a spouse regarding HIV testing. Because a high proportion of coinfected patients are eligible for ART (88%), all HIV-positive TB patients are offered enrollment in HIV care to streamline referral systems. However, despite treatment literacy education, only 59% of HIV-positive patients completed HIV department enrollment. These results are worrying, given the high proportion eligible for ART initiation according to WHO and national guidelines.

Anecdotally, patients report the primary reason for not enrolling in ART care is the concern that they will automatically be initiated on ART; some patients fear the pill burden and side effects of cotreatment, while others believe that cotreatment is fatal. Patients may be psychologically prepared to accept TB treatment but not be ready for the additional emotional burden of a coincident HIV diagnosis. Similar reasons for not starting ART were found in a qualitative study conducted among HIV-infected women in Lusaka.16 High patient volume, staff shortages, and long waiting times at HIV departments also likely contribute to TB patients’ not enrolling in treatment.17 Anecdotally as well, there is concern in the community that patients may be shunning the TB department to avoid health-care worker requests to undergo HIV counseling and testing. Enhanced community education about TB-HIV coinfection, use of peer educators, and qualitative research to further explore these issues are under way.

Integration of TB-HIV Cotreatment

Many recommendations suggest that the optimal integration of TB and HIV care is to comanage both diseases in one setting.5,18-20 This was attempted in one clinic; care was streamlined for patients to receive both TB and ART at the HIV department. Due to large patient numbers, limited space, logistical limitations, concerns over nosocomial transmission, and staff shortages, it was decided that this approach was not practical in a large urban health center. During the pilot program, patient waiting times increased because pharmacy staff could not manage the additional workload generated by the distribution of TB drugs. Ultimately, patients preferred to receive care in both departments. While the current program improves both TB and HIV case findings, its limitations reflect the constraints of the public health-care system.

Infection Control

With enhanced referral of TB patients to HIV departments, as well as the threat of undiagnosed TB among HIV-positive patients, infection control became a priority for integration activities. To address this, a delay period was instituted for new TB patients so that all patients complete at least two weeks of TB treatment to reduce infectiousness before enrolling in HIV care. Plans are being developed for low-cost waiting areas with adequate ventilation for both TB and HIV departments to reduce nosocomial transmission.

TB Diagnosis in HIV Departments

To improve clinical care in HIV departments, CIDRZ staff monitor TB screening, diagnosis, and cotreatment practices in HIV departments and provide one-on-one mentoring to clinicians. Critical to the success of these programs is the scaling-up of TB laboratory diagnostics to cope with the increased numbers of patients undergoing screening. As TB screening of HIV-infected patients increases, the number of smears requiring examination has increased. Sputum-smear microscopy is the primary tool for TB diagnosis in Zambia, and HIV-positive persons are more likely to be smear negative.21,22 Although many Lusaka health centers have labs that
perform smear microscopy, these labs are generally understaffed given the smear examination load. The result is that many TB-HIV coinfected patients are either missed or diagnosed as smear negative and treated empirically based on history, physical examination, or chest X-ray, where available. To address this shortfall, two NGOs have recently hired and trained lay microscopists to increase smear examination capacity in MOH health centers. In addition, the role of lower-cost fluorescence microscopes are being evaluated in this setting. New low-cost diagnostics will be available in the coming years, which should continue to improve the diagnosis of TB in HIV-positive patients.

**Communication between TB and ART Clinics**

Comanagement of patients in vertical TB and HIV departments has resulted in communication challenges that are exacerbated by high patient loads and staff shortages. TB nurses often do not know which patients are on ART, and staff in HIV departments may not be aware that patients have started anti-TB drugs. To address this, referral forms from HIV to TB departments and from TB to HIV departments have been designed and implemented. In addition, weekly missed-visit reports are generated by the HIV department’s electronic medical record system and given to TB department staff so that they can locate patients who default in HIV care.

**LESSONS LEARNED: MODEL MODIFICATIONS**

Each health center has adapted patient flow and monitoring systems to address specific needs of its site and staff. For example, some health centers found that patients were more willing to enroll in HIV care if enrollment was initiated by TB nurses who were familiar to and trusted by the patients. As a result, much of the HIV enrollment process in these centers is performed in the TB department before the patient is escorted to the HIV department. This also decreases waiting time for the first HIV department appointment. In other health centers, this is not practical, and staff have instead implemented an “expedited HIV enrollment” process for TB patients. These patients avoid the usual elective enrollment waiting list and are fast-tracked to reduce loss to follow-up. This is an important step that enables TB patients, the majority of whom have advanced-stage HIV disease, to access HIV care expeditiously.

To address space constraints, counseling rooms were built by modifying existing clinic space and, where necessary, constructing new buildings. In health centers with high numbers of TB patients, nurses were paid to work overtime shifts to perform PITC in an attempt to clear the backlog of TB patients on treatment when PITC was implemented. Further pilots are under way to assess alternative approaches to address health-care worker shortages, such as group pretest counseling and the use of peer educators and lay counselors to assist with counseling and referral systems. It is hoped that such approaches may help reduce the workload of already overburdened TB staff. In Zambia, changes in patterns of clinical care can generate community misconceptions and confusion, such that community consultation and education prior to implementing new programs is critical. Finally, by working closely with the MOH, NGOs can develop sustainable programs with early transition of responsibility to district teams.

**CONCLUSIONS**

TB-HIV integration in large, urban primary health centers in Lusaka has enabled identification and comanagement of many TB-HIV coinfected patients who otherwise would have been missed. The building of capacity to meet the demands of large patient loads and the development of linkages between vertical TB and HIV departments
are ongoing challenges. The largest obstacles encountered are those posed by staffing and infrastructure limitations.

The level of service integration that is feasible at individual sites will vary depending on many factors, including health-care worker supply, infrastructure availability, infection control issues, and patient numbers. Although we did not achieve full integration of patient care in the large, urban primary health centers in Lusaka, it is likely that this is achievable in smaller clinics and rural settings. Current integration models in developing country settings will evolve to maximize utilization of scarce resources, resulting in improved patient outcomes.
REFERENCE LIST


Integrating TB and HIV Care: Lessons Learned from Rwanda

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TUBERCULOSIS (TB) CONTINUES TO be one the leading causes of morbidity and mortality in developing countries. The World Health Organization (WHO) estimated that worldwide there were 8.8 million new cases of TB in 2005, with the majority (84%) occurring in Asia and Africa. In Rwanda, the number of TB cases more than doubled between 1995 and 2005 (3,054 cases in 1995 versus 7,220 in 2005). Many factors are contributing to the increasingly high prevalence of TB in resource-limited settings, including poverty, demographic changes, and the rapid spread of HIV.

HIV is the greatest risk factor for the progression of latent TB infection (LTBI) to active disease. A person who is dually infected with TB and HIV has a 30% to 50% percent lifetime risk of developing TB. In addition, individuals living with HIV, particularly those who are severely immunocompromised, generally develop active TB disease soon after becoming infected with Mycobacterium tuberculosis.

Several studies have demonstrated that TB preventive therapy (PT) is an effective means of preventing TB in HIV-positive individuals. Therefore, it can be inferred that the implementation of TB PT within a community may be an effective means of reducing the TB burden within that community. Since TB PT requires the identification of HIV-positive individuals, HIV voluntary counseling and testing (VCT) centers are an ideal place to offer such therapy.

Besides M. tuberculosis, studies have shown that various bacterial and parasitic pathogens, such as Salmonella typhi, Streptococcus pneumoniae, Toxoplasma gondii, and Isospora belli, are major causes of morbidity and mortality in HIV-positive people in sub-Saharan Africa. Data from many developed countries have shown that before the introduction of antiretroviral therapy (ART), survival of HIV-positive people was improved mainly through prevention of opportunistic infections with antibiotic prophylaxis. In developing countries, the use of antibiotic prophylaxis to reduce the incidence of opportunistic infections was initially evaluated in two clinical trials conducted in Abidjan, Côte d’Ivoire, between 1995 and 1998. The two studies demonstrated a significant decrease in the rate of severe events and in the incidence of serious opportunistic infections in people who received cotrimoxazole (CTX) compared to those who received a placebo. As a result of these studies and following consultative meetings, the Joint United Nations Program on HIV/AIDS
UNAIDS) and WHO made the recommendation that CTX be used for prophylaxis in HIV-positive adults and children in sub-Saharan Africa as part of a minimum care package.

Aware of the danger presented by the deadly combination of TB and HIV, and recognizing that many people living with HIV were dying of preventable diseases, IMPACT-Rwanda (Implementing AIDS Prevention and Care, Rwanda), in collaboration with the Programme National de Lutte contre le SIDA (PNLS; National AIDS Control Program) and the Programme National Intégré de Lutte contre la Lépre et la Tuberculose (PNILT; National Leprosy and Tuberculosis Program), agreed to pilot interventions that would integrate TB and HIV services. Lessons learned from the pilot project were then to be used to inform policy on how TB and HIV services should be integrated in the country. At the time this pilot project was implemented, the WHO guidelines on CTX PT had just been published but had not yet been adopted in many countries. For this reason, little was known about the feasibility of CTX PT in such settings, and access to CD4 counts and antiretrovirals (ARVs) was almost nonexistent. This pilot project was funded by the United States Agency for International Development (USAID) under the IMPACT-Rwanda project.

PILOT PROJECT OBJECTIVES

The objectives of the pilot project on integrating TB and HIV care were as follows:

1. To integrate TB PT into existing HIV VCT services
2. To introduce services for prevention of opportunistic infections with CTX for HIV-positive clients
3. To initiate and increase access of TB patients to HIV VCT services
4. To introduce active screening for TB among partners of HIV-positive TB patients

PILOT PROJECT DESCRIPTION

Site Identification

The pilot project was implemented at Kabgayi and Rwamagana Hospitals, two district hospitals where IMPACT-Rwanda was supporting the implementation of HIV counseling and testing services. The choice of these two sites was based on the relatively high HIV prevalence and number of TB cases recorded in the two districts. At the time of the project initiation in 2000, it was estimated that HIV prevalence rates among women attending antenatal clinics were 10% in Kabgayi and 16% in Rwamagana according to PNLS sentinel surveillance reports. In 1999, the PNILT reported 247 and 271 TB cases in the districts of Kabgayi and Rwamagana, respectively.

Site Preparedness

The intervention team decided that PT services would be offered as part of the HIV counseling and testing services within the hospitals. A room at each site was prepared and used specifically for the project.

The successful implementation of TB and opportunistic infection PT interventions required the following components:

- Appropriate training of all staff in the hospitals on TB, HIV, the relationship between TB and HIV (e.g., prevalence, clinical presentation, treatment, and drug interaction), and preventive treatment for TB and opportunistic infections
- Establishment of formal linkages between various service providers
- Development of data collection tools
- Development of eligibility criteria for various interventions
- Ensuring drug availability (e.g., isoniazid [INH] through the PNILT)
**Staff Training**

The PNILT was responsible for providing training on TB and TB PT to counselors at HIV VCT centers. Training curricula and materials were developed for the following subjects: (1) recognition of TB symptoms, (2) TB diagnosis, (3) exclusion of active TB, (4) TB treatment and monitoring, and (5) TB preventive treatment.

PNLS and Family Health International (FHI) were responsible for training staff at the district hospitals on HIV/AIDS clinical staging and all aspects of CTX PT. Training curricula and materials were developed for this portion as well, and covered the following subjects: (1) clinical definition and staging of HIV/AIDS, (2) overview of common HIV-related opportunistic infections and their treatment or management, (3) PT for opportunistic infections, (4) practical implementation of CTX prophylaxis, (5) monitoring treatment compliance, and (6) client confidentiality.

**Establishment of Formal Referral Linkages between Services in Hospitals**

The interventions being implemented as part of the pilot project required strong collaboration between various service providers within the hospitals and among community-based organizations (CBOs). In order to develop an effective community-based referral system, a number of meetings were held between hospital service providers and CBOS. At the conclusion of these meetings, a system was developed that comprised of a referral coordinator, a referral coordination working group, and referral materials (i.e., referral cards and registry). To ensure the flow of information within the hospital, arrangements were made with laboratory and X-ray services to ensure that chest X-ray and laboratory results were interpreted and returned to the HIV VCT centers.

**Development of Data Collection Tools**

The project team designed a data collection form that captured relevant data for the exclusion of active TB, monitoring of adherence to treatment, and occurrence of adverse effects (including active TB). In addition to the data collection form, the team also developed a treatment card, which was used by clients to record each drug dose taken. Information from the data collection form was entered into the computer using a predesigned data entry spreadsheet.

**Eligibility Criteria**

A flowchart outlining the steps involved in determining eligibility for inclusion in the project was developed (see Figure 1); it was decided that those age 13 and older living with HIV would be targeted by the project. While children younger than 13 were not included in the pilot project, it was soon discovered that there was a great need for such services for children. Future policies regarding PT took this need into consideration.

To be eligible to receive INH PT, patients had to meet the following criteria:

- Provide full consent to receive INH
- Have no history of allergies to INH
- Have no symptoms suggesting active TB (e.g., cough, fever, enlarged cervical lymph nodes); in case of the presence of symptoms, a decision would be made by a medical doctor following a two-week course of antibiotics
- Have no symptoms suggestive of hepatitis (e.g., jaundice, abnormal liver function, elevated liver enzymes)
- Have no history of TB in the last three years
- Have a normal chest X-ray

To be eligible to receive CTX, patients had to meet the following criteria:

- Be willing to provide informed consent to receive CTX
Figure 1. Flowchart for TB preventive therapy for people living with HIV infection

Source: Adapted from Botswana NTP, Botusa and National AIDS Control Programme
• Have no contraindications for receiving CTX (e.g., allergy, anemia, hepatitis, pregnancy in third trimester)*
• Have no allergy to any sulpha-containing drugs
• Be classified as WHO HIV stage II, III, or IV with no opportunistic infections that could have been prevented by CTX

Patients presenting with signs suggestive of terminal AIDS were offered CTX but were not eligible to start INH PT. (The team decided to exclude this population from TB prophylaxis, as it would have been difficult to exclude active TB in those patients.)

Ensuring Drug Availability
FHI/IMPACT-Rwanda purchased all the products (INH, pyridoxine, and CTX). Since the project was funded by USAID, FHI/IMPACT-Rwanda was able to purchase Pharmamed’s INH and CTX from the International Dispensary Association (IDA). The importation of the medication was facilitated by the PNILT, which remains the only structure authorized to import TB medicines into the country. Sites made drug requisitions based on the number of clients seen and clients actually enrolled. The PNILT supplied the sites with medication during monthly supervision activities.

IMPLEMENTATION OF INTEGRATED TB AND HIV ACTIVITIES

Integration of TB PT into HIV VCT Services
A flowchart for screening eligibility to receive INH PT was developed (see Figure 1). All HIV-positive individuals identified through HIV counseling and testing services were informed of the availability and benefit of TB PT. These patients were then referred to a medical officer for a clinical examination to determine their eligibility for TB prophylaxis. All clients eligible for TB preventive treatment who wished to receive it were given TB PT. The regimen consisted of daily INH (5 mg/kg up to 300 mg) for nine months. Pyridoxine (10 mg daily) was given with the INH to protect against peripheral sensory neuropathy. Before the administration of treatment, patients underwent extensive adherence counseling and were encouraged to visit the hospital if they developed adverse drug reactions.

Follow-up of patients was performed at monthly clinic visits. During each visit, patients were screened for adverse drug events, adherence to treatment was emphasized, and a 30-day supply of medicine was provided. Treatment was interrupted for clients who developed TB symptoms or hypersensitivity to INH. Clients with TB symptoms were referred to TB services for diagnosis, and, if found to have active TB, they were referred to the TB program for initiation of treatment as per the national TB protocol.

Provision of CTX Prophylaxis to HIV-Positive Patients
All individuals found to be HIV-positive through VCT were informed of the availability of CTX PT. Clients were then screened for eligibility to start CTX PT using a simple flowchart. A medical history and physical examination were conducted to determine the client’s tolerance to CTX or other sulpha-containing drugs and to exclude anemia and existing opportunistic infections that could be prevented with CTX (e.g., toxoplasmosis, bacterial infections, or Pneumocystis pneumonia [PCP]).

HIV-positive individuals who met the established criteria and who wished to receive CTX were given a daily dose of 960 mg (one double-strength or two

*Contraindications for CTX have since been revised by WHO. Revised guidelines are available at http://www.who.int/hiv/pub/guidelines/ctx/en/index.html.
single-strength tablets). Clients were asked to collect a monthly supply of CTX at the health centers. At each visit to the health center, the medical staff (nurses and physicians) in charge of the HIV VCT center monitored clients for drug toxicity, adherence to treatment, and occurrence of clinically significant events (e.g., opportunistic infections). Hemoglobin and white blood cell counts were taken every six months or when clinically indicated. Treatment was interrupted for clients who developed an opportunistic infection that could be prevented by CTX (e.g., toxoplasmosis, bacterial infections, or PCP) or who reported an adverse event.

**Provision of HIV VCT to TB Patients**

All TB patients visiting the TB clinics were educated and informed about HIV (i.e., transmission, symptoms, and management of HIV-related illnesses), the interaction between TB and HIV, and the benefits of VCT and were offered HIV counseling and testing. Patients who agreed to be tested for HIV were referred to VCT services using a referral card. TB patients received pre- and posttest HIV counseling and were asked to bring their spouses or partners to the center for TB screening. All patients were also informed about existing services for the prevention of opportunistic infections with CTX.

**Identification of Secondary Cases of TB**

Spouses or partners of HIV-positive TB patients are more likely to be HIV-positive than spouses or partners of HIV-negative TB patients, and are therefore also at an increased risk of developing or acquiring TB if in contact with an infectious case of TB. For this reason, all TB patients were asked to bring their spouses or partners and anyone else in their household to the TB clinic for screening. All household members who came in for screening were provided with information about TB (i.e., symptoms, transmission, and diagnosis) and TB/HIV interaction. Patient contacts displaying TB symptoms underwent evaluation, including a sputum smear examination for acid-fast bacilli (AFB) and a chest X-ray. Patients identified as having active TB were provided with appropriate TB treatment and referred to HIV counseling and testing for an HIV test.

**Cost of Care**

All treatment was provided at no charge to the patients. FHI/IMPACT-Rwanda supported the pilot project cost, which included medication, chest X-rays, examinations, laboratory work, forms, and so on.

**PROJECT FINDINGS**

**INH and CTX PT: Patient Enrollment and Characteristics**

Between December 2001 and May 2003, 6,551 people living with HIV were offered TB and/or opportunistic infection PT at the two hospitals (2,751 in Kabgayi and 3,800 in Rwamagana). Figure 2 shows the enrollment trend over the three years of the project.

At the time of this writing, the first 2,394 people living with HIV expected to have completed a nine-month course of INH PT. Results and lessons learned from this project are based on this patient population. Of these 2,394 patients, 206 were excluded from the analysis for a variety of reasons.

More than half the patients in Rwamagana Hospital were residing outside the province where the hospital is located, with the majority of them residing in Kigali, about 60 km from Rwamagana (Table 1). In Kabgayi, however, 68% of patients were residing in the same province as the hospital. The differing distances of the patient populations from the treatment sites were expected to have an impact on adherence to treatment.

The sociodemographic characteristics of patients enrolled in the project are represented in Table 2.
Figure 2. Client enrollment per site per year

Table 1. Province of Residency among Enrolled Clients by Project Site

<table>
<thead>
<tr>
<th>Province of Residency</th>
<th>Kabgayi N (%)</th>
<th>Rwamagana N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gitarama</td>
<td>568 (58)</td>
<td>–</td>
</tr>
<tr>
<td>Kigali</td>
<td>207 (21)</td>
<td>813 (67)</td>
</tr>
<tr>
<td>Butare</td>
<td>12 (12)</td>
<td>–</td>
</tr>
<tr>
<td>Kibungo</td>
<td>–</td>
<td>243 (20)</td>
</tr>
<tr>
<td>Other</td>
<td>83 (9)</td>
<td>151 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>981 (100)</td>
<td>1,207 (100)</td>
</tr>
</tbody>
</table>
Table 2. Sociodemographic Characteristics of Clients Receiving Preventive Therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Site</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kabgayi N (%)</td>
<td>Rwamagana N (%)</td>
<td>Total N (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>725 (74)</td>
<td>934 (77)</td>
<td>1,659 (76)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>256 (26)</td>
<td>273 (23)</td>
<td>529 (24)</td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>6 (1)</td>
<td>7 (1)</td>
<td>13 (1)</td>
<td></td>
</tr>
<tr>
<td>16–25</td>
<td>102 (10)</td>
<td>102 (8)</td>
<td>204 (9)</td>
<td></td>
</tr>
<tr>
<td>26–35</td>
<td>447 (46)</td>
<td>529 (44)</td>
<td>976 (45)</td>
<td></td>
</tr>
<tr>
<td>36–45</td>
<td>314 (32)</td>
<td>450 (37)</td>
<td>764 (35)</td>
<td></td>
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<tr>
<td>46–55</td>
<td>89 (9)</td>
<td>107 (9)</td>
<td>196 (9)</td>
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</tr>
<tr>
<td>56+</td>
<td>22 (2)</td>
<td>9 (1)</td>
<td>31 (1)</td>
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<tr>
<td>Average age (years)</td>
<td>35.3</td>
<td>35.6</td>
<td>35.4</td>
<td></td>
</tr>
<tr>
<td>Median age (years)</td>
<td>34</td>
<td>35</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never been to school</td>
<td>70 (7)</td>
<td>116 (10)</td>
<td>186 (9)</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>586 (60)</td>
<td>538 (45)</td>
<td>1,124 (51)</td>
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<tr>
<td>Secondary school</td>
<td>96 (10)</td>
<td>206 (17)</td>
<td>302 (14)</td>
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</tr>
<tr>
<td>University</td>
<td>2 (0.2)</td>
<td>6 (0.5)</td>
<td>8 (0.4)</td>
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<tr>
<td>Not specified</td>
<td>227 (27)</td>
<td>341 (28)</td>
<td>568 (26)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>102 (10)</td>
<td>92 (8)</td>
<td>194 (9)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>364 (37)</td>
<td>436 (36)</td>
<td>800 (37)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>426 (43)</td>
<td>550 (46)</td>
<td>976 (45)</td>
<td></td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>68 (7)</td>
<td>112 (9)</td>
<td>180 (8)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>21 (2)</td>
<td>17 (1)</td>
<td>38 (2)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>981</td>
<td>1,207</td>
<td>2,188</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Client Distribution by WHO HIV Clinical Stage

<table>
<thead>
<tr>
<th>HIV Clinical Stage</th>
<th>Project Site</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kabgayi N (%)</td>
<td>Rwamagana N (%)</td>
<td>Total N (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>567 (58)</td>
<td>754 (62)</td>
<td>1,321 (61)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>270 (28)</td>
<td>253 (21)</td>
<td>523 (24)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>137 (14)</td>
<td>200 (17)</td>
<td>337 (15)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>974 (100)</td>
<td>1,207 (100)</td>
<td>2,181 (100)</td>
<td></td>
</tr>
</tbody>
</table>
The majority of clients were female and between the ages of 26 and 45. Most of the clients (51%) had at least a primary (elementary) level of education.

With regard to HIV clinical stage, 61% of clients were at stage I, 24% were at stage II, and 15% were at stage III (Table 3).

**Enrollment in INH PT**
Out of the 2,394 patients who were screened for eligibility to start INH PT, 434 were excluded. The main reasons for exclusion were presence of TB symptoms (74%), past episodes of TB (33%), and abnormal liver functions (1%). All 1,960 of those found to be eligible were given INH PT.

**Enrollment in CTX PT**
Of the 2,391 patients screened for eligibility to start CTX PT, 1,632 HIV-positive clients did not meet the stated criteria. The majority of clients were excluded because they were at WHO clinical stage Ia (79%). Other reasons for exclusion included the presence of opportunistic infections (2%), first trimester of pregnancy (1%), and anemia (0.4%). In total, 762 HIV-positive individuals were given CTX prophylaxis.

**Total Enrollment in INH and CTX Prophylaxis**
A total of 2,188 clients were given one or both treatment regimens (Table 4). A total of 206 (8.6%) clients were not eligible to receive either of the two prophylactic regimens. Sociodemographic characteristics of ineligible clients did not differ significantly from those of clients who were found to be eligible to receive prophylaxis.

### Patient Outcomes at Six and Nine Months of INH and/or CTX Prophylaxis
An assessment of treatment adherence was performed at six and nine months. The adherence rate was defined as the percentage of people who spontaneously came back to the clinic every month to collect their medications.

Six months after initiating PT, the percentages of clients who were adhering to INH prophylaxis, INH and CTX prophylaxis, and CTX prophylaxis were 73%, 65%, and 54%, respectively (Table 5). Adherence was higher among patients receiving INH compared to those receiving CTX (73% versus 54%, respectively). Treatment interruption was mostly due to loss to follow-up.
A comparison of treatment outcomes for CTX prophylaxis at Kabgayi and Rwamagana (Table 6) indicates that the loss to follow-up was greater in Rwamagana compared to Kabgayi (44% versus 35%). At each site, there was a higher rate of treatment interruption for CTX prophylaxis among patients whose place of residence was Kigali (53% in Kabgayi and 62% in Rwamagana).

After nine months, 58%, 49%, and 41% of patients were still adherent to INH, INH and CTX, and CTX only treatment, respectively (see Table 7). Overall, the rate of clients who remained adherent to treatment decreased consistently over time, regardless of the treatment regimen received (see Figure 3).

### Causes of Treatment Interruption

Treatment interruption was due to voluntary drop-out, patient death, or the decision by a health-care worker to stop treatment because of the presence of side effects or the development of opportunistic infections known to be prevented by CTX. If treatment was interrupted for the latter reason, the...
patient was evaluated and given the proper treatment for his or her condition.

Information regarding the causes of treatment interruption due to voluntary dropout was obtained through informal discussions with clients, information provided by clients to groups for people living with HIV, and from qualitative research conducted by the project team in February 2003 among people who participated in the preventive treatment project. The survey included 38 clients who completed the nine-month regimen of INH prophylaxis and six people who voluntarily dropped out of the program. The following reasons for treatment interruption were recorded:
- Transportation costs, especially for patients living in provinces outside those of the project sites.

Table 7. Nine-Month Outcomes for Clients on Preventive Therapy

<table>
<thead>
<tr>
<th>Type of Treatment (# of Patients Started on Treatment)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adherent</td>
</tr>
<tr>
<td>INH (1,426)</td>
<td>58</td>
</tr>
<tr>
<td>INH + CTX (534)</td>
<td>49</td>
</tr>
<tr>
<td>CTX (228)</td>
<td>41</td>
</tr>
</tbody>
</table>

CTX = cotrimoxazole; INH = isoniazid

Figure 3. Adherence rate at six and nine months by treatment regimen

PREVENTION AND MANAGEMENT OF TUBERCULOSIS
• Availability of CTX from sources other than the project hospital. Some clients receiving CTX treatment obtained their drugs from another source (e.g., other health services/projects or private pharmacies). Those who bought the drugs directly from private pharmacies claimed that the cost of the drug was cheaper than the cost of monthly transport to and from the project sites. Some associations of people living with HIV, nongovernmental organizations, and other health structures in Rwanda have been providing CTX. Many patients previously enrolled in the projects at Kabgayi or Rwamagana began procuring drugs from these other sources because of their closer location.

• Perceived lack of health improvement, especially in patients with advanced-stage HIV infection.

• Lack of motivation to take medicine for long periods of time, especially when the patient does not feel sick (e.g., patients in WHO stage I).

• Lack of information (e.g., patients stopped taking their medication because they began taking medications to treat another illness).

• Fear of discrimination. Some patients stopped treatment because they did not want their neighbors to find out they were HIV-positive. They felt their status might be discovered due to their frequent visits to the project sites.

• Fear of rejection or reprisal. Based on previous experiences, irregular patients assumed that they would be rejected or punished if they were late coming to the clinic and decided to just stop treatment instead of facing punishment. In some cases, patients were put off by the disrespectful language and/or attitudes of some providers toward their patients.

Cases of TB Identified during the Intervention

During the intervention, 22 cases of TB or suspected cases of TB were identified, justifying the discontinuation of INH treatment for those already receiving INH prophylaxis. Of those, 13 cases were identified in Kabgayi and 9 cases in Rwamagana. All 13 of the patients in Kabgayi were receiving INH plus CTX prophylaxis. Among the nine cases identified in Rwamagana, seven were receiving INH plus CTX and two were receiving CTX only. Four of the seven clients with TB or suspected TB were found to have TB symptoms at their initial evaluation. Thus, INH treatment should not have been initiated in these patients.

Client Perceptions of the Services

Information about clients’ perceptions of the services they received was collected from the following sources:

• Client testimonies recorded by health-care workers during regular meetings

• Interviews of seven patients from Kabgayi during the baseline survey conducted to find out more about the management of people living with HIV under the ART program

• A qualitative survey given to a selected number of people living with HIV who were enrolled in the project, on factors influencing their adherence to treatment

According to the results of the qualitative survey, which was conducted after patients had received education and counseling, the general expectation among patients prior to treatment was that chemotherapy would enable them to live longer and prevent the occurrence of opportunistic infections, especially diarrhea and skin rashes, or that therapy would at least reduce the intensity of the condition. According to the same survey, the majority of clients knew that the medications they would receive were to prevent TB and other opportunistic infections but not to cure HIV/AIDS. However, there were a small number of patients who thought that the prophylaxis medications could cure HIV/AIDS. The majority of
Patients felt that the availability of prophylaxis was a good thing, and suggested that in order to increase access, distribution should be located closer to clients’ homes and health centers. Others suggested an increase in the variety of medications available for people living with HIV.

**Increasing Access to HIV Counseling and Testing Services for TB Patients**

From September 2001 to March 2003, 347 cases of TB were registered in Kabgayi Hospital. Among the 347 cases, 166 (48%) accessed VCT services. Of those tested, 51 (31%) were found to be HIV-positive. In Rwamagana, 220 cases of TB were registered, among which 149 (68%) were tested for HIV. Of those tested, 49 (33%) were found to be HIV-positive.

At the beginning of the project, some TB patients did not access VCT services (especially in Kabgayi) because of the requirement that all VCT clients pay a fee of RWF300 (approximately US$0.50). These TB patients thought the fee was too high considering the fact that they were receiving TB tests (e.g., AFB sputum smear) and TB drugs for free. As a result, measures were taken to provide free VCT services to TB patients, through the use of a form indicating to the VCT providers that the patient had been referred from the TB program.

**Active TB Testing among Partners of TB Patients**

Only two patients out of all those enrolled brought their partners in for TB testing. An inquiry about the low uptake of this service revealed that many partners didn’t feel compelled to come to the TB clinic since they didn’t have TB symptoms. They had learned from the PNILT campaign that only people presenting with TB symptoms would be screened for TB at TB clinics. It is also possible that partners failed to come in for screening due to fear of stigma or HIV screening, or because they were just not told to do so by their partners.

**CHALLENGES OF INTEGRATING TB AND AIDS CARE**

Following is a summary of the principal challenges experienced during implementation of the intervention:

- Monitoring of clients (e.g., education, distribution of medications) was carried out by trained personnel (training of nurses and counselors was conducted as part of the pilot). However, when trained personnel were on leave, they were for the most part replaced by untrained personnel.
- A rapid review of chest X-ray films revealed that a good number of films were of poor quality and had been improperly stored.
- The quality of the services provided diminished as the number of clients increased. Therefore, it was difficult to follow up properly with patients who didn’t show up at the clinic.
- For about nine months at the beginning of the intervention, Rwamagana Hospital was dealing with a shortage of doctors; there were only two doctors stationed at the facility (one of whom was the director of the health district, who was never at the site because of his multiple responsibilities). Consequently, the intervention suffered due to the lack of critical involvement by doctors, especially in the area of patient enrollment. For instance, the resultant delays in the reading and interpretation of X-rays resulted in patients being lost to follow-up before a decision could be made about whether or not they should receive INH.

*At the time of the pilot project, the PNILT performed active screening only of children known to be in contact with someone infected with TB. This strategy was later changed to include screening of all contacts, partially as a result of the poor uptake by partners during the pilot project.*
• The drug procurement system experienced various logistics problems. For instance, FHI/IMPACT-Rwanda received the authorization to purchase CTX manufactured by Pharmamed through IDA. During the months of March and May 2003, the manufacturer had production problems, which forced FHI to find other ways of procuring CTX to avoid shortages.
• The pilot project attracted many patients who came from different regions of the country. Those patients were traveling every month to Kabgayi or Rwamagana for follow-up visits and medication provision. A good number of patients with very limited resources mentioned that most of the time they were not able to pay for transportation or had to walk long distances to get to Kabgayi or Rwamagana.
• The great demand for prophylaxis treatment created a work overload among health-care providers who were already overworked due to staff shortages. They often found themselves obligated to continue providing services until late in the day.
• Providing prophylaxis treatment is psychologically draining; providers have to offer continuous counseling to many patients throughout the day.
• The project did not have the resources to assist the two hospitals in the therapeutic management of patients who developed opportunistic infections other than TB during prophylaxis treatment.
• Health information given to patients by providers was often incomplete. Providers usually failed to emphasize the importance of the intervention, to remind patients during follow-up visits of the length of the treatment, to encourage them to continue treatment, and to talk to them about possible side effects.
• When the intervention was first implemented, there were many deficiencies regarding determination of clinical stages of HIV, adhering to eligibility criteria, and data recording on patient cards. Errors in staging and eligibility were corrected during supervisory activities, and the initial patient card was replaced with another card in the form of a checklist.

LESSONS LEARNED
The following lessons were learned during the implementation of this project:
• Prophylaxis treatment (INH and CTX) is feasible given adequate training of doctors and nurses with respect to inclusion criteria and with a minimum level of clinical and biological monitoring.
• INH and CTX prophylaxis services have been well received by care providers and people living with HIV, without the presence of a media-driven public information campaign. There is a clear demand for prophylaxis treatment among people living with HIV.
• Implementing an intervention such as this requires additional human resources and infrastructure.
• Individual patient cards that contain all the information to be verified in a checklist format help guide nurses in the selection of eligible patients. This is needed in addition to a flowchart posted on the wall or on the caregiver’s desk.
• The training of providers does not always guarantee that those trained will be involved in the implementation of the intervention. During the pilot phase, there was a large turnover of trained personnel, which led to spontaneous training sessions and difficulties with regard to protocol compliance. The implementation of such an intervention requires the involvement of senior staff at the institutions that will be providing services, as well as a mechanism for ensuring continuous training and mentoring of staff.
• An intervention such as this will consist not only of the medical management of people living with
HIV but also of the psychological management of clients. In the pilot project, service providers spent a large share of their time providing psychological support to clients.

• Regular review of monthly statistical reports from sites, along with effective supervision (in this case, by the PNILT), are key to facilitating the rapid identification and correction of problems (e.g., cases of clients with TB signs under INH prophylaxis treatment, patient cards filled out incorrectly, and TB patients who had difficulties accessing VCT services).

• Supervision activities help service providers improve their management of patients and level of organization (e.g., record keeping and improving patient flow). Supervision can also help providers implement a better strategy for the application of the prophylaxis protocol.

• Informing communities about the intervention is critical. Providers indicated that some patients came to the hospital thinking they would receive ARVs or that by accepting prophylaxis treatment they would benefit from other services.

• Interventions such as this can help strengthen national TB control activities in the hospitals involved, through close supervision of the management of TB patients.

• Prophylaxis treatment is needed for children.

• Patients prefer a decreased pill burden. In this project, patients preferred the 960 mg CTX over the 480 mg pills and the 300 mg INH over the 100 mg pills.

• The high number of HIV-positive patients from Kigali who sought prophylaxis treatment in Rwamagana and Kabgayi demonstrates that there is a great need for prophylaxis services in the capital.

• Greater clarity and coordination are required in the area of TB testing for partners of TB patients. Despite promoting the importance of having partners of TB patients access TB testing services, there was almost no partner uptake. Partners who refused to be tested did so in compliance with the PNILT recommendation that only individuals with TB symptoms should be screened for TB.

• There is a great deal of interest (more than expected) in prophylaxis among people living with HIV, as was demonstrated by the high demand for services after the launch of the pilot intervention, especially among those living far away from the pilot sites. The number of registered clients seeking PT was far greater than expected at the time of project implementation.

• A large influx of patients can compromise the quality of service. In the pilot project, for instance, little time was dedicated to each patient during visits, and patient cards were usually filled out in a hasty fashion.

• Interventions such as this will likely attract many people living with HIV who are, for the most part, indigent. This greatly affected the project hospitals’ social budgets (funds designated to pay for indigent health fees), given that fees for other services (not covered by the project) sought by enrolled patients were covered by the hospitals’ social budgets.

• Adherence may decrease over time. Adherence was higher for the six-month INH treatment compared to the nine-month treatment.

• Information, education, and communication are critical to project success. Messages diffused through information, education, and communication programs encouraged patients to access prophylaxis services at Kabgayi and Rwamagana and emphasized the importance of adherence to treatment.

• Data collection tools could be improved by including reasons for ineligibility, weight at enrollment, and the names by which patients are called in their communities.

• Feedback from TB clinics would provide a more complete picture of the TB situation. It was not
possible to perform a follow-up of clients who presented with TB symptoms to determine whether they really had TB, given that the system was not set up to receive feedback from the TB clinics on patients who were referred for TB screening. As a result, there was no confirmation of the number of referred cases who turned out to have active TB.

**RECOMMENDATIONS**

Based on the findings from this intervention, the following recommendations were made to the Ministry of Health:

- Kabgayi and Rwamagana Hospitals should continue offering INH and CTX prophylaxis, while putting a strong system in place to follow up with patients who do not return for continued treatment.
- INH and CTX prophylaxis services should be offered in other health facilities that meet the following minimum requirements:
  - Have enough trained and competent personnel to perform the following tasks:
    - Administer prophylaxis
    - Screen and manage TB cases
    - Conduct regular monitoring of clients, even outside health facilities, to avoid TB cases being treated with an inappropriate regimen (e.g., monotherapy)
    - Provide HIV/AIDS counseling
  - Have funding available to cover medication needs
  - Be able to provide biological follow-up (e.g., hemoglobin level, white blood cell counts, and liver function)
  - Have access to reliable X-ray services and to trained staff able to interpret X-ray films and exclude active TB
  - Have a doctor on staff for INH prophylaxis prescription
- The health facility should receive the approval of the PNILT prior to introducing INH prophylaxis treatment.
- The PNILT, in collaboration with its partners, should look for ways to conduct a study among patients who were under INH prophylaxis treatment to determine the incidence of TB and conduct a drug sensitivity test on any isolates coming from patients who have undergone INH PT. It is recommended that a study also look at the number of patients who develop opportunistic infections while on CTX prophylaxis.
- The Ministry of Health and IMPACT-Rwanda, in collaboration with their partners, should develop information, education, and communication programs to inform communities about the nature of the intervention, the benefits of the program, and the importance of adhering to the program.
- Health facilities that offer prophylaxis treatment should also manage opportunistic infections that develop during treatment. Ideally, patients with opportunistic infections would receive ART as well.
- Health facilities that offer INH prophylaxis should be able to screen for TB. They should systematically refer clients excluded from prophylaxis treatment to TB screening services.
- INH prophylaxis treatment should last six months, as recommended by WHO, instead of nine months. There is no significant additional benefit from three extra months of treatment, considering that clients may experience side effects and be more likely to drop out between six and nine months.
REFERENCE LIST

HIV PREVENTION, COUNSELING, AND TESTING
Rethinking Approaches to HIV Prevention

Marie Laga

Institute of Tropical Medicine, Antwerp, Belgium

IN THE 1980s, DURING THE FIRST DECADE of the HIV pandemic, the main focus of the international community’s response was prevention of new infections, as well as psychosocial support and care for people living with HIV. The “discovery” of combination antiretroviral therapy (ART) in the mid-1990s transformed HIV from a deadly infection into a chronic, treatable condition. This profound change had major implications for global response efforts. In early 2000, the international community and grassroots organizations issued a call to make life-saving drugs available to the majority of people living with HIV in the developing world. The “3 by 5 Initiative” was a joint effort led by the World Health Organization (WHO) and major international donors, partners, and nongovernmental organizations (NGOs) that committed to making antiretroviral (ARV) medications available to three million people by the year 2005. By December 2006, WHO announced that an estimated two million people were accessing ARVs in low- and middle-income countries, compared to only 400,000 in 2003. Even though the original 3 by 5 target was not reached, the recent increase in access to treatment is an unprecedented success story in view of the multiple challenges faced by those countries with the highest HIV burdens.

Scaling up ART and keeping millions of patients on treatment will be sustainable and feasible only if the number of new HIV infections can be dramatically reduced in the next 10 years. On a global scale, it took the international community and individual countries several years to make ART available to 1.3 million people in sub-Saharan Africa. Yet in 2007 alone, 1.7 million people in sub-Saharan Africa became newly infected with the virus. At the country level, Uganda made ART available to an estimated 100,000 people during a period of five to seven years, yet in 2006 an estimated 135,000 new infections occurred in the country. If this trend in new infections cannot be reversed, treatment efforts will never be able to reach all those infected and HIV-related mortality will increase once again.

Since ART reduces an individual’s viral load, treatment scale-up could theoretically have a beneficial impact on prevention. However, lessons learned from developed countries, mainly among men who have sex with men (MSM), indicate that the large-scale introduction of ARVs does not
automatically result in prevention gains. In this population, the anticipated benefit of individual viral load reduction was outweighed by an increase in risky behavior due to increasing numbers of HIV-positive men returning to sexual activity. The impact of treatment on prevention in developing countries is not yet known, but it is likely that similar trends as seen in developed countries will occur if attention to prevention is not intensified. With greater access to treatment, it is expected that millions of people living with HIV in developing countries will resume sexual activity because of their improved health status. Even if the frequency of unsafe sex does not increase among those receiving ART (current data on this are inconclusive), the pool of people living with HIV who can transmit the virus will keep increasing as a result of decreased mortality.

The question at this stage should not be whether treatment is a greater priority than prevention or vice versa, but rather how treatment and prevention can be jointly scaled up to achieve the maximum benefits of both. Mathematical modeling indicates that a scenario in which treatment and prevention are scaled up simultaneously can decrease the number of new HIV infections as well as avert the greatest number of deaths among those living with HIV. Interestingly, modeling also indicates that a treatment-centered approach prevents the fewest new infections and also the fewest AIDS-related deaths (see Figure 1).

Prevention is ultimately our greatest weapon against escalating rates of new infections and can also help make treatment efforts more accessible and sustainable. However, any efforts to strengthen prevention should go hand in hand with treatment scale-up. All possible synergies should be sought to ensure that the outcomes of combined efforts are greater than those of an increased focus on either prevention or treatment alone.

OBSTACLES TO PREVENTION SCALE-UP

Despite increased international recognition that prevention efforts should be intensified, the reality on the ground is bleak. The 2003 report by the Global HIV Prevention Working Group reported that less than one in five people at risk of HIV infection had access to basic HIV-prevention services. In a more detailed report issued by the United States Agency for International Development (USAID) and the Joint United Nations Program on HIV/AIDS (UNAIDS) in 2004, similarly low rates of coverage for prevention interventions were reported, even considering wide variations in coverage by region. According to this report, only 0.1% of people in Southeast Asia had been counseled or tested for HIV. In Eastern Europe, only 7.6% of injecting drug users (IDUs) had access to harm-reduction programs, and in sub-Saharan Africa, less than 5% of pregnant HIV-positive women had access to prevention of mother-to-child transmission of HIV (PMTCT) services.

While the situation may have improved somewhat since 2004, prevention coverage is still largely insufficient. A 2007 WHO report indicated that in the 10 countries with the highest number of HIV-positive pregnant women worldwide (nine African countries and India), PMTCT coverage ranged from less than 1% in Nigeria to 25% in South Africa. Five of the countries still had coverage rates of less than 10%.

There are many reasons why the prevention response continues to fall far short of what is needed. We still have no magic bullets or so-called “technological fixes,” such as a protective vaccine. HIV prevention deals with issues such as sex, condoms, sex workers, and drug use, topics that are considered “uncomfortable” by many individuals and societies. Cultural, religious, or social resistance to talking about these issues stifles efforts to provide
Figure 1. Projected new adult infections and total adult deaths in sub-Saharan Africa, in millions, by the year 2020: Impact of three scenarios compared to baseline

Source: Salomon et al.¹
access to a full range of prevention strategies. Lack of leadership at all levels and lack of activism that specifically focuses on prevention are key reasons why many countries have not made progress in the area of prevention. Many countries also lack the necessary technical, human, and financial resources to implement large-scale prevention programs, such as PMTCT, that are wholly dependent on functional health-care systems. Adding to these challenges is the fact that there is still disagreement among experts on what works and what doesn’t, especially with regard to the best mix of prevention interventions for high-prevalence countries.

It is important to recognize the potentially negative effect that treatment scale-up efforts could have on prevention. A great deal of energy can easily be absorbed by treatment programs, resulting in an even greater reduction in the scale of prevention activities. For instance, in sub-Saharan Africa, many organizations that have traditionally been involved in community mobilization and prevention efforts, such as grassroots organizations and NGOs working with people living with HIV, have now shifted their entire focus to ART-related patient support.

**Opportunities for the Scale-up and Intensification of Prevention Efforts**

Despite the many obstacles to the scale-up of prevention, there are now more opportunities than ever before to intensify prevention efforts. At the level of international policy, there have never been so many resources available to fight HIV/AIDS, and commitments to greater investments in HIV prevention are growing. In high-prevalence countries, access to life-saving drugs has broken the cycle of death and dying and is undoubtedly an incentive for the uptake of HIV testing. A 2007 demographic health survey from Kenya indicated that 13.1% of all men and 18.2% of women knew their HIV status, and in Uganda these figures were 12.7% and 23.5%, respectively. This level of coverage may still be unsatisfactory, but it represents a major increase compared to the era when ART was not yet widely available.

The growth and expansion of chronic-care services for patients receiving ART also represents a new opportunity to expand prevention within the health-care setting. During health workers’ multiple interactions with patients, prevention messages can be included as part of discussions about medication adherence, side effects, and other treatment-related issues. It will be important for ART programs to find innovative ways to fully integrate prevention with treatment-related activities. Perhaps even more importantly, an increasing number of HIV-positive people who are aware of their status and are experiencing improved health as a result of treatment can become agents for change and advocates for prevention among their peers.

**Development and Application of New Prevention Technologies**

**PMTCT**

Since the beginning of the AIDS pandemic, research has focused on identifying biomedical prevention technologies to prevent sexual and mother-to-child transmission (MTCT) of HIV. In regard to MTCT, the PMTCT package (ARVs for mother and baby, avoidance of breast-feeding, and C-section delivery) has been successful in nearly eliminating this type of transmission in developed countries. Yet millions of children in developing countries still acquire HIV from their infected mothers, mainly due to program failure (i.e., the inability to provide the best care package) rather than the failure of the technology itself. The main biomedical technologies that have been developed to prevent sexual transmission are summarized in Table 1.
Female Microbicides and Other Female-Controlled Methods

The search for a female microbicide (i.e., a vaginal gel containing an anti-HIV substance) may be more promising in the short term, but success remains elusive. After the earlier failure of trials involving nonoxynol-9, two more recent trials of a cellulose sulfate gel were ended when results indicated that the gel may have increased the risk of HIV infection compared with the placebo. All phase III trials containing ’second generation’ products except for Pro-200 gel have been interrupted, and hopes are now
ANTI-HIV MICROBICIDES: PAVING THE WAY FORWARD
Jeremy Nuttall, a Saul Walker, b Caroline Galbreath, a Pamela Norick a and Zeda Rosenberg a

International Partnership for Microbicides, United States
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IT IS ESTIMATED THAT ALMOST 33.2 million people worldwide are now living with HIV and that 68% of all adults and children living with HIV reside in sub-Saharan Africa. Increasingly, women bear the greatest impact of the epidemic, particularly in developing countries. In sub-Saharan Africa, women account for nearly 61% of the adults who live with HIV. In several African countries, women 15 to 24 years of age are more than three times more likely to be infected than men the same age. In South Africa, one in four women is infected by 22 years of age.

These staggering statistics clearly demonstrate the urgent need for female-initiated HIV prevention options suitable for use in resource-limited settings. Microbicides are products that can be applied vaginally by women to impede sexual transmission of HIV. They can be formulated in a variety of ways, including gels, films, vaginal tablets, sponges, and intravaginal rings.

The following is a discussion of issues facing the microbicide field regarding the creation of a product that is proved to be safe and effective and that can be made available to women who are most in need of such an intervention.

Microbicides and Other Prevention Strategies
Several microbicides have been tested, or are currently being tested, in phase III clinical trials. These early-generation products are nonspecific compounds that work by electrostatically binding the virus and preventing it from interacting with its target cells in the vagina (i.e., entry inhibitors, such as polyanions). All of these compounds are formulated in clear gels and are intended to be applied vaginally just prior to sex (i.e., they are coitally dependent). A new generation of microbicides is now in development that consists primarily of products based on antiretroviral (ARV) drugs specifically targeting HIV or the cells it infects. These include reverse transcriptase inhibitors, entry inhibitors, and chemokine receptor blockers.

Microbicides are not designed to replace other prevention strategies, but rather to add to existing options and to increase overall HIV prevention effectiveness, and potentially address some existing prevention gaps. For example, abstinence is not a viable option for married women, those who wish to become pregnant, or those involved in coercive sex. Additionally, being faithful in a monogamous relationship will not protect women with an unfaithful partner from exposure to HIV. In fact, in many countries, being a married and monogamous woman is one of the highest risk factors for HIV infection. And although the consistent use of male or female condoms is highly effective in preventing infection, women in many developing countries are not able to insist that their partner use a condom.
The ability of a woman to bear children is also often critical to her status within her marriage and within society, making neither abstinence nor condoms a practical option.

Regulatory Issues
Microbicides are pharmaceutical products, and therefore they must be approved and registered by the drug regulatory authorities in the countries in which they will be marketed. In many developing countries, obtaining regulatory approval can be complicated due to the generally limited regulatory resources and experience in these regions; also pathways to approval often are unclear. Since microbicides represent a new class of pharmaceutical product, the review and approval process may require even higher levels of resources and expertise. In fact, new pharmaceutical products in developing countries are often approved on the basis of prior approval and use in the United States or Europe. However, the ability to obtain registration of a microbicide in Europe or the United States may be affected by the context of its use in a given population, since it is likely that a microbicide will be only partially protective. In developed countries, where the risk of HIV infection is relatively low and treatment for infected individuals is readily available, a risk-benefit assessment of a partially effective microbicide may indicate that there is insufficient benefit to support registration. In many developing countries, where rates of HIV infection are high, a risk-benefit assessment of microbicides is much more likely to support registration.

To overcome some of these difficulties, Article 58 of Regulation (EC) No. 726/2004 of the European Parliament and the Council established a mechanism whereby the European Medicines Agency (EMEA), in cooperation with the World Health Organization, is able to support authorities in developing countries by providing a scientific opinion on certain medicinal products intended exclusively for markets outside the European Union. However, this procedure is still relatively new and has yet to be used for products that have not been previously licensed elsewhere. Alternative processes, including the Conditional Marketing Authorisation established by the EMEA under Regulation (EC) No. 726/2004 and the Notification of Compliance with Conditions instituted by Health Canada, may also prove useful for the registration of microbicides. Both processes reduce the burden of clinical data required for an initial registration, provided a commitment is made to the provision of further data postregistration; to date, neither process has been applied to the registration of products intended for use in developing countries.

Introduction, Use, and Future Access
The potential of microbicides will only be realized if they can be successfully and appropriately introduced into HIV prevention programs and used effectively by women and their partners. With over 97% of people living with HIV residing in low-income countries, 68% of whom are in sub-Saharan Africa, microbicides hold the greatest potential benefit for women in developing countries. However, reaching these women will require early planning and timely mobilization of a network of partners and resources. Microbicides will need to be available in sufficient quantities to meet demand, geographically accessible at appropriate distribution points, acceptable to women (and to policymakers and health professionals),
and affordable (both for end users and others financing their use). As a point of comparison, it is estimated that only one in five people living in developing countries currently has access to existing HIV-prevention services.18

To meet these prerequisites for success, “access” must be integrated into microbicide development from the early stages. Candidate products must be designed to meet the needs of women in developing countries, and therefore market and product preference research should be conducted to establish what these needs are. Products must also be stable under the environmental conditions found in the intended country or region of use, and it must be possible to manufacture them in large quantities and at a low unit cost. Intellectual property agreements should allow flexibility in manufacturing and pricing strategies, thereby supporting affordability and sufficient and secure supply.

Epidemiological modeling can help guide decisions on where and how to most effectively introduce microbicides as part of a broader array of HIV prevention tools. Such modeling should be complemented by studies that seek to understand the factors that may influence the adoption and continued use of microbicides by women. As promising microbicide candidates progress through clinical testing, studies to estimate microbicide demand are needed to inform the scaling of manufacturing facilities and to mobilize necessary financing. Programs also need to be developed, budgeted, and implemented to build demand for microbicides, to distribute them, and to provide the necessary services and education to support their use as part of existing HIV prevention and reproductive health programs. A range of policy and advocacy activities are needed to make the case for and to inform decisions on the introduction of microbicides; these activities can be aided by a range of stakeholders to help mobilize both local and international support.

In anticipation of the first product that is demonstrated to be safe and effective, the microbicide field is progressively working on issues of access,19 and efforts will continue to gradually build an evidence base that can help to mobilize partners, support successful introduction of future products, and ensure that they provide the maximum health benefit.

Progress To Date
As of this writing, nonoxynol-9 (N-9) and Carraguard are the only microbicides that have completed phase III efficacy trials.20,21 Efficacy was not demonstrated for either product, and in fact, there was evidence that N-9 increased the likelihood of HIV infection. Trials of cellulose sulfate (CS) were stopped early when an interim analysis determined that cellulose sulfate use was not protective and could possibly lead to an increased risk of HIV infection.22 Final analysis of the data showed, however, that the difference in HIV seroconversions between the CS group and the placebo group was not statistically significant. Trials of another product, Savvy, were terminated early because of an unexpectedly low HIV incidence and low level of protection at interim analysis that made it unlikely that the trial could adequately demonstrate that Savvy protects against HIV.23 However, in a recent multi-center Phase II/IIb clinical evaluating the safety and effectiveness of BufferGel and PRO 2000, an approximately 30% reduction in the number of seroconversions was seen in the PRO 2000 gel (0.5%) arm, although this was not statistically significant.24
BufferGel was shown to be safe as tested, but had no detectable effect on HIV infection. A Phase III trial of PRO 2000 and BufferGel is currently in progress, with results due by the end of 2009.

None of the above products acts by specifically targeting HIV. However, a phase II/IIIB trial of a gel formulation of tenofovir was initiated in May 2007 and is the first trial with an efficacy endpoint to be conducted with an HIV-specific, ARV-based microbicide. Over the next few years, it is likely that phase III trials of other ARV-based microbicides will also be conducted.

14. Committee for Medicinal Products for Human Use (CHMP). Guideline on...
being placed on ART-containing microbicides, but those products are still in the development phase.\textsuperscript{13}

The diaphragm has also been proposed as a female-controlled method to protect against HIV, because it creates a physical barrier to the cervix, believed to be the most important point of entry for HIV in women. However, a phase III trial in South Africa and Zimbabwe found that the strategy of combining diaphragms, lubricant gel, and condom advice was no more effective than condom advice alone in preventing HIV infections in high-risk women.\textsuperscript{14}
Management and Prevention of Sexually Transmitted Infections

Since the 1980s, several studies have shown that sexually transmitted infections (STIs) can enhance the transmission of HIV, by increasing both the infectiousness of the virus and the host’s susceptibility. For this reason, STI control has become an integral part of HIV prevention. Only more recently has attention been focused on the interaction between a viral STI, herpes simplex virus type 2 (HSV-2), and HIV, and it has become increasingly clear that HSV-2 may be a more potent cofactor for HIV infection than any other STI. Recent studies have shown that treatment of HSV-2 in HIV-positive patients reduces HIV viral load in blood and genital secretions, thus reducing the infectiousness of the host. However, there has yet to be evidence demonstrating that systematic suppressive therapy for HSV-2 infection in people living with HIV will reduce HIV transmission. A large multicenter intervention trial among women in Africa and MSM in the Americas receiving HSV-2 suppressive therapy (800 mg of acyclovir daily) did not show any reduction in HIV acquisition among the treatment arm compared to the placebo arm. So far, the only policy implication for findings related to the relationship between HSV-2 and HIV has been the modification of the WHO STI treatment guidelines, which now recommend that acyclovir be given for the syndromic treatment of genital ulcers.

Pre- and Postexposure HIV Prophylaxis

HIV postexposure prophylaxis (PEP) was initially developed and evaluated as a strategy to reduce acquisition of HIV among health workers who had experienced needle sticks or other accidental exposure to potentially HIV-infected blood, other body fluids, or tissue. The use of PEP for prevention of sexual transmission in developing countries is limited to very specific applications, such as in cases of rape. Preexposure prophylaxis (PrEP), the newest and most controversial approach, includes the daily oral intake of tenofovir or Truvada by HIV-negative people with the goal of reducing their susceptibility to HIV. Large-scale phase III trials on the effectiveness of PrEP are currently under way, and results are not expected until at least 2010.

Male Circumcision

Male circumcision has been associated with a reduction in HIV susceptibility in observational studies since the beginning of the HIV pandemic. In Africa, it has been found that circumcised men and populations with high levels of circumcision are less likely to be HIV-positive than are their uncircumcised counterparts. Three recent randomized controlled trials in South Africa, Uganda, and Kenya showed that circumcision provided a 45% to 60% rate of protection against HIV acquisition. These findings led to the recommendation by WHO and other partners that male circumcision should be recognized as an additional strategy for the prevention of heterosexually acquired HIV in men. The greatest benefits are expected to be in settings with generalized heterosexual epidemics and where levels of male circumcision are low.

The challenge of implementing adult male circumcision (AMC) programs will lie in adequately preparing health systems and communities so that the provision and acceptance of AMC can become more widespread.

THE MEANING OF EVIDENCE-INFORMED PREVENTION

Prevention planning should be evidence informed, meaning that approaches are based on two levels of evidence. The first level of evidence ensures that the response matches the dynamics of the epidemic (i.e., what we know about the epidemiology of the target...
population). The second level of evidence confirms that the choice of strategies is based on their efficacy and effectiveness (i.e., what we know from science).

**The Value of Epidemiological Evidence**

Epidemiological information should form the basis of every national prevention strategy. Prevention programs can be successful only if they appropriately respond to the specific characteristics of the populations they serve. For this reason, a thorough understanding of the epidemiologic spread of the virus in a particular setting is essential. Mismatches between epidemiological patterns and prevention investments are common. For example, in Mexico, although the majority of new infections occur in MSM, most prevention interventions are directed toward the general population and young people. In Ghana, HIV is still largely concentrated among female sex workers and their clients, but only a small portion of the prevention efforts target this group.

The question that must be asked is, “Where and among whom are the new HIV infections occurring?” Classic surveillance methods, such as measuring prevalence among pregnant women.
indicate that most new infections occur among MSM and the general population, in contrast to the early 1990s when HIV was spread predominantly among sex workers and their clients. This type of detailed information can help countries to better prioritize their prevention efforts, and ensure there is a greater focus on groups that have historically not been targeted, such as MSM in Kenya or discordant couples in Thailand.

The Value of Scientific Evidence

Sexual transmission of HIV is influenced by a range of factors, from individual behavior to environmental factors, as represented in Figure 3. Prevention programs should therefore include a set of biomedical, behavioral, and contextual interventions, which are often interrelated and context-specific. Providing evidence for the effectiveness of these interventions
is often a complex and difficult task (with the exception of biomedical prevention tools, for which randomized controlled trials are the gold standard).

Several systematic reviews on the effectiveness of HIV prevention strategies have been published, yet their relevance to prevention program planning has remained limited (with the possible exception of needle-exchange programs). The main reasons for this limited impact include the following: (1) evidence is largely incomplete, because most studies are discarded due to invalid methodology; (2) most evidence addresses one single intervention, not a package of interventions or a complete program; and (3) it is unclear how findings from one research setting are applicable to other settings in other parts of the world. Yet the absence of perfect evidence should not be an excuse for delaying action or failing to implement large-scale prevention programs. The need for intensified prevention efforts is too urgent to await conclusive scientific evidence before taking interventions to scale.

In addition to information about local epidemics and scientific evidence (whether conclusive or not), there is an increasing amount of program data available that should be analyzed and used to inform program planning and implementation. Every prevention program should also pay more attention to monitoring and evaluation (i.e., learning by doing) in order to continually improve programs and learn what is actually working in real-world settings as opposed to what has been shown to work in the context of a research project.

PREVENTION STRATEGIES FOR DIFFERENT TYPES OF EPIDEMICS

Strategic planning for prevention at the country level should be largely based on knowledge of the epidemic and scientific and programmatic evidence. However, other factors should also be taken into consideration when designing an appropriate intervention, including the potential impact on the overall epidemic, the cost of inaction (e.g., an explosive spread of HIV among IDUs), feasibility given the context of constrained health-care systems, acceptability by the community, and any additional benefits to other health problems or health systems.

UNAIDS has developed practical guidelines for intensifying prevention according to different epidemiologic scenarios.

Low-Level Scenario

In a low-level scenario, HIV has not spread to significant levels (i.e., prevalence is less than 1%) in any subpopulation. This is an indication that risk networks are nonexistent or very diffuse, or that the virus has just recently been introduced in the region. Countries where this scenario can be found include Fiji, Turkey, and Afghanistan. In these settings, it is essential to collect information about the most vulnerable and potentially most at-risk populations in an ethically sound manner (i.e., with respect to their rights, voluntary participation, and confidentiality). Stigma and coercive measures, such as criminalization of commercial sex work or harm-reduction programs, are significant barriers to participation in prevention efforts by marginalized groups and should be avoided and discouraged at all times.

Concentrated Scenario

In a concentrated scenario, HIV has spread (i.e., prevalence is greater than 5%) in one subpopulation but is virtually nonexistent in the general population. Classically, these subpopulations tend to be MSM, sex workers, or IDUs. In Argentina, for example, HIV prevalence is greater than 15% among MSM, greater than 5% among sex workers, and less than 1% in the general population. In such a scenario, prevention programs should
specifically target the populations most at risk, with sufficient scale and intensity. Attention should also be paid to bridge populations (in the case of Argentina, bisexual men), and sufficient information given to the general population. Prevention messages should also address stigma and discrimination against these subpopulations.

**Generalized Scenario**

In most parts of sub-Saharan Africa, HIV has spread within the general adult population, with prevalence of 1% to 10% or higher in some countries. In these generalized epidemic scenarios, HIV is still more prevalent in higher-risk groups (such as sex workers and their clients), but a significant proportion of new infections occur among young people and discordant couples. Prevention approaches should include both targeted interventions and interventions addressing the general population, such as youth programs and programs addressing both men and women.

Examples of programmatic prevention actions, as listed in the UNAIDS guidelines for generalized epidemics, include the following:

- Providing evidence-informed sexual and reproductive health education for youth in school and out of school
- Ensuring universal access to HIV counseling and testing, including provider-initiated voluntary HIV counseling and testing
- Ensuring universal and uninterrupted condom availability and integrating condom promotion into reproductive and primary health-care services in the public and private sectors
- Prioritizing programs for men and women that address risk behaviors and gender vulnerability
- In areas with low levels of male circumcision, progressively expanding access to safe male circumcision services within the context of ensuring universal access to comprehensive HIV prevention, treatment, and care and support

**Hyperendemic Scenario**

In southern Africa, HIV has spread in the general population at exceptionally high levels (i.e., prevalence greater than 15%), calling for varied and widespread prevention measures. In a situation in which all sexually active people are at risk, entire communities must be mobilized to change sexual behavior as well as social norms. Campaigns should address the particular vulnerabilities of women while also promoting the roles and responsibilities of men in prevention.

It should be noted that there is still much uncertainty about which mix of prevention interventions will have the most impact in the shortest amount of time, especially in the most affected countries in southern Africa. In 2006, a group of experts met in Lesotho to reflect on the key drivers of the epidemic in southern Africa and to suggest approaches to accelerating prevention. Their conclusions, summarized in the sidebar entitled “Key Priorities for Intensification of HIV-Prevention in High-Prevalence Countries in Southern Africa,” illustrate not only the complexity of prevention programming, but also the challenges inherent in evaluating the impact of national programs on HIV incidence.

**CONCLUSION**

A renewed emphasis on prevention is the only way to achieve universal access to treatment in resource-limited settings. The current momentum of high-level AIDS funding and ART rollout should be harnessed for the scale-up of prevention activities, and synergies with treatment programs should be sought. Aside from condoms, male circumcision is the only effective biomedical prevention technology that has been found so far to reduce the sexual spread of HIV. While evidence concerning “what works” in behavioral prevention programs is incomplete, there is still
KEY PRIORITIES FOR INTENSIFICATION OF HIV-PREVENTION IN HIGH-PREVALENCE COUNTRIES IN SOUTHERN AFRICA

Following are the core areas of focus for HIV prevention in high-prevalence southern African countries:

1. **Significantly reduce multiple and concurrent sexual partnerships for both men and women.** Explore possibilities for mass campaigns or social movements with strong political, religious, and community leadership (both top down and bottom up.) The mass media can help to expose and discourage multiple partnerships as a threat to individual and public health.

2. **Prepare for the potential national roll-out of male circumcision.** Male circumcision should be embedded within a broader context of strengthening male sexual and reproductive health, STI treatment, condom use, and counseling and testing for HIV.

3. **Address gender issues especially from the perspective of male involvement and responsibility.** These issues include sexual and reproductive health and HIV prevention and support, specifically to reduce multiple and concurrent partnerships, intergenerational/age-disparate sex, and sexual violence through multiple channels, including those noted for (1) above.

4. **Continue to program for delayed sexual debut and for consistent and correct use of male and female condoms.** This prevention strategy should be especially emphasized for young people and others at higher risk.

In addition to and in support of these core focus areas, other key priorities include the following:

1. **Increase access to counseling and testing.** Emphasize national “know your status” campaigns backed by posttest services for both HIV-negative people and people living with HIV.

2. **Aim to provide universal access to sexual and reproductive health services and to care and treatment.** A special focus should be on expanding youth-friendly services.

3. **Challenge the drivers of the epidemic to build more cohesive societies.** Addressing underlying structural drivers, notably the complex interaction between poverty, socioeconomic inequality, mobility, and the like, can build more cohesive societies. Risky cultural practices and unequal gender norms should be challenged to achieve overall improvements in health and social welfare.

4. **Intensify multiple approaches.** This would include involving people living with HIV and the media to reduce stigma and increase openness and discussion about sexuality, and to promote and uphold human rights.

5. **Emphasize STI control and prevention.** Expand and make treatment more effective, including treatment for HSV-2.

*Source: Adapted from SADC*
much that countries can do to optimize their prevention efforts.

The scale of the response should match the scale of the epidemic and should be comprehensive in scope (i.e., address individual, community, and contextual factors). In concentrated epidemics, the most important challenges will be to overcome the political, social, and cultural barriers to reach the most vulnerable groups, such as sex workers, MSM, or IDUs, with effective prevention programs at a national scale. In countries with generalized epidemics, the challenge will be in mobilizing the necessary leadership, commitment, and financial and technical resources so that entire communities can be encouraged to change their sexual behavior. In addition, preventive services should be made available to all, to assist in changing social norms and helping to create a supportive environment for all sexually active adults to protect themselves and their partners from HIV.

The current absence of perfect evidence cannot be used as an excuse for delayed action or lack of implementation of large-scale prevention programs. In short, no time can be wasted; it is time to take action. Experience will continue to accumulate as a result of “learning while doing,” and program evaluation data will guide future prevention planning in the years to come.
# REFERENCE LIST


Despite some reductions in global HIV prevalence, the enormous human tragedy represented by an estimated 1.7 million new HIV infections in sub-Saharan Africa in 2007 highlights the inadequacy of current HIV prevention efforts. Although considerable expansion of antiretroviral therapy (ART) programs is occurring in Africa, prevention efforts have not kept pace. In low-income countries, substantial investment in prevention may be cost-effective because future care and treatment costs will be averted. New approaches and new resources might reinvigorate underfinanced HIV prevention efforts and help avoid a widening gap between the numbers of individuals needing ART and those receiving it.

**Positive Prevention**

Internationally, HIV prevention efforts have traditionally concentrated on reducing HIV acquisition risk, focusing primarily on uninfected individuals or ignoring the serostatus of target populations. When HIV prevention efforts began in Africa nearly 20 years ago, HIV testing was not widely available, and concerns about potential stigma and negative social outcomes related to knowledge of HIV status were paramount. These factors may have diverted attention from prevention approaches targeting HIV-positive individuals and, instead, focused efforts on mass media and community and peer education that targeted all those at risk. However, only HIV-positive people—a much smaller population than all those at risk—can transmit HIV. Thus, preventive interventions for HIV-positive individuals (“positive prevention”) can help reduce the risk of transmission, based on the principles of infectious disease epidemiology that focus on the infectious source.

Several approaches to positive prevention have proven efficacy. For example, HIV transmission is reduced by 80% with consistent condom use by HIV-positive individuals and their partners, and in Africa, provision of voluntary counseling and testing (VCT) to serodiscordant couples reduced transmission by 56%. In the United States, clinician-initiated communication, group counseling, and partner testing reduced the frequency of unprotected sexual acts and numbers of sexual partners among HIV-positive adults. In addition, ART has been associated with an 80% reduction in transmission within HIV-discordant couples.

Positive prevention has been recommended by the Joint United Nations Program on HIV/AIDS (UNAIDS), the United States Department of Health and Human Services, the World Health Organization, and the International AIDS Society-USA.
of Health and Human Services, and others, and is currently being implemented in industrialized countries. It should now also become a priority in Africa and other high-prevalence regions. We propose 12 approaches for implementing positive prevention in Africa that prioritize interventions with the largest potential impact on HIV transmission. These include a range of services for HIV-positive individuals: ensuring that HIV-positive individuals learn their status, supporting HIV status disclosure, testing and counseling sexual partners, providing ART, offering behavioral interventions, and selecting low-risk blood donors.

### Table 1. Positive Prevention Action Plan for Africa

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<tr>
<th>Intervention</th>
<th>Potential Benefits</th>
<th>Possible Approaches to Implementation</th>
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<tr>
<td>Ensure HIV-positive individuals learn their status</td>
<td>■ Allows for efficient targeting of prevention efforts</td>
<td>■ Implementation of a range of testing approaches, including routine HIV counseling and testing in clinical settings; 100% access to voluntary counseling and testing (VCT) through door-to-door programs; and stand-alone, mobile, and family-based VCT</td>
</tr>
<tr>
<td>Support HIV status disclosure to sexual partners by HIV-positive individuals</td>
<td>■ Involves partner in prevention, care, and support</td>
<td>■ Disclosure by HIV-positive individuals&lt;br&gt;■ Counselor-assisted disclosure&lt;br&gt;■ Voluntary partner notification</td>
</tr>
<tr>
<td>Test and counsel sexual partners of HIV-positive individuals</td>
<td>■ Identifies previously undiagnosed HIV infections and HIV-discordant couples</td>
<td>■ Integration of partner testing as routine component of prevention, care, and treatment programs&lt;br&gt;■ Provision of facility, mobile, and home-based VCT&lt;br&gt;■ Couples’ counseling</td>
</tr>
<tr>
<td>Provide ART</td>
<td>■ Reduces viral load and risk of HIV transmission</td>
<td>■ Access to and provision of ART for those clinically eligible&lt;br&gt;■ Education emphasizing that ART does not eliminate transmission risk&lt;br&gt;■ Incorporation of free condom and family planning services into ART programs</td>
</tr>
<tr>
<td>Offer behavioral interventions for HIV-positive individuals</td>
<td>■ Focuses on source of new infections&lt;br&gt;■ Reduces frequency of unprotected sexual acts&lt;br&gt;■ Reduces HIV transmission risk</td>
<td>■ Individual, group, and structural interventions for HIV-positive individuals that promote abstinence, reduced frequency of sex, partner reduction, condom use, and nonpenetrative means of sexual expression&lt;br&gt;■ Addiction treatment and behavioral interventions for HIV-positive drug users&lt;br&gt;■ Use of clinical providers as well as counselors and peer supporters&lt;br&gt;■ Ongoing interventions for HIV-discordant couples</td>
</tr>
<tr>
<td>Select low-risk blood donors</td>
<td>■ Reduces risk of HIV transmission through blood transfusions</td>
<td>■ Screening of volunteer blood donors based on locally determined risk factors&lt;br&gt;■ Emphasis on repeat donors</td>
</tr>
</tbody>
</table>

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620  FROM THE GROUND UP: ESTABLISHING A FRAMEWORK FOR SUCCESS
Table 1. Positive Prevention Action Plan for Africa (cont.)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Potential Benefits</th>
<th>Possible Approaches to Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent unin-</td>
<td>■ Prevents vertical</td>
<td>■ Integration of family planning</td>
</tr>
</tbody>
</table>
tended pregn- | transmission | counseling and services | |
tancies among | ■ Reduces HIV infection | into care, treatment, and | |
HIV-positive | risk for HIV-negative | PMTCT programs               | |
individuals | women in HIV-discordant | ■ Training for AIDS service          | |
| Provide universal | ■ Reduces HIV | ■ Routine HIV testing and | |
access to more | transmission risk from | counseling for all pregnant | |
effective PMTCT | HIV-positive mothers to | and delivering women       | |
for HIV-positive | their infants   | ■ Full package of PMTCT interventions, | |
pregnant and | | including ART prophylaxis and | |
delivering women | | treatment             | |
| Screen HIV- | ■ Reduces HIV transmission | ■ Provision of breast milk | |
positive individu- | and acquisition risks | alternatives and early weaning | |
als and their par- | | counseling according to country | |
tners for STIs and | | guidelines            | |
provide treatment | |                          | |
as appropriate | |                          | |
| Provide male | ■ Reduces HIV trans- | ■ Consider routine STI screening | |
circumcision (MC) | mission risk within discord- | for all HIV positives in | |
of HIV-negative | ant partners within care and | care and treatment and partner | |
male partners in HIV- | treatment and PMTCT | notification               | |
discordant couples | settings               |                          | |
| Promote lead- | ■ Supports a human and | ■ Supports HIV/AIDS organizations | |
ership by HIV- | civil rights approach and | that promote the development | |
positive individu- | ownership by target group | of individuals living with HIV into | |
sals in positive | ■ Limits or avoids | implementers and leaders in advocating positive | |
prevention | discrimination | prevention                     | |
| Support posi- | ■ Helps identify an | ■ Support from donor organizations | |
tive prevention | expanded portfolio of evidence-based | and institutions for promising ideas, including further research on | |
research | approaches to | early initiation of ART; potential prevention benefits | |
| Selecting low-risk blood donors, | positive prevention | of opportunistic infection prevention; and additional | |
preventing unin- | implementation | behavioral interventions, including peer-led initiatives and psychosocial support | |
tended pregnancies, providing universal access to | | interventions. | |
to more effective prevention of mother-to-child | |                          | |
transmission (PMTCT), screening for and treating | |                          | |
sexually transmitted infections (STIs), providing | |                          | |
male circumcision of HIV-negative male partners, | |                          | |
promoting leadership by HIV-positive individu- | |                          | |
als, and supporting positive prevention research | |                          | |
(Table 1). Some of these approaches have proven | |                          | |
efficacy, some are being piloted, and some would | |                          | |
benefit from further exploration and development | |                          | |
of evidence-based policy. | |                          | |
THE POSITIVE PREVENTION PROJECT: STRENGTHENING POSITIVE PREVENTION IN UGANDA

Through the PP (positive prevention) program I have learned that with proper care and guidance from health workers, I can, when I am ready, get a partner and have the joys of sex while reducing risk of transmitting HIV to my partner.

—An 18-year-old girl who was born with HIV infection

PP training empowered me with knowledge, the right attitude and skills to openly discuss sex and sexuality issues with my clients; I am no longer shy . . . I had my own biases about family planning, but these were well handled . . . I can now adequately support people living with HIV on their family planning options.

—A 27-year-old counselor from an AIDS service organization

The preceding quotes are from participants of a new training program on positive prevention (PP) in Uganda. To scale up positive prevention in Africa, large numbers of service providers and people living with HIV need to be trained so that they can implement PP interventions.

One vibrant example of rapid training dissemination is being implemented through the Positive Prevention Project of the Strengthening Counselor Training Project (SCOT) in Uganda. SCOT is a five-year collaborative project of the Ugandan Ministry of Health, The AIDS Support Organization (TASO), and major HIV counselor training institutions in Uganda. Initiated in September 2004, SCOT’s mandate is to strengthen and standardize HIV counselor training in Uganda. This is done with the objective of catering to the growing needs of HIV counselors as they deal with the complexities of HIV prevention, care, and treatment. The overall goal of the program is to improve the quality of HIV counseling in the country. SCOT achieves this goal through standardizing HIV counselor curricula and materials, developing evaluation instruments, strengthening quality assurance, promoting coordination of HIV counselors, and implementing innovative training programs. The specific goal of the SCOT PP project is to contribute to a reduction in the transmission of HIV and other sexually transmitted infections (STIs) in Uganda by building capacity for HIV prevention among people living with HIV and health-service providers.

The PP program has four main objectives, each associated with several key activities, as outlined in Table 2.

The strategies employed by the SCOT PP program include the following:

- Engage people living with HIV at the front lines of HIV prevention. For example, people living with HIV and their national networks are involved in planning prevention strategies, implementing training programs, developing curricula and key messages, educating communities, establishing support groups, and using group forums to share experiences, skills, or tips for better living.
- Build the capacity of both HIV/AIDS service providers and people living with HIV to contribute to the reduction of HIV transmission in Uganda.
Table 2. Objectives and Related Activities of the SCOT Positive Prevention Program

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. To develop and strengthen strategies for positive prevention (PP)</td>
<td>■ Mobilizing people living with HIV and their networks</td>
</tr>
<tr>
<td></td>
<td>■ Obtaining buy-in from AIDS service organizations</td>
</tr>
<tr>
<td></td>
<td>■ Establishing networking and advocacy activities with other PP stakeholders</td>
</tr>
<tr>
<td>2. To improve PP counseling curricula, service provider training, and supportive supervision</td>
<td>■ Reviewing and developing a PP curriculum for HIV counselors</td>
</tr>
<tr>
<td></td>
<td>■ Orienting trainers in the use of the new PP curriculum</td>
</tr>
<tr>
<td></td>
<td>■ Training HIV counselors from partner organizations</td>
</tr>
<tr>
<td></td>
<td>■ Counseling people living with HIV in PP issues</td>
</tr>
<tr>
<td></td>
<td>■ Integrating family planning (FP) at health facilities by providing FP commodities and facilitating FP inventory management</td>
</tr>
<tr>
<td>3. To integrate PP into existing individual, family, and community prevention efforts and to strengthen networks of people living with HIV and their family support systems</td>
<td>■ Reviewing and developing a curriculum for community and peer education</td>
</tr>
<tr>
<td></td>
<td>■ Training members of peer support groups in new curriculum</td>
</tr>
<tr>
<td></td>
<td>■ Sensitizing community members about the benefits of PP in HIV prevention, care, and treatment</td>
</tr>
<tr>
<td></td>
<td>■ Referring individuals for institutional PP counseling</td>
</tr>
<tr>
<td>4. To establish monitoring and evaluation systems that integrate PP with other HIV/AIDS interventions</td>
<td>■ Integrating PP data into national monitoring and evaluation (M&amp;E) systems</td>
</tr>
</tbody>
</table>

- Integrate family planning services into HIV prevention, care, and treatment activities.
- Advocate for greater efforts to slow the epidemic in Uganda.

Topics covered in the SCOT PP curriculum include the following:
- HIV and AIDS in Uganda
- Positive prevention overview
- Advanced counseling techniques
- Stigma and discrimination
- HIV counseling in special situations (e.g., alcohol and substance abuse, disability, spirituality)

- Disclosure counseling
- Counseling HIV-discordant couples
- Sexuality and safer sex negotiation
- Family planning
- Adolescent counseling in relation to positive prevention
- Preventing mother-to-child transmission of HIV

Through their work, SCOT has learned that the involvement of people living with HIV at all levels of prevention helps give a meaningful context in which other people living with HIV can more easily adopt positive behaviors. Members of established peer support groups
say that it is easier for them to listen and follow advice from their peers than from a person who is HIV negative. In addition, the SCOT training of trainers approach includes capacity-building support for partner institutions, which enables them to rapidly roll out PP interventions following training.

The SCOT PP project is playing an important role in expanding positive prevention services in Uganda. By working through established support groups for people living with HIV and existing care and treatment centers, SCOT has been able to rapidly dissemnate positive prevention services throughout the country. It is hoped that the experiences of SCOT can help inform other efforts throughout sub-Saharan Africa to expand positive prevention services.

**Ensuring HIV-Positive Individuals Learn Their HIV Status**

The World Health Organization (WHO) and UNAIDS have called for universal access to HIV prevention, treatment, and care by 2010,11 and HIV counseling and testing is the entry point for HIV care and treatment. The majority of individuals living with HIV in Africa have never had an HIV test,12 even though knowledge of HIV status has been associated with preventive behavior by HIV-positive individuals.13 For example, in a nationally representative sample in Uganda, condom use was three times as high among people living with HIV who had knowledge of their HIV status compared with those who had never had an HIV test.14

Expanded approaches to HIV counseling and testing have been recommended to increase the proportion of individuals living with HIV who know their status.7,15 In several countries, expansion of traditional VCT, of provider-initiated testing and counseling (PITC) in clinical settings, and of mobile, community-based, and door-to-door testing is underway. In Uganda, very high participation rates have been reported in PITC16 and in district-wide door-to-door HIV counseling and testing programs.7,17 In Lesotho, a government-sponsored campaign aims to offer VCT to all adults in order to achieve universal knowledge of serostatus.18 These initiatives should help allow preventive behavior,13 inform partner selection, and increase access to care and treatment for all HIV-positive individuals.

**Disclosure of HIV Status to Partners**

Traditional HIV programs focus on individuals rather than on couples or families. However, a shift in approach is required in order to reach partners of HIV-positive individuals. One challenge in Africa is disclosure of HIV status, as rates of disclosure to sexual partners are generally low.19 Yet, disclosure, especially to partners, facilitates effective prevention of sexual transmission of HIV, PMTCT, and treatment access and adherence, as well as anxiety relief. Mathematical models suggest that increasing rates of serostatus disclosure could result in large reductions in HIV transmission risk.7,20 In Uganda, counselor-assisted disclosure for couples in their home or at a facility is being piloted. In Kenya, partner disclosure by HIV-positive women has been associated with a fourfold increase in reported condom use to nearly 70%.21

Nondisclosure in South Africa has been associated with HIV transmission risk behaviors, including having unprotected sex with discordant partners and having multiple partners.22,23 Partner notification for STIs has been implemented in
some African countries; although it has had mixed results, this system could be adapted, in contextually appropriate ways, for HIV. Operational research is required to determine how to make HIV partner disclosure routine, expected, and safe, while also protecting the rights of HIV-positive individuals. In addition, promotion and support of disclosure should be culturally appropriate, should incorporate counseling on both positive and negative disclosure processes and outcomes, and should support those who have fears of negative disclosure outcomes, as those fears have been shown to inhibit sexual partner disclosure.

Extra disclosure support services for HIV-positive women are particularly important, given the gender power dynamics in much of Africa, as well as the potential dual impact on both sexual and vertical transmission risk reduction.

HIV Testing of Partners
HIV discordance within couples is common in Africa. Of married people living with HIV in East Africa, 40% to 50% have HIV-negative spouses. Yet in Kenya, for example, less than 20% of adults living with HIV are aware of their infection status, and condom use within marriage is low. In Rwanda and Zambia, an estimated 55% to 93% of all new adult heterosexual HIV infections occur within married and cohabitating couples. Seronegative partners in such discordant couples are likely to be Africa’s largest single risk group for HIV infection. In this context, knowledge of a partner’s HIV status, in addition to safer sexual activity, is needed in conjunction with faithfulness by HIV-positive people to reduce HIV transmission.

Many providers and HIV-positive individuals assume that sexual partners of infected people must also be HIV-positive and see no need for partner testing. Yet ensuring that partners of HIV-positive individuals receive VCT is an essential part of a basic prevention and care package. As partner testing increases, “serosorting” or partner selection based on concordant HIV status, may be an important option for HIV-positive individuals as a means of transmission risk reduction.

Provision of Antiretroviral Therapy
Provision of ART to people living with HIV in discordant relationships also reduces the risk of HIV transmission by reducing viral load in the HIV-positive individual. Because ART is indicated for those with advanced HIV disease and the highest viral loads, widespread provision of ART could impact HIV incidence, provided that the preventive effects of ART are not offset by increases in risk behavior resulting from reduced fear of HIV infection and transmission. Although rigorous evaluations assessing ART-associated risk compensation are still limited in Africa, no empirical evidence to date suggests that it would offset the prevention effects of ART. In Côte d’Ivoire, access to ART was not associated with increased HIV transmission risk behavior. Likewise, in Uganda, integrated prevention and ART programs that include partner testing, behavioral interventions, counseling, condom provision, and ART have been associated with a 92% reduction in HIV transmission risk over a three-year follow-up period.

Reduction of Behaviors that Put Others at Risk
In addition to disclosure and partner testing, individual and small-group behavioral interventions designed for use by HIV-positive people should be developed, evaluated, and expanded. The purpose of such interventions should be to support HIV-positive individuals who choose to be sexually active to reduce sexual HIV transmission through condom use, partner reduction, serosorting, reduced frequency of sex, and nonpenetrative sexual activity. Clinician attitudes, discomfort, and
lack of skills in discussing sex need to be addressed to ensure that HIV-positive individuals who choose to be sexually active can be supported to do so with minimal transmission risk and without stigma.

Although prospective cohort data suggest that integration of prevention interventions into treatment programs can reduce HIV transmission risk, randomized evaluations of different behavioral intervention models, including clinician-initiated communication, are needed in sub-Saharan Africa. Psychosocial support interventions may also result in HIV transmission risk reduction in sub-Saharan Africa, though more operational research is needed. In addition, the special sexual and reproductive health needs of HIV-positive adolescents merit focused attention and development of tailored interventions.

Alcohol use has been associated with sexual risk behavior among HIV-positive individuals in South Africa, Côte D’Ivoire, and elsewhere. Effective interventions to support reduction of alcohol use are needed. In areas where HIV is spreading in drug-using populations, harm-reduction techniques, such as addiction treatment, and behavioral interventions, such as the use of bleach for disinfecting needles and syringes, should be implemented.

Finally, people living with HIV who are unaware of their HIV status and who donate blood can unknowingly transmit HIV to others. Thus, selection of low-risk blood donors is an effective component of positive prevention. Selection criteria should be based on current HIV incidence patterns in generalized epidemics and will require periodic review.

**Prevention of Unintended Pregnancies and of Mother-to-Child Transmission of HIV**

After HIV-negative individuals in discordant relationships, infants born to HIV-positive mothers constitute the numerically largest group at risk for acquiring HIV in Africa. In 2007, the estimated 420,000 new infections in children worldwide constituted approximately 17% of a total of 2.5 million new infections, and nearly 90% of those were in Africa. Prevention of HIV infection in women and of unintended pregnancy among HIV-positive women are the most cost-effective ways to prevent HIV infection of infants. However, in 2007, PMTCT coverage remained very low, with less than 20% of HIV-positive pregnant women in sub-Saharan Africa receiving ART prophylaxis. In addition, many PMTCT programs do not provide any family planning education or services. In Uganda, 35% of 1,092 untreated, HIV-positive adults reported having sex without contraception in the previous three months, yet 73% of these individuals did not want more children. A substantial number of HIV-positive women who do not want more children may have their previously suppressed fecundity restored by ART.

Additional challenges regarding family planning are also emerging. Life circumstances and a feeling of well-being change with ART, and desire for children may increase. Nearly one-third of HIV-positive men and women on ART in South Africa reported a desire for more children. In addition, HIV-positive South Africans reported a reluctance to discuss their reproductive intentions openly with HIV care providers who they perceived to be unsupportive. Thus, training for health-care providers in safe reproductive options for HIV-positive individuals is needed. Additional training in family planning for staff, as well as provision of free family planning services for clients, should be included in the context of ART scale-up.

For women who are pregnant, only routine, universally available HIV testing can ensure
equitable access to and delivery of PMTCT services. Introduction of routine HIV testing within antenatal care settings increased knowledge of HIV serostatus from 47% to 78% among HIV-positive pregnant women in Botswana. Providing the service beyond the antenatal clinic and throughout the intra- and postpartum periods substantially increased uptake of the service in Uganda. It also increased involvement of male partners, who play a key role in supporting women to accept HIV testing; to adhere to HIV prophylaxis and appropriate infant-feeding choices; and to attend referrals for HIV care and treatment for themselves, their baby, and their family. Prioritizing ART eligibility assessment and access to treatment for eligible pregnant women is particularly important given the beneficial effect that triple therapy has on PMTCT.

In this regard, for HIV-positive women who desire more children in resource-limited settings, research on use of ART for viral suppression through late pregnancy, delivery, and time-limited exclusive breastfeeding suggests promise for maximally reducing MTCT. However, in settings where breastfeeding is the only safe and feasible infant-feeding option, it is equally important to help HIV-positive pregnant women who receive PMTCT services understand that premature weaning in the hope of avoiding HIV transmission can seriously endanger the life of their babies given the risk of severe gastroenteritis. In addition, they should understand that exclusive breastfeeding can further reduce the risk of HIV transmission through breast milk. These facts have been underscored by the recent revision by WHO of its infant-feeding recommendation for PMTCT to exclusively breastfeed for at least six months and not to wean unless safe replacement feeding is accessible, feasible, affordable, safe, and sustainable.

Management of Sexually Transmitted Infections
Although population-based STI interventions have shown mixed results regarding HIV risk in Africa, at the individual level, STIs do increase risk of HIV transmission and acquisition and are associated with increased HIV viral load in genital secretions. A syndromic approach to STI management, which is widely used in resource-limited settings with limited laboratory diagnostics, has not been evaluated for HIV-positive individuals in Africa. These individuals have higher rates than the general population of herpes simplex virus type 2, syphilis, and other genital infections. Effective approaches for STI diagnosis and treatment for individuals living with HIV and their partners should be identified and systematically integrated into all HIV care and treatment programs. An especially important group to target for STI control, consistent condom use, and other aspects of positive prevention is commercial sex workers and their partners, who have the potential to transmit HIV across sexual networks.

Male Circumcision
Randomized trials in South Africa, Uganda, and Kenya have demonstrated that circumcision of HIV-negative men is associated with a 60% reduction in HIV acquisition. As an important component of positive prevention services for discordant couples, male circumcision services or referrals should be integrated into care, treatment, and PMTCT programs for HIV-negative male partners of HIV-positive women. Education and referral for male circumcision should also be integrated into HIV counseling and testing efforts, including provider-initiated and home-based, door-to-door programs in which many discordant couples are identified.
Leadership by HIV-Positive Individuals
To effectively reduce HIV transmission in Africa, individuals living with HIV/AIDS should be active leaders in positive prevention efforts. Involvement of HIV-positive individuals will help prevent discrimination and ensure that positive prevention is seen as a necessary approach that is mutually beneficial for infected and uninfected individuals.

For individuals living with HIV, positive prevention not only provides protection from acquisition of other STIs, it also protects those they love from HIV infection and their children from orphanhood. Widespread commitment to the pledge “HIV stops with me” among HIV-positive individuals is needed, without reducing the responsibility of HIV-negative individuals to remain so.

PROMISING INTERVENTIONS AND PREVENTION RESEARCH
 Increased resources for evaluating the efficacy of new prevention interventions and for rapid translation of research into policy are needed concurrently with increased prevention programmatic resources. Ideas for many new positive prevention interventions are often best developed by those currently working on program implementation. Therefore, those involved in implementation should be provided with both the technical and the financial resources necessary for scientifically rigorous evaluations. Two areas of current promising research for HIV prevention are early initiation of ART and HIV care interventions that slow HIV progression.

Although universal ART initiation at CD4 counts above 200 cells/mm$^3$ may still be prohibitively expensive in a region where ART access remains low, there could be prevention benefits to initiation at higher CD4 cutoffs. For example, in a model using a South African township population, the impact of ART on annual risk of HIV transmission was estimated to increase from 11.9% with a CD4 cutoff of 200 cells/mm$^3$ to 71.8% if a CD4 cutoff of 350 cells/mm$^3$ were used. ART initiation at higher CD4 cutoffs may be cost-effective, particularly for potentially high transmitter groups, such as HIV-positive sex workers. The prevention benefits of earlier ART initiation are currently being assessed in a randomized trial (Myron Cohen, MD, personal communication, February 2008) that could inform international guidelines on this potentially important intervention.

HIV Care Interventions that Slow HIV Progression
In addition to ART, other interventions that have been shown to prevent HIV opportunistic infections, to slow HIV progression, and to reduce viral load in HIV-positive individuals could theoretically have an effect on transmission. Several of these interventions are recommended in the WHO guidelines on essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings, while others require further investigation.

Multivitamins, as an example, have been associated with decreased viral load, delayed CD4 count decline, and reductions in severe morbidity and mortality. As another example, HIV-positive individuals with malaria have been shown to have a sevenfold increase in HIV viral levels; cotrimoxazole prophylaxis and bed nets have both been shown to reduce incidence of malaria in HIV-positive individuals, with the former being associated with reduced viral load. Similarly, acyclovir prophylaxis reduces HIV shedding in the genital tract and reduces viral load, at least during short-term follow-up. Current trials are under way to assess the impact of acyclovir prophylaxis on HIV transmission from HIV/HSV-2 coinfected members of HIV-discordant couples (Connie Celum, MD, personal communication, February 2008). Helminth infection in HIV-positive pregnant women has been
associated with a significantly higher rate of mother-to-child HIV infection, but further research is needed to assess the impact of treating helminths on both vertical and sexual HIV transmission.

Although operational research is needed to assess the synergistic benefits of interventions that are efficacious in reducing viral load, providing HIV-positive individuals with these interventions holds promise not only to reduce incidence of opportunistic infections but also to reduce HIV transmission risk (J. Walson, MD, and G. John-Stewart, MD, personal communication, March 2008).

CONCLUSION

There is an ethical and public-health imperative to implement positive prevention and treatment. Epidemiologic surveillance can indicate in which populations HIV transmission is most intense. Combining prevention services for the most at-risk HIV-negative groups with universal access to HIV testing and positive prevention offers the best opportunity to control HIV/AIDS in Africa.

Note: The findings and conclusions in this chapter are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or The AIDS Support Organisation. A version of this chapter was previously published as: Bunnell R, Mermin J, De Cock KM. HIV prevention for a threatened continent: implementing positive prevention in Africa. *JAMA*. 2006;296(7):855-858.

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ESPIE THE PROVEN EFFECTIVENESS of current approaches to HIV prevention, fewer than one in five people worldwide have knowledge of and access to HIV-prevention tools.1 In this chapter we will discuss two such tools: the treatment of sexually transmitted infections (STIs) and adult male circumcision (AMC).

Limited evidence comparing results from randomized clinical trials suggests that treatment of bacterial STIs may be more effective in preventing HIV infection in settings with low to emerging HIV epidemics and where there is a high background prevalence of bacterial STIs.2-9 However, there are other compelling reasons why STI treatment services should be strengthened. Because STI control and prevention strategies are highly synergistic with the “ABC” approach (abstinence, being faithful [i.e., sexual partner reduction], and consistent and correct condom use), an effectively implemented STI health service intervention can substantially improve quality of care and education among high-risk populations, contributing in turn to HIV prevention.

A wealth of observational evidence from many epidemiologic studies and recent randomized clinical trials in South Africa, Uganda, and Kenya have demonstrated the efficacy of AMC in preventing HIV acquisition.10-19 AMC may be most effective in settings of generalized epidemics, but because of the unique cultural and biological implications of this surgical procedure, many logistical and societal obstacles must be overcome before implementation can occur on a global scale.

TREATMENT OF SEXUALLY TRANSMITTED INFECTIONS

STIs are an important cause of morbidity worldwide with substantial economic, social, and health consequences, particularly for women and their reproductive outcomes.20 There are an estimated 340 million new cases annually of curable STIs (i.e., syphilis, gonorrhea, trichomoniasis, chancroid, and chlamydia) and more than a billion prevalent cases of chronic viral STIs (i.e., genital herpes simplex virus type 2 [HSV-2], hepatitis B virus, genital human papillomavirus, and HIV) around the globe. STIs have been implicated strongly as cofactors for increased sexual transmission of HIV in many observational epidemiologic studies.21-23
Biological and Epidemiological Rationale

One biological rationale for the observed increase in sexual HIV transmission is that a substantially increased HIV viral load is detected in the genital secretions of people who have either urethral or cervical inflammation and/or ulceration. Furthermore, treatment of STI reduces genital tract HIV viral loads, thereby reducing the infectiousness of the index case and lowering the probability of transmission. It has been shown that ulcerative STIs (e.g., syphilis, chancroid, HSV-2) disrupt the integrity of the epithelial mucosa and facilitate contact of HIV with the lymphatic and circulatory systems.

Although inflammatory and exudative STIs (those without frank ulcers, such as chlamydia, gonorrhea, and trichomoniasis) have less of an effect on epithelial tissue, these infections do cause inflammation and associated recruitment of HIV-susceptible white blood cells (exudate). Inflammation results in microulcerations and engorgement of capillaries, facilitating contact of HIV with target cells. Ulcerogenic STIs increase the risk of sexual transmission of HIV by 5- to 10-fold, compared with a 2- to 5-fold increase caused by inflammatory, nonulcerogenic STIs. The population-attributable risk for the latter group of infections is substantial, however, because of their high prevalence. HIV-1 infection, particularly in the setting of advancing immunosuppression, may lead to an increased susceptibility to some STIs. Many HIV-1-infected individuals have higher than average rates of STI, probably because of shared behavioral risk factors that facilitate transmission of both HIV-1 and STIs. STI prevention and control is therefore a logical component of a comprehensive HIV-prevention program.

Community Randomized Trials

The magnitude of the effect of improved STI treatment on HIV transmission at a population level was examined extensively in three community randomized trials in rural East Africa, where HIV infection was prevalent and STI control and prevention services were exceedingly limited. The aim of these studies was to examine the effect of STI treatment on HIV incidence. The two major approaches to STI treatment used in these studies were syndromic management of STI (Box 1) and mass treatment. Improved community-level syndromic management of symptomatic bacterial STI with antibiotics was associated with a 38% reduction in incidence of HIV infection over the course of two years in the Mwanza region, Tanzania.

In contrast, over a similar time period and with a seemingly comparable proportional reduction in treated STI, periodic (every 10 months) mass treatment in Rakai, Uganda, led to only a nonsignificant 3% reduction in HIV incidence. The results of a third trial in the nearby Masaka district in Uganda demonstrated that syndromic treatment had no effect on the incidence of HIV infection. A more recent cluster-randomized trial from eastern Zimbabwe, where interventions included education, condom distribution, and improved syndromic STI treatment, suggested a paradoxical and unexplained nonsignificant increase in HIV incidence in the intervention communities.

Several hypotheses have been proposed to explain the contrasting findings from these studies. A simulation modeling study of HIV and STI transmission suggested that the low trial impact in Rakai and Masaka could be explained by a low prevalence of curable STIs due to the comparatively lower frequency of higher risk sexual behaviors in Uganda. The mature HIV epidemics in Rakai, Masaka, and Zimbabwe resulted in most HIV transmission occurring outside core groups having high STI rates. As such, the treatment of STI in groups that were not primarily responsible for the spread of HIV would not have resulted in a significant decrease in HIV incidence. An alternative explanation highlights the high
herpetic genital ulceration rates in Uganda and Zimbabwe compared with Tanzania, which is exacerbated by HIV-related immunosuppression. In this scenario, the intervention using antibiotic treatment would not have had an effect on HSV-2 lesions. However, suppression of HSV-2 with oral acyclovir to reduce the risk for HIV seroconversion has proven unsuccessful in a recently completed multinational, placebo-controlled, clinical trial through the HIV Prevention Trials Network.

The studies described above demonstrate the complex relationship between STI treatment and its effect on HIV incidence. However, the biological links between STI and HIV infectivity and susceptibility, the success in Mwanza, and the broad benefits of STI treatment programs highlight the need to include STI treatment as an integral part of comprehensive case management. Such an effort toward “highly active HIV prevention” includes ABC health education, including condom education, promotion, and distribution; voluntary counseling and testing advocacy; AMC; access to antiretroviral therapy; and injection harm reduction.

**Challenges in Service Delivery and Scale-Up**

Significant challenges remain for delivering STI services in resource-limited settings, including innumerable infrastructure, personnel, and supply constraints. The implementation strategies for STI control are twofold: (1) train providers in STI clinical management, and (2) improve strategies for service delivery for both the general population and specific high-risk groups. The standardized STI treatment flowcharts recommended by the World Health Organization are based on the syndromic management approach used in the Mwanza and Masaka studies. This approach enables a majority of providers, who often lack access to adequate examination or laboratory facilities, to manage symptomatic patients. The syndromic management approach is simpler than the classic dermatovenereology approach. With the syndromic approach, treatment is provided during the same clinic visit as the screening evaluation, promptly preventing the risk of spreading the infection further as well as decreasing the risk of sequelae that may develop from untreated infections. Because there is no need to return for laboratory results, this approach also results in cost savings for the system and the patient (Box 1).

Women represent a major challenge in STI control using the syndromic management approach.

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**Box 1. Syndromic Management: Method to Treat Sexually Transmitted Infections in Resource-Limited Settings**

Syndromic management is a diagnostic tool used in resource-constrained settings to treat sexually transmitted infections (STIs). It relies on the presence of a syndrome—a group of symptoms and signs associated with a few well-defined etiologies—that, once identified, dictates appropriate treatment for most of the causative organisms. It is a useful tool in resource-constrained settings because sophisticated laboratory techniques are not needed. Instead, patients present at a clinic, syndromes are identified, and based on those syndromes clinical flowcharts are used to diagnose and treat patients. Diagnosis and treatment occur at the same visit, which prevents the risk of spreading the infection further and decreases sequelae that may develop from untreated infections. The advantages of syndromic management include that standardized treatment is used, treatment is given at one visit, health workers do not need specialized skills to diagnose the syndrome, and expensive laboratory tests are not needed. On the other hand, syndromic management can result in the overtreatment of patients, potential drug resistance, and an inability to treat asymptomatic patients.
because of the asymptomatic nature of many STIs in women and the relatively poor specificity of most clinical manifestations.74,48 Syndrome-based flow-charts for lower genital tract infections in women are less valid, and laboratory tests are preferable for detecting STI in asymptomatic and high-risk women.49 Although low-cost, rapid, simple tests for diagnosis of syphilis are widely available, they remain underutilized, often because of programmatic and managerial obstacles.50-54 There remains an unmet need for point-of-care diagnostic tools for the diagnosis of chlamydia, gonorrhea, and other STIs in women.52,55 In settings where access to laboratory tests is feasible, assessing risk before testing could be a cost-effective approach.48 Rapid testing for HSV-2 may prove to be an important tool to enable aggressive suppression of HSV using antiviral suppressive therapy.29,56

Many demonstration projects and well-designed studies in a wide range of settings, such as Brazil, Cameroon, Democratic Republic of the Congo, Haiti, India, Jamaica, Kenya, Nepal, Peru, and Thailand, have shown that managerial implementation of improved service delivery and uptake of STI treatment can lead to improved effectiveness in STI control.21,51,57-66 The integration of STI treatment and HIV-prevention and care programs is an efficient approach to public-health service delivery.

ADULT MALE CIRCUMCISION
AMC is the surgical removal of most or all of the foreskin (or prepuce) from the penis.67,68 It can be performed with almost no pain, and benefits of the procedure go beyond protection against HIV.69 This procedure can be performed using one of three methods: dorsal slit, sleeve resection, and forceps guided. The choice to use one method over another depends on the location of the operation and the availability of staff.70 Table 1 provides a brief synopsis of the methods most commonly used for AMC as well as their advantages and disadvantages.70-72

The World Health Organization's Manual for Male Circumcision with Local Anesthesia is an excellent guide for performing AMC in resource-limited settings.70 Evidence suggests that AMC is effective because the inner mucosa of the foreskin has less keratinized skin than the exposed external skin surface and has a higher density of target cells for HIV infection in the form of dendritic and Langerhans cells. Without the keratinized epithelial barrier, these cells are in proximity to HIV, given exposure. Furthermore, the foreskin may have comparatively greater susceptibility to traumatic epithelial disruptions (tears) during intercourse, providing a portal of entry for pathogens, including HIV.18,19 Uncircumcised men have higher rates of sexually transmitted genital ulcerative disease, such as syphilis and HSV-2, than do circumcised men from comparable socioeconomic and religious backgrounds, increasing their susceptibility to HIV infection.14,73 The microenvironment of the prepucial sac between the unretracted foreskin and the glans penis may be conducive to viral survival, keeping infected vaginal or anal fluid in a warm, moist state.74

Lower prevalence of HIV has been noted in regions with higher rates of circumcision (e.g., North Africa, the Middle East, and selected parts of Central/West Africa).75 To account for other behavioral and biological factors and to quantify the strength of association, multiple ecologic (population-based), cross-sectional, case-control, and cohort studies have been conducted; but these were often limited by potential confounding factors and methodological factors.11,14 When comparing circumcised Muslim men to uncircumcised Christian or Buddhist men in Africa or Asia, for example, the former often had more conservative sexual lifestyles in the context of polygamy such that a protective association with circumcision (practiced at nearly 100% levels among Muslims) and HIV might have
A systematic review and meta-analysis focusing on heterosexual transmission of HIV in Africa was published in 2000. After adjustment for confounding factors in these population-based studies, the relative risk for HIV infection was found to be 44% lower in circumcised men. The strongest association was seen in high-risk men, such as patients at STI clinics, for whom the adjusted relative risk for circumcised men was 71% lower than for uncircumcised men. A later systematic review published in 2003 included astringent assessment of 10 potential confounding factors and was stratified by study type or study population. The one large, prospective cohort study in this group showed a significant protective effect, with odds of HIV infection 42% lower in circumcised than in uncircumcised men. The 19 other studies were conducted among high-risk men and found a consistent, substantial, protective effect that increased with adjustment for confounding. Overall, after adjustment for potential confounders, the risk ratio was 0.56 (95% CI, 0.44-0.70) in general populations and 0.29 (95% CI, 0.20-0.41) in high-risk populations. Given the promise of AMC as a tool in HIV prevention yet the unreliability of ecological observations and the confounding potential in observational studies, three seminal randomized clinical trials were begun.

**Table 1. Advantages and Disadvantages of Common Circumcision Methods**

<table>
<thead>
<tr>
<th>Circumcision Method</th>
<th>Dorsal Slit</th>
<th>Sleeve Resection</th>
<th>Forceps Guided</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Forceps are used to pull prepuce above glans and dorsal slit is made along prepuce to incision line. Excess prepuce is cut away until 5 mm of preputial skin remains proximal to the corona.</td>
<td>A sleeve of skin is created after incisions are made on foreskin. Care must be taken when making the incision to cut only to subcutaneous tissue and no deeper. Used in Uganda trial.</td>
<td>Forceps are placed just above the glans at the incision mark. Scalpel is used to cut above forceps to remove excess prepuce. Used in Kenya and South Africa trial.</td>
</tr>
</tbody>
</table>
| **Advantages**      | ■ Most widely used method used throughout the world  
                      ■ Can be performed without an assistant | ■ If bipolar diathermy is available, procedure can be almost bloodless  
                      ■ Produces the tidiest results | ■ Can be performed without an assistant  
                      ■ Already used successfully in an African setting  
                      ■ Simple procedure to teach inexperienced surgeons |
| **Disadvantages**   | ■ Can produce asymmetrical result  
                      ■ Requires more surgical skill than forceps guided | ■ Requires an assistant  
                      ■ Greatest chance for surgical error  
                      ■ Should be performed in a hospital, not a clinic setting | ■ Leaves 0.5–1 cm of mucosal skin proximal to corona |

been confounded by lower sexual mixing rates among the circumcised men. Ecological observations have strongly implicated lack of circumcision as a risk factor for HIV infection; the prevalence of HIV infection is several times higher in Africa and Asia where the prevalence of male circumcision is less than 20% than in countries where greater than 80% of men are circumcised.
circumcisions were quite safe, even in remote rural areas, when performed by trained medical personnel and accompanied by appropriate postsurgical follow-up to ensure the management of infections or problems with wound healing.10,12,13

Although the scientific evidence overwhelmingly supports AMC for HIV prevention, the effects of promulgating AMC in real-world settings are unknown. There is the potential for behavioral disinhibition (also termed “risk compensation”), wherein males who are circumcised in the context of HIV prevention may engage in high-risk behavior without using condoms under the false expectation that their circumcised status will prevent them from acquiring HIV. In fact, the South African study participants in the circumcised group actually reported higher risk sexual behaviors; however, the group had a lower incidence of HIV, further suggesting that AMC is highly protective. The other studies did not show significant behavioral disinhibition, although this may be due to extensive risk-reduction counseling and education.77 Other studies examining this concern suggest that participants appreciate concepts of risk reduction as opposed to risk elimination.78,79

Concerns for Program Scale-Up
Substantially more resources were made available for the three clinical trials than will be available in a “real-world” scale-up of AMC in a public-health context. Whether acceptability will decline without the attentiveness of research staff added to the AMC service program is unknown. A systematic review of acceptability throughout southern and eastern Africa suggested that traditionally non-circumcising communities were highly receptive to circumcision. Across the studies reviewed, the median proportion of uncircumcised men willing to be circumcised was 65% (range 29%–87%), and 71% (range 50%–90%) of men were willing to circumcise their son.78-80 The major reasons for high

Clinical Trials
Three proof-of-efficacy clinical trials in Africa were conducted in settings with a high incidence of HIV.10,12,13 The French-funded Orange Farm trial in South Africa published in 2005 is hailed as the first randomized, controlled study of the effect of AMC on HIV incidence.11 In this trial, 3,128 HIV-negative men aged 18–24 years were randomly assigned to immediate versus delayed circumcision and were followed prospectively while receiving STI/HIV-prevention counseling and voluntary counseling and testing services. Men in the intervention (immediate circumcision) arm were at strongly reduced risk of HIV infection (risk ratio 0.4; 95% CI, 0.2-0.7).11 This corresponded to a protection of 60% (95% CI, 32–76) in the intervention group. Despite these results, there was debate among clinicians, policymakers, and the international community about whether these results could be generalized to different populations. In December 2006, trials in Uganda and Kenya provided additional scientific evidence for the role of AMC in HIV prevention.10,12 Their data safety and monitoring boards stopped all three randomized, controlled trials earlier than planned after interim analyses demonstrated overwhelming statistical evidence of efficacy. In Uganda, AMC reduced men’s risk of acquiring HIV infection by 51% (95% CI, 16–72) and in Kenya by 53% (95% CI, 22–72).10,12 In all three trials, men in the control (i.e., delayed intervention) group were offered circumcision immediately after the trials were halted. To understand the long-term impact of AMC, substudies will continue to measure HIV infection rates and to study the risk-taking behavior and attitudes of participants. Despite the surgical methods used (the foreskin clamp method in South Africa and Kenya and the sleeve method in Uganda),
acceptability included improved hygiene, reduction in STI, and earlier detection of ulcers. A less significant proportion of participants did equate circumcision with reduced risk of HIV. Cost, fear of pain, and concern for safety were all major barriers to the acceptability of circumcision. Although not consistently a barrier or facilitator in the studies reviewed, cultural norms, ethnic identity, and religious affiliation were central factors determining acceptability. Given that studies have examined acceptability through hypothetical questions posed to individuals or focus groups, data are lacking to determine if those services were actually used when they were provided.78-79 Hence, acceptability to patients, sexual partners, health-care workers, and community (and family) opinion leaders must be studied in the context of AMC program expansion.78-79

Effect on Women
The assumption has been made, correctly we believe, that secondary benefits to women are substantial given that each man who remains HIV uninfected represents one fewer potential transmitter of HIV infection to women (or to other men when men have sex with men). The attribute of AMC that makes it an attractive prevention modality is the permanent benefit from a single intervention.36 STI treatment, condom use, and ABC behavior change do not share this feature, though the need to avoid disinhibition (also termed “risk compensation”), and the fact that it is not fully efficacious suggests that ABC messages should not change even in the face of higher circumcision rates. AMC may be even more critical in settings where condom use has continued at low rates despite intensive intervention campaigns, often due to gender power inequities resulting in a lack of successful negotiation of condom use. AMC may decrease male-to-female transmission of HIV as well as female-to-male; among serodiscordant couples in Rakai, HIV incidence in wives of HIV-positive circumcised men was 6.6 per 100 person-years, compared to 10.3 per 100 person-years in partners of uncircumcised men.81 According to an earlier study from Rakai, when circumcised HIV-positive men had a viral load of less than 50,000 copies/mL, no transmission to their female partners occurred. Among uncircumcised men with similar viral loads, the transmission rate was 9.6 per 100 person-years (95% CI, 6.1-13.1 per 100 person-years; \( P=0.02 \)).15 Data from Uganda and Zimbabwe, however, did not suggest an association between women’s HIV risk and partner circumcision status.82

There is a risk to women when circumcised men engage in intercourse before complete wound healing has occurred. Those men who are actually HIV infected at the time of AMC but are in the window period before testing positive by antibody may transmit to sexual partners at increased efficiency, as has been noted in a Rakai, Uganda, substudy (M. Wawer, MD, oral communication, October 2007). Sex before wound healing also increases AMC complication rates for the men themselves. Concerns have been raised about the safety of the surgical procedure when implemented on a mass scale. Although all three randomized, controlled trials reported very low complication rates, these circumcisions were performed by well-trained medical personnel with regulated follow-up—a less than realistic situation in resource-limited settings where widespread implementation will occur.83 Data on complications from circumcisions performed in low-resource settings are limited, and it is universally appreciated that long-term complications in real-world settings must be assessed in the context of program scale-up.84,85

Policy Issues
Neonatal circumcision is safer and less expensive than AMC and should be considered an important long-term investment to reduce global HIV infection.79,80,86,87 If neonatal circumcision and AMC were
scaled up concurrently and aggressively, long-term costs might decline (due to fewer AMCs needed in the future), with short-term benefits complemented by long-term ones. Neonatal circumcision can be linked to existing maternal and child health services and perhaps to the expansion of the prevention of mother-to-child transmission (PMTCT) programs. Women’s acceptance of male circumcision, which is essential for achieving high rates of neonatal circumcision and advantageous for adult circumcision, is reported to be high in Africa.\textsuperscript{79,88} Attitudes of fathers are also favorable, but the attitudes of grandmothers, who are often influential, need further investigation.

Although AMC is efficacious in trials, its implementation will be determined by the societal context, including its cultural and religious acceptability; so far, acceptability appears to be far higher than expected among noncircumcising communities in sub-Saharan Africa.\textsuperscript{79} It is critical for targeted and tailored communication messages to highlight both the benefits and limitations of this method. Health manpower and surgical infrastructures are not presently available for expanded AMC in the nations of high HIV incidence that need it the most. Yet the boon that a single intervention is likely to confer and its cost-effectiveness suggest that adult and neonatal circumcision should be emphasized in new global prevention investments. A model using data from the randomized, controlled trials predicts a 45%–67% reduction in HIV prevalence with 80% circumcision uptake and a 25%–41% reduction with 50% uptake, with full impact most apparent at least a decade after the investments are made.\textsuperscript{49} Using a model with a lower condom utilization rate, circumcision combined with antiretroviral therapy appears to be more effective than circumcision and condom use to reduce disease burden.\textsuperscript{90}

If promulgated properly, AMC has enormous potential for providing some protection to at-risk uninfected people, especially when coupled with the ABC behavioral strategy at a population level.\textsuperscript{76} A combination approach with the strategies of AMC, ABC, STI control, voluntary counseling and testing advocacy, antiretroviral therapy availability, and community/political activism toward social acceptance of HIV testing and engagement in “prevention promotion” may be the best bet in HIV prevention.

The United Nations Work Plan on Male Circumcision and HIV\textsuperscript{91} as well as analysts and experts worldwide have recommended a renewed focus on improving the safety of current AMC practices and on assisting countries to obtain the data necessary for informed and evidence-based decision making regarding the role of AMC in HIV-prevention programming.\textsuperscript{92-95} Although surgery is rarely used for public health and prevention, circumcision of men, male adolescents, and male infants may represent exactly such an opportunity.
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HERPES SIMPLEX VIRUS TYPE 2 (HSV-2) is a primary cause of genital ulcers and is one of the most common sexually transmitted infections worldwide. HSV-2 infection is more common in women than men, and as many as 85% of HIV-positive people are infected with HSV-2. Once recognized as an opportunistic infection and indicator of the onset of AIDS, HSV-2 is once again the focus of attention because of increasing interest in the role of HSV-2 treatment to prevent HIV acquisition, transmission, and disease progression.

GENITAL HERPES IS FREQUENTLY ASYMPTOMATIC OR UNRECOGNIZED

The key to understanding the widespread nature of HSV-2 infection is the recognition that while infection typically causes recurrent genital ulceration, it is frequently asymptomatic or unrecognized. Although little data on symptom recognition exists outside of the United States, the evidence suggests that as many as 63% to 87% of individuals who are seropositive for HSV-2 deny a prior history of genital ulcer disease (GUD). Similarly, in the recently published HPTN 039 trial, only 16% of men who have sex with men from Peru and 33% of African women reported a history of GUD, despite the fact that all trial participants were HSV-2 seropositive. However, after counseling in symptom recognition, the proportion of those reporting a history of GUD may increase. For example, 50% to 75% of HSV-2 seropositive people without a reported history of genital herpes reported subsequent symptomatic episodes after receiving health education about genital herpes. Even in the absence of symptoms, the majority of those infected with HSV-2 will shed virus in the genital tract and are therefore likely to transmit infection unknowingly.

HSV-2 INFECTION IN THE HIV-POSITIVE INDIVIDUAL

Coinfection with HIV alters the natural history of HSV-2, exacerbating the clinical course of HSV-2 infection. Individuals with HIV are likely to experience more frequent episodes of recurrent genital ulceration. Such episodes may also have more varied clinical presentation, leading to an increased frequency of unrecognized episodes of genital herpes at higher CD4 counts. At lower CD4 counts, recurrent lesions may be atypical in location or appearance, leading to delays in diagnosis and treatment initiation. As the host becomes
increasingly immunocompromised, these lesions are likely to be more severe and of longer duration and may in some instances take longer to respond to treatment.

In addition to worsening the clinical course of HSV-2 infection, coinfection with HIV also appears to enhance mucosal replication of HSV-2. As with HIV-negative individuals, most HIV-positive people are likely to experience asymptomatic HSV-2 infections. However, while most are asymptomatic, they are almost all likely to shed HSV-2 from the genital tract on up to 20% of days, irrespective of whether they have a history of genital herpes.\textsuperscript{12,13} It is this state of frequent, asymptomatic reactivation of HSV-2 that may be responsible for the interactions with HIV, and the subsequent increased risk of HIV transmission from coinfected individuals.

Surprisingly, the initiation of antiretroviral therapy (ART) does not appear to have any impact on HSV-2 reactivation rates, despite the clinical perception that ART reduces episodes of genital herpes. In a U.S. study, patients on ART reported fewer days with genital lesions, but objective measures of genital mucosal shedding confirmed similar levels of HSV-2 DNA in patients both on and off ART.\textsuperscript{14} Although ART restores T helper cell responses, it seems that this may not be a critical development in the control of HSV-2 reactivation. A more recent study of women in the United States showed that even women who had used ART for at least one year and had optimal CD4 gain and HIV viral suppression reported significantly more episodes of genital sores than similar HIV-uninfected women.\textsuperscript{15}

**HSV-2 Infection Enhances HIV Acquisition, Transmission, and Disease Progression**

Given that HSV-2 is a common infection in areas of high HIV prevalence, the growing body of evidence that points to a synergistic interaction between the two infections is a cause for concern.

Recent meta-analyses have shown that prior infection with HSV-2 increases the risk of HIV acquisition by as much as threefold in women and twofold in men, and that interventions to control HSV-2 infection could prevent as many as 50% to 60% of new HIV infections.\textsuperscript{16} Observational studies also suggest that recent infection with HSV-2 is associated with a higher risk of HIV infection, possibly because of the severity of genital lesions associated with primary genital herpes.\textsuperscript{17-20} Similarly, evidence from observational studies suggests that coinfection with HSV-2 can increase the risk of HIV transmission.

There are several possible biological mechanisms that HSV-2 could use to act as a cofactor in HIV acquisition or transmission. First, HSV-2 reactivations result in a mucosal or epithelial disruption, creating a portal of exit or entry for HIV, to which activated CD4 cells are recruited. There also appear to be several cellular interactions that promote the establishment of HIV infection; coinfection with HSV-2 may lead to the creation of “pseudotypes” (i.e., particles containing HIV viral genome that are enveloped in HSV surface glycoprotein), allowing HIV to infect cells that could not be infected by HIV alone.\textsuperscript{21,22} HSV-2 infection may also promote the increased expression of HIV target cells (i.e., CCR5+ CD4 cells and immature dendritic cells).\textsuperscript{21}

There are also several mechanisms that may explain how HSV-2 increases levels of genital and plasma HIV, thus enhancing HIV transmission. In coinfected individuals, HSV-2 proteins may increase replication of HIV at mucosal sites by transactivation of the HIV long terminal repeat.\textsuperscript{24} Cytokine release may also stimulate HIV replication.\textsuperscript{25,26} A recent study demonstrated that coinfection with HIV can lead to a depletion of immune cells responsible for controlling HSV-2 reactivation, resulting in impaired immune control of HSV-2, and leading to further HSV-2
reactivation and subsequent increases in HIV levels in the genital tract.23

Up-regulation of HIV replication by HSV-2 reactivation could have important clinical consequences. Observational studies have shown that reactivation of genital HSV-2 leads to an increase in HIV plasma viral load that may be sustained for up to six weeks.27 This observation is not restricted to clinical episodes of HSV-2 reactivation.28,29 Several studies have shown that in both early and chronic HIV infection, HSV-2 seropositivity is associated with a higher mean plasma viral load. A persistent increase in plasma viral load can lead to a shortened time and progression to AIDS; thus, HSV-2 infection and reactivation could be associated with more rapid HIV-1 disease progression.

These findings may explain the results of earlier studies that observed that treatment by acyclovir—an HSV-specific antiviral—was associated with a modest but consistent survival advantage, even though some of the trials were not originally designed to assess this effect. A meta-analysis of eight randomized trials of acyclovir in the era prior to combination ART indicated that high-dose acyclovir (greater than or equal to 3,200 milligrams per day) offered a significant survival benefit for HIV-positive people.30 The studies were not large enough or designed to answer the question about the effect of HSV-2 on HIV disease progression, but the results suggest that HSV-2 suppression may offer clinical benefits to coinfected people.

**CURRENT INTERVENTION OPTIONS FOR CONTROLLING HSV-2**

Currently, intervention options for controlling HSV-2 are limited to patient education and promotion of condom use or treatment with oral medications. Nucleoside analogues (acyclovir, valacyclovir, famciclovir) have been available for the treatment of HSV-2 for more than two decades. These drugs are considered safe and are well tolerated. They require no sophisticated monitoring and have no significant interactions with antiretroviral medications. Clinical trials have shown that these drugs are equally effective at standard doses in HIV-positive individuals.32-34 While resistance is frequently identified as a concern by clinicians, the frequency of resistance in immunocompetent patients despite widespread use over 20 years has remained at less than 1%. Among immunocompromised patients, resistance rates have been observed to be higher but have remained stable at less than 5% over the past 15 years.35-37 In cases of resistance, it may be possible to overcome clinical resistance by increasing the standard doses of the nucleoside analogues. In refractory cases, alternative drugs such as foscarnet or cidofovir may be used.

**COULD HSV-2 THERAPY BE EFFECTIVE IN CONTROLLING HIV?**

Despite the plethora of observational studies demonstrating a bidirectional and synergistic interaction between HSV-2 and HIV, such observations need to be tested in randomized controlled intervention trials in order to prove a causal relationship between HSV-2 infection and HIV acquisition, transmission, and disease progression. There are two possible treatment strategies for HSV-2 to be evaluated for their impact on HIV:

- **Episodic therapy.** This treatment strategy is aimed at providing relief to symptomatic episodes of HSV-2. Treatment for genital ulcers is usually given for five days and reduces pain, decreases time to ulcer healing by one to two days, and reduces HSV-2 shedding by one to two days. Episodic therapy has no effect on recurrence rates.

- **Suppressive therapy** is continuous daily therapy to prevent frequent recurrences of genital herpes. Suppressive therapy is also effective in reducing asymptomatic shedding of HSV-2 and HSV-2 transmission as shown in a recent trial
of suppressive therapy with valacyclovir where HSV-2 transmission between HSV-2 serodiscordant couples was reduced by 50%.38

At least three trials have evaluated whether treating symptomatic episodes of genital herpes will have an impact on HIV transmission. Those trials, conducted among populations in Ghana, Central African Republic, South Africa, and Malawi, considered whether the addition of acyclovir to the current syndromic management guidelines for the management of GUD resulted in improved clinical and virological outcomes. The studies all showed modest impact on ulcer healing time among HIV-positive individuals, with a shortening of the duration of ulcers by one to two days if patients presented early enough (within 72 hours). By contrast, there was little evidence for an impact of treatment on genital HIV shedding in women, although decreased lesional HIV shedding was observed in men.39,40

Several proof-of-concept studies evaluating the effect of HSV-2 suppressive therapy on genital and plasma HIV levels have been completed among women in Burkina Faso, South Africa, Thailand, and Peru.41-44 A similar trial has also been completed among men who have sex with men in Peru.45 All five trials demonstrated significant reductions in both genital and plasma HIV replication after one to three months of daily treatment with either valacyclovir or acyclovir. A more recent trial conducted among high-risk women in Tanzania did not show any impact of treatment on genital HIV but did show a reduction in plasma HIV. Although lower rates of genital HIV shedding were observed in the treatment group, this was not significant. Investigators suggest that the treatment effect was somewhat weaker because of the extended duration of the trial (two years) and difficulties in sustaining high levels of adherence over this long period.46

While the results of these trials are heartening, the impact of suppressive therapy in reducing the sexual transmission of HIV remains to be demonstrated. A large, multicenter trial involving more than 3,000 HIV-serodiscordant couples in which the HIV-positive partner is seropositive for HSV-2 and does not meet national guidelines for ART initiation (i.e., CD4 > 250) is currently evaluating whether 12 to 24 months of acyclovir will lead to a reduction in HIV incidence among the uninfected partners.47 That trial, and another trial conducted in Uganda, will also provide insight into whether longer-term therapy with acyclovir has an impact not just on systemic plasma HIV levels but on CD4 count decline and subsequent HIV disease progression. In all of these trials, the effects of acyclovir on plasma HIV viral load are believed to be mediated through the suppression of symptomatic and asymptomatic reactivations of HSV-2, and not the result of direct pharmacological action against HIV.

More recently, the results of the first trial evaluating the impact of acyclovir suppressive therapy on HIV incidence were released. In a trial involving high-risk women from Tanzania, there was no significant impact on HIV incidence after two years of treatment with acyclovir. The investigators concluded that although there was no overall protective effect of treatment on HIV acquisition, there was some evidence (although nonsignificant) of a protective effect of treatment among women with very high levels of adherence (greater than 90%). Given the impact of poor compliance on the overall trial result, the results of HPTN 039, a similar trial conducted among 3,277 men who have sex with men in the United States and Peru, and women in South Africa, Zambia, and Zimbabwe, were eagerly anticipated. However, although adherence to the study drug was high (an average of 94% of pills dispensed taken by pill count and
self-report), acyclovir 400 milligrams twice a day did not reduce HIV incidence.

**PRACTICAL IMPLICATIONS OF THESE TRIALS**

These trials have provided valuable experience in the management of HSV-2 infection, with or without HIV coinfection, to sites outside of the United States. Several key lessons have been learned, which should be used to guide the development of public health programs while further trial results are awaited.

**Patient and Provider Education**

Genital herpes is a largely unrecognized disease in the developing world. Greater efforts need to be put into increasing patient education about genital herpes, the symptoms of herpes, and the associations between HSV-2 and HIV in developing-country settings. Many providers are unaware of the high prevalence of HSV-2 infection in their setting and of the associations between HSV-2 and HIV. Health-care provider education is required in such settings to ensure that patients receive prompt diagnosis and, where necessary, treatment.

**Counseling and Testing for HSV-2**

Participants in these clinical trials frequently had unrecognized HSV-2 infections. Through effective counseling and testing for HSV-2, trial participants learned to recognize previously unrecognized signs and symptoms of HSV-2 infection and to seek treatment for recurrences early. Although serological testing may not be feasible in all settings, counseling about HSV-2 should be part of the package of care for HIV-positive individuals, the majority of whom are likely to be coinfected with HSV-2. Health-care providers working in HIV clinics should be trained to diagnose the clinical manifestations of genital herpes. They should have a high index of suspicion for genital herpes when patients have genital complaints and be trained to prescribe the appropriate treatment promptly when required.

Additionally, episodic therapy trials have shown a high prevalence of unrecognized HIV infection in individuals with GUD. Education efforts should also focus on encouraging patients with genital ulcers to accept HIV counseling and testing. Services should ensure that HIV testing is offered to genital ulcer patients and, if necessary, that HIV management services are easily accessible.

**Access to Acyclovir**

Given that the World Health Organization has recommended the addition of acyclovir to the syndromic management guidelines for GUD, efforts need to be made to ensure that patients have, at a minimum, access to episodic therapy at the primary health-care level. In addition, suppressive therapy should be made available to those with troublesome HSV-2 recurrences for relief of symptoms initially, and, if trial results are positive, also to prevent HIV. In many cases, providers are reluctant to provide suppressive treatment because of concerns about the perceived cost. Although generic acyclovir is available in most countries, further research is needed to anticipate potential obstacles to future availability, including cost.

**Adherence to Therapy**

If the suppressive therapy trials are successful, there may be initial reluctance to accept this as an intervention to limit HIV disease progression and transmission. Concerns are likely to be raised regarding the feasibility of this intervention and the capacity of patients to achieve high levels of adherence. The experience of these trials has shown that patients in resource-limited settings can achieve high levels of adherence if they receive adequate support in the form of regular adherence counseling and the use of pill reminders.
Vaccine Research and Development
Ideally, a safe and effective HSV-2 vaccine, if it were available, would address many of the concerns regarding the implementation of HSV-2 control strategies as a public health intervention. Given the successful outcomes observed in five different trials of the effect of HSV-2 suppressive therapy on genital and plasma HIV, research into an effective HSV-2 vaccine should rank higher on the international research agenda.


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Theory and Practice of HIV Counseling and Testing
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THE ROLE OF HIV COUNSELING AND TESTING (CT)* has long been recognized as an important entry point to HIV prevention, care, and support in resource-limited settings.\(^1\) Yet, while appreciable efforts have been made in many countries to expand HIV counseling and testing services, much remains to be done to reach satisfactory coverage in most countries. The current availability and use of HIV voluntary counseling and testing (VCT) services are far from optimal: only a small proportion of people living in developing countries are aware of their HIV status. It is estimated that in sub-Saharan Africa, the region of the world most severely affected by HIV, only 12% of men and 10% of women know their HIV status.\(^2\)

This chapter focuses on the theory and practice of HIV counseling and testing in resource-limited settings. The chapter opens with an overview of the theory of HIV counseling and testing, including its efficacy, client motivation, and demographics. The second section presents past and present models of counseling and testing services, key lessons learned, and research gaps. Three case studies appear in the third section, and the chapter concludes with a summary and recommendations for the way forward.

THEORY OF HIV COUNSELING AND TESTING

The core components of HIV counseling and testing include pretest counseling, HIV testing, and posttest counseling. HIV counseling and testing interventions are promoted as voluntary and confidential, an approach believed to contribute to (1) people’s right to know their HIV serostatus; (2) prevention of HIV transmission, because knowledge of HIV serostatus helps in decision making (e.g., changes in sexual behavior, prevention of mother-to-child transmission [PMTCT] uptake); and (3) access to treatment, care, and support services. Yet the traditional definition of counseling and testing must be broadened to recognize other aspects related to the various models of care, treatment,
and prevention, such as the need for diagnostic testing and referrals, linking family members with needed care services, adherence to treatment, and other complex issues. At the same time, a paradigm shift is under way that supports moving beyond the standard VCT service model. In many countries, policies that support approaches like routine offer (i.e., provider-initiated) of HIV testing have now been implemented or are under consideration.

HIV counseling is defined by the World Health Organization (WHO) as a confidential dialogue between client and counselor aimed at enabling the client to cope with stress and make personal decisions related to HIV/AIDS. Based on the Stages of Change model, the HIV counseling intervention is client centered. In other words, the intervention is tailored to address each client’s specific situation, concerns, and readiness for action. Carrying out such an intervention requires an understanding of the client’s needs and the ability to provide the client with appropriate education. The counselor must also assist the client with the development of an individualized action plan (e.g., risk reduction methods, seeking of care) and provide appropriate, ongoing support in implementing that plan.

Efficacy
Existing data from several studies conducted in developing countries suggest that HIV counseling and testing is efficacious in promoting behavior change (as a proxy for prevention) and therefore has a critical role to play in comprehensive HIV prevention and care programs. While an exhaustive literature review is beyond the scope of this chapter, a few of the more notable outcomes are discussed here.

Most published studies on HIV counseling and testing in resource-limited settings are observational, with the exception of one randomized controlled trial published to date. Several observational studies have reported significant behavior changes among individuals and couples receiving HIV counseling and testing. For example, a study in the Democratic Republic of Congo reports increased condom use during all episodes of sexual intercourse among discordant couples following HIV counseling and testing. Allen et al report on a study conducted among discordant couples in Rwanda showing that HIV testing and counseling was associated with an increase in condom use and with lower rates of new HIV infections. An evaluation of the AIDS Information Center in Uganda, where behavior changes were observed among more than 2,500 clients at three and six months following pretest counseling, reports significant reduction in risk behaviors among both HIV-positive and HIV-negative individuals, with greater decreases noted among HIV-positive individuals. Furthermore, Muller et al report decreased sexual activity, fewer sexual partners, and increased use of condoms during the last three incidences of sexual intercourse following HIV counseling in a study among HIV-positive individuals in Thailand.

In addition to the evidence from the observational studies just described, a multicountry randomized controlled study conducted in Kenya, Tanzania, and Trinidad comparing HIV counseling and testing and health information demonstrated a significantly greater decrease in unprotected intercourse with nonprimary partners among participants who received the HIV counseling and testing intervention compared with those in the health information arm of the study.

It should be noted that a small number of observational studies in resource-limited settings have found that HIV counseling and testing was not associated with the desired outcomes (e.g., lowered rates of pregnancy among women). Furthermore, some authors have questioned the prevention benefits of scaling up HIV counseling and testing in resource-limited settings. Nonetheless, the general consensus is that HIV
counseling and testing is a useful and integral part of any meaningful, comprehensive HIV/AIDS program. Moving forward, the focus should be on developing and implementing the most appropriate CT models of HIV counseling and testing provision to respond to the evolving challenges of the HIV/AIDS epidemic.

**Client Motivation and Demographics**

The decision to undergo HIV testing remains difficult for many people. This difficulty is compounded by factors such as stigma and discrimination, distance to services, and cost of services. Various motivations have been reported for those who choose to be tested for HIV, including curiosity, fear of having been exposed to HIV, feeling sick, an important life commitment (e.g., marriage, new partner), and requirement for a benefit (e.g., visa, scholarship). These motivations and others need to be taken into consideration when setting up HIV counseling and testing services.

Likewise, the demographic characteristics of CT clients may vary according to the service delivery model and setting. For example, integrated models of HIV counseling and testing may reach more women than do stand-alone models, where more men may be seen. On the other hand, mobile services may be more likely to reach young people and hard-to-reach groups (e.g., migrants, sex workers, drug users). Program planners should be mindful of the characteristics of their target populations and the strengths and weaknesses of various CT models when establishing HIV counseling and testing services.

**FROM RESEARCH TO PRACTICE**

The transition from research to practice in the area of HIV counseling and testing has been relatively successful. Findings from a variety of studies, ranging from randomized trials to observational and operations research, have provided knowledge and tools for developing and implementing HIV counseling and testing programs. Since the early 1980s, the many studies conducted in resource-limited countries have informed the evolution of HIV counseling and testing. As a result, innovative and context-specific approaches have been adopted, facilitating program expansion. Some of the key discoveries and advances that have spurred the evolution of CT practice are discussed in the following sections.

**Evolution from 1980s to the Present**

HIV counseling and testing has evolved significantly since the development of the first HIV test kits. In resource-limited settings, the evolution of HIV counseling and testing can be divided into three eras: the 1980s, the 1990s, and from 2000 to the present.

The 1980s were characterized by high stigma, discrimination, fear, and lack of HIV treatment. Consequently, the first counseling and testing models (e.g., VCT) emphasized the voluntary aspect and informed consent, and placed a strong emphasis on the role of testing in HIV prevention. During that time, HIV counseling and testing in most resource-limited settings was confined to research and blood transfusion sites, with minimal or no counseling. People tested rarely collected their test results.

The early 1990s saw a progressive but slow interest in HIV counseling and testing in resource-limited settings and the establishment of a few anonymous HIV counseling and testing sites. HIV counseling and testing remained hard to “sell” to governments and donors because its efficacy was still under review, and it offered little to those found to be HIV-positive, beyond the promise of prevention benefits, the ability to plan for the future, and, to some extent, psychosocial support.

In the mid- to late 1990s, support for HIV counseling and testing grew further, facilitated by factors
like (1) the demonstration that services other than antiretroviral therapy (e.g., psychosocial support, treatment for opportunistic infections) were beneficial to people who tested positive and that the demand for testing existed even in the absence of treatment; (2) the release of results from the VCT efficacy study demonstrating the efficacy of VCT on behavior change and its cost-effectiveness; and (3) the release of results from the HIVNET 012 study demonstrating the efficacy of nevirapine in preventing mother-to-child transmission of HIV, which facilitated the introduction and widespread use of HIV counseling and testing in the context of that area of prevention. The period saw the introduction of the use of rapid HIV testing with same-day results, a shift from anonymous to confidential testing, and an emphasis on the improvement of posttest support services. The main focus remained on prevention, although recognition was growing that counseling and testing is a major entry point to care and support services.

The first six years of the 21st century witnessed a dramatic expansion in HIV counseling and testing programs in several countries and a shift in approaches to HIV testing. The push for access to treatment in resource-limited settings and the subsequent antiretroviral (ARV) treatment programs (e.g., WHO “3 by 5” initiative, U.S. President’s Emergency Plan for AIDS Relief [PEPFAR]) revealed the inability of the VCT model to identify most people living with HIV who would benefit from treatment programs. That discovery led to a radical shift in the global HIV testing policy, from a predominantly client-initiated model to one in which providers aggressively and routinely promoted HIV testing in health facilities to boost access to treatment and prevention. That shift in policy also called for modifying terminology from what had historically been called voluntary counseling and testing to HIV counseling and testing in the broader sense.

The Changing Landscape
As stated earlier, the last six years have seen a shift in the global approach to HIV testing. The need to increase coverage and uptake of antiretroviral therapy and boost access to treatment and prevention services makes it critically important to expand and broaden HIV testing entry points, allowing more venues to routinely offer HIV testing (while preserving the client’s right to refuse). As depicted in Figure 1 (next page), counseling and testing programs must move from a client-initiated approach to a combined approach, where provider-initiated testing and counseling is offered in various clinical settings in addition to client-initiated testing.

To increase access to HIV counseling and testing, both client-initiated and provider-initiated models must be used (Table 1). These models are not mutually exclusive; a strategic mix of approaches is needed to meet different needs in different settings and to increase opportunities for people to learn their HIV status. Whatever model is used, the following key ethical principles hold: the test must remain voluntary, the results must be kept confidential, and the test must be accompanied by counseling.

LESSONS LEARNED
Many valuable lessons have been learned during several years of CT research and programming. The key lessons presented here are based on the authors’ personal experiences with counseling and testing programs in resource-limited settings and with reading the existing literature.

Political commitment is a key ingredient for scale-up. It is needed to identify counseling and testing as a priority, lead and coordinate national counseling and testing programming efforts, pass measures aimed at reducing stigma and discrimination, and ensure access to prevention and care services.

Creating local and national ownership is critical to sustainability. Counseling and testing programs that promote local ownership are more
and evaluation helps correct problems and inform future planning. Activities must be built into the design of all counseling and testing programs.

Quality assurance and quality improvement (QA/QI) require more attention. As counseling and testing services are taken to scale, a well-thought-out QA/QI process must be part and parcel of these efforts to ensure their quality and allow for continuous improvement.

Demand creation is critical. As with any service, HIV counseling and testing services must be promoted to create demand and increase their use.

Provider-initiated testing and counseling contributes significantly to increasing access. There are many missed opportunities for CT in health-care settings. Many people are not being tested—not because they are opposed to being acceptable to the community, which will then work to ensure their use and longevity.

No one model serves all needs. Different models of counseling and testing help meet the needs of various potential users, ensure more equitable access, and facilitate cross-referrals.

Special care must be taken to reach the most vulnerable groups, especially women. Although CT has many benefits, it can have harmful consequences for some vulnerable groups (e.g., women, men who have sex with men, injecting drug users). Appropriate measures are required to ensure equitable access, protect the individual’s right to privacy, and cater to the special needs of those groups.

Monitoring and evaluation should not be an afterthought. Although it requires significant technical and financial investment, monitoring and evaluation helps correct problems and inform future planning. Activities must be built into the design of all counseling and testing programs.
HIV counseling and testing for couples has the potential to reduce transmission among partners. Couples counseling and testing must be encouraged among couples planning marriage or those in relationships. This is especially critical

tested, but because testing is not being offered. A shift in attitudes among providers is required to successfully implement provider-initiated testing and counseling, because many still do not consider HIV testing a part of their job.
given the high prevalence of HIV discordance that has been reported.\textsuperscript{19,20} Shared knowledge of HIV serostatus assists in adopting preventive behaviors to reduce the risk of HIV transmission to the negative partner (in the case of discordant couples) and facilitates access to other HIV-related services (e.g., PMTCT, clinical care). (See chapter in this section entitled “Couples HIV Counseling and Testing as an Entry Point to HIV Care.”)

There is no single “magic bullet”; rather, creativity and innovation help address challenges in the local context. Program planners, managers, and providers must use their skills and familiarity with the local setting to design innovative approaches to CT (e.g., use of lay counselors, group pretest counseling) that are effective despite human and financial resource constraints.

Operational research helps shape CT programs. Operational research built into programs helps answer programmatic questions and contributes to the design of locally appropriate solutions.

Stigma and discrimination remains a great barrier to the uptake of HIV counseling and testing. Bold actions are needed at all levels to normalize HIV and protect the rights of those living with the virus so people feel secure in seeking out and/or accepting HIV testing.

**RESEARCH GAPS**

The knowledge base required for the design and implementation of large-scale HIV counseling and testing programs already exists. However, continued research is still needed to inform and improve present and future programs. The following are some research questions to be considered:

- What is the impact of the availability of ARV treatment on the demand for counseling and testing services?
- How does routinely offering of HIV testing in health facilities affect the use of other health services?
- What is the behavioral impact of HIV counseling and testing in contexts in which ARV drug therapies are available?
- What is the impact of antiretroviral therapy on stigma and discrimination and normalization of HIV testing?
- What are effective measures or interventions to significantly reduce stigma and discrimination and normalize HIV testing?
- What is the prevention value of HIV counseling and testing programs at the population level beyond individual behavior change?
- What is the cost effectiveness of the various counseling and testing models?
- Given the strong push for access to CT, what would be required (e.g., infrastructure, commodities, human resources) for existing systems to cope with the hoped-for increase in demand?

**CASE STUDIES**

From among the many examples of successful counseling and testing programs worldwide, this section draws on the experiences of Family Health International (FHI) with CT service delivery in a variety of resource-limited settings.

**Kenya’s Rapid Scale-Up of VCT**

With support from the U.S. Agency for International Development (USAID), the Government of Kenya hosted the first Technical Consultative Meeting on VCT in 2000. The meeting brought together government, donors, and technical agencies interested in promoting VCT in Kenya. As a follow-up to the meeting, a VCT committee was formed in 2001 under the auspices of the National AIDS and STD Control Program (NASCOP). That committee spearheaded the development of the national VCT guidelines and the national training curriculum. Various technical agencies, including the Centers for Disease Control and Prevention (CDC), FHI, the Liverpool School of Tropical Medicine, and the
In 2002, the government of Kenya elected to establish a VCT center of excellence to serve as a model and a training site. Through a grant from the Embassy of Japan in Kenya, FHI supported the government of Kenya in the construction of the Kenyatta National Hospital VCT Center of Excellence. With technical assistance from the IMPACT Project (Implementing AIDS Prevention and Care) of USAID, that center became the first high-volume VCT center in the country, with about 1,000 clients per month, and became a model for many other VCT centers around Nairobi and throughout the country. The Kenya Medical Research Institute was enlisted to support quality assurance of HIV testing, and a widespread orientation of health professionals was organized nationally.

To popularize VCT among the general public, a branding campaign was financed by USAID, whereby a logo for VCT signs was designed. The logo was supported by a mass media campaign that covered radio, TV, newspapers, and billboards and continued over a three-year period.

In 2004, NASCOP developed a roll-out strategy and a quality assurance strategy with technical assistance from various agencies. In addition, based on an assessment conducted by FHI showing the need and desirability of family planning (FP) and VCT integration, a national FP/VCT integration strategy was developed. Through implementation of the roll-out strategy and with support from donors and technical partners, services are currently under way across the country.

As shown in Figure 2, the country has seen an impressive upsurge in the availability of counseling and testing services, going from only 45 sites in 2001 to more than 720 sites in 2006. The IMPACT Project managed by FHI directly supported the establishment of 217 of these sites. As of June 2006, NASCOP reported that 1,323,858 Kenyans accessed counseling and testing services at sites around the country.

Key factors contributing to the success of this effort included the development of supportive national policies and strategies, addressing procurement limitations, ensuring quality, and popularizing the services to generate demand. Despite the impressive achievements of the program, however, many challenges were encountered, such as the need for reliable supply chain management for HIV test kits, limited human resources, suboptimal physical infrastructure, and difficulty in maintaining quality in the context of rapid scale-up.

**Rapid Scale-Up of CT Integration in Ethiopian Health Facilities**

With funding from USAID, PEPFAR, the World Bank, the Global Fund, the Japan International Cooperation Agency, and the Development Cooperation of Ireland, FHI assisted the government of Ethiopia to integrate more than 550 counseling and testing centers into existing government health facilities, including hospitals and health centers in four regions of the country (Addis Ababa; Amhara; Oromia; and the Southern Nations, Nationalities, and Peoples Region).

A baseline assessment of existing HIV/AIDS care and support services, including voluntary counseling and testing, was conducted in 2002 and 2003 in those four regions. The assessment demonstrated an unmet need for counseling and testing, lack of standardization in service provision and lack of quality control. Based on those results, the regional health bureaus prioritized the establishment of counseling and testing services in all government health centers in the regions as part of their standard service packages. FHI worked with the regional health bureaus to support them in the CT scale-up effort.

The design of the counseling and testing scale-up was also informed by an assessment of the preparedness of health facilities to integrate counseling
and testing. A scale-up plan was designed, with health facilities prioritized for a phased introduction of counseling and testing services based on elements such as demand for the services, concentration of population at risk, size of the population, availability of rooms, and availability of health professionals.

The four regions then proceeded with accelerated and synchronized implementations of their plans, which included simultaneous launchings of the sites ready to start. The implementation of the scale-up plan entailed infrastructure improvement (e.g., setting up counseling rooms; purchasing furniture, laboratory supplies, small equipment); development of CT guidelines and training curriculum; ongoing capacity building for personnel (e.g., counselors, supervisors, laboratory technicians); establishment of the VCT Counselors Support Association; development of monitoring and evaluation tools; strengthening of referral systems between counseling and testing and clinical care services (e.g., tuberculosis, antenatal care, family planning), as well as home- and community-based care services for people living with HIV; and ongoing technical assistance (for implementation support, quality assurance and improvement, etc.).

As indicated in Table 2, the scale-up efforts resulted in the integration of counseling and testing in more than 450 health facilities between 2003 and 2006, with more than 400,000 individuals receiving counseling and testing in 2006 alone through these facilities. The success of these efforts demonstrated that integrating counseling and testing services in health centers can be effective in expanding access to CT services.

The counseling and testing scale-up efforts were an important contribution to the national HIV/AIDS response and enhanced the overall strength of health facility services. They also fostered the development of referral systems between communities and health centers and helped to expand health service coverage in targeted communities. The regional health bureaus and nongovernmental organizations adopted the training curriculum and the monitoring and evaluation system.
approach. Brazil’s experience includes firm advocacy of human rights for people living with HIV and strong civil society participation and mobilization. This approach helps to identify the critical elements of improving access to counseling and testing and contributes to the goal of universal access.

Brazil employs two models of counseling and testing: integration within existing health facilities and client-initiated testing at freestanding centers. Between 1997 and 2002, the number of people tested at both freestanding centers and health facilities doubled.21,22

The Brazilian government used various media campaigns to promote universal HIV testing. The central message of the campaigns was that everyone in the country should know their HIV status. One major initiative, known by the slogan Fique Sabendo (“Be in the Know”), enlisted the help of models and other celebrities to promote testing. Before unveiling the campaign through television and newspaper advertisements in 2003, the government promoted it at one of the country’s biggest fashion shows in São Paulo. Models wore T-shirts decorated with the campaign’s logo: a smiling face with plus and minus signs for its eyes, representing the two possible results of an HIV test. In many countries, such an event would be unimaginable given the stigma and taboo surrounding HIV.23,24

### A Balanced Approach to Counseling and Testing Scale-Up in Brazil

Brazil has been successful in building and sustaining a comprehensive national HIV/AIDS treatment program using a balanced prevention and treatment approach. The capacity-building process, including the training curriculum and accompanying methodology, is now being used at regional levels and has been adopted by many local and international nongovernmental organizations.

Elements that were instrumental to the success of this experience include the involvement of the government at various levels (Ministry of Health, regional health bureaus, etc.), the development of local ownership in the regions and at the health facilities, the ongoing training of personnel to help fill the human resource gaps, and the leveraging of donor funding and partner contributions to support program activities. The program encountered some challenges as well, including frequent turnover of personnel, weak commodity management and communication logistics, insufficient funds to meet all costs related to the rapid scale-up of services, and the intricacy of timely data collection given the large number and geographic spread of sites.

### Table 2. Scale-Up of CT Sites in Ethiopia by Region

<table>
<thead>
<tr>
<th>Regions</th>
<th>Number of sites 2003/04</th>
<th>Number of clients 2003/04</th>
<th>Number of sites 2005/06</th>
<th>Number of clients 2005/06</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addis Ababa</td>
<td>25</td>
<td>15,291</td>
<td>31,992</td>
<td></td>
</tr>
<tr>
<td>Amhara</td>
<td>0</td>
<td>0</td>
<td>138,609</td>
<td></td>
</tr>
<tr>
<td>Oromia</td>
<td>102</td>
<td>18,425</td>
<td>101,179</td>
<td></td>
</tr>
<tr>
<td>SNNPR*</td>
<td>0</td>
<td>0</td>
<td>75,490</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>127</td>
<td>33,716</td>
<td>347,270</td>
<td></td>
</tr>
</tbody>
</table>

*Southern Nations, Nationalities, and Peoples Region
In addition to the media campaign, special outreach teams were developed to increase access to counseling and testing for specific populations, such as pregnant women, men who have sex with men, and injecting drug users. VCT centers have now become gathering places for larger-scale community development and human rights initiatives. These links have evolved out of community outreach activities and have fostered partnerships between community members and leaders, VCT center staff, and university researchers.

Despite the success of the initiatives and substantial improvements in access to counseling and testing in Brazil, more people need access to testing facilities. Many people are still not being diagnosed until the late stages of HIV infection, emphasizing the need for early and widespread testing. As of 2006, only an estimated one-third of HIV-positive Brazilians were aware of their status, and just 20% of Brazil’s sexually active population had been tested for HIV.

**SUMMARY AND WAY FORWARD**

HIV counseling and testing is a vital component of comprehensive HIV/AIDS prevention and care programs. The evidence of its effectiveness in changing individual behavior has been provided by several studies conducted in developing countries, and it is playing a growing role as an entry point to other HIV services, including care and treatment.

Through the years, the practice of counseling and testing has undergone substantial change. Starting as part of research and small-scale counseling and testing projects, it has evolved to mostly client-initiated testing (VCT) and is now expanding to include broader programs combining both client- and provider-initiated counseling and testing.

There is a wealth of knowledge, tools, experiences, and successful counseling and testing programs from which to learn. However, because of the many constraints to program scale-up and utilization, those lessons have rarely translated into universal access.

Clearly, no problem or constraint justifies inaction. A strong commitment is needed at all levels to advance the scale-up of counseling and testing. That endeavor must aim for universal access to prevention, care, and treatment while preserving the rights of individuals and communities. Moving forward, it will be particularly important to articulate clear national policies promoting a broad range of counseling and testing services, while ensuring human rights and protecting individuals against mandatory testing. Other necessities are planning for human resource capacity development, strengthening existing health-care systems so they can cope with the demands of counseling and testing, and last but not least, mobilizing sufficient funding to support the implementation and sustainability of meaningful programs. Only then will universal access be within reach.
REFERENCE LIST


HIV TESTING HAS BEEN PROVIDED AT public health facilities throughout Botswana since the late 1980s. In 2000, a nationwide network of voluntary counseling and testing (VCT) centers, known as Tebelopele (“look into the future” in Setswana), was established. Soon after, in 2002, Botswana became the first African country to provide widespread access to free antiretroviral therapy (ART) for eligible patients (those with a CD4 count of less than 200 cells/mm³ or an AIDS-defining illness) through their national treatment program known as Masa (“new dawn”).1-4

For the first two years of the Masa program, HIV testing and initiation of ART occurred at a much slower pace than anticipated; by January 2004, only 17,500 out of an estimated 110,000 eligible individuals were enrolled.1 Underutilization of testing and treatment services was thought to be due in part to people’s fears of receiving a positive test result and widespread HIV-related stigma and discrimination. This situation resulted in many people not getting tested until they became seriously ill.2,4 Consequently, in January of 2004, the government of Botswana introduced a policy of routine HIV testing (RHT) in which all patients would be tested for HIV when they visited their doctor unless they specifically refused to give consent for testing.7 This new approach had two primary goals: (1) to reduce the stigma and discrimination associated with HIV by treating the HIV test like any other routine medical test; and (2) to make every patient aware of his/her HIV status so that they could take advantage of both prevention of mother-to-child transmission of HIV (PMTCT) and ART services.8,9

As the RHT policy was being implemented, the Botswana Ministry of Health (MOH) issued some basic guidelines regarding who would be tested under this new strategy. This list included pregnant women, individuals presenting with symptoms of HIV infection including tuberculosis, individuals presenting with a sexually transmitted infection, any patient aged 16 years or older visiting a health facility, any individual presenting for a general medical examination, and any individual desiring a test.10 Provisions for testing of individuals who were rape survivors or had experienced a needlestick injury were subsequently added. Botswana’s provider-initiated testing policy followed an opt-out approach, in which the patient is informed that an HIV test is going to be conducted and that they have the right to decline the
test. The policy also stated that all patients should receive essential information about HIV testing, but that pretest counseling, in most settings, was to be abbreviated.

During the initial roll-out of the policy, although the guidelines indicated who should be tested for HIV, there were limited details regarding the specifics of how to implement RHT. There was also no systematic monitoring of the national implementation of this new policy, making it difficult to ensure standardized practices between different sites. Consequently, while the policy specified an opt-out approach, the definition of what constituted “informed consent” varied between health centers.

From the outset, various groups voiced concerns about the new policy. Some people living with HIV, community groups, and local human rights organizations had concerns that testing had ceased to be voluntary under this new program and that people would be dissuaded from visiting their doctors for fear of being tested. There was also a concern that the potentially negative consequences associated with this policy would disproportionately affect women. For instance, since women typically have more frequent health-care contacts, some feared that they would be at an increased risk of abuse and violence if identified as HIV-positive, as had historically been the case. Many were also uneasy with what they perceived as inadequate informed consent and counseling.

As provider-initiated testing policies are being expanded to other countries, it is important to improve our understanding of the consequences and specific human rights concerns associated with the implementation of the RHT policy in Botswana. In the following sections, we summarize data from several recently published studies on RHT in Botswana. We begin with a summary of findings from the earliest study published on this topic, and then summarize more recent data from a number of additional studies.

PHYSICIANS FOR HUMAN RIGHTS STUDY

Between November and December of 2004—11 months after the implementation of Botswana’s routine testing policy—Physicians for Human Rights (PHR) conducted the first large-scale study looking at attitudes and experiences with this policy among adults aged 18 to 49 selected from among the general population. The goals of this study were to determine the prevalence and correlates of HIV testing, assess knowledge of and attitudes toward routine testing, and compare experiences with RHT with those of VCT. This cross-sectional, population-based study was conducted in the five districts of Botswana with the highest number of people living with HIV. Using a stratified, two-stage probability design, 1,433 households were randomly selected, and 1,268 respondents (89%) completed the survey. Approximately half of the respondents were women, the mean age was 29, and 54% of participants had completed high school or had some postsecondary education.

Correlates of and Barriers to Testing

Nearly half (48%) of the interviewees reported having had an HIV test, either by routine testing or VCT. Adjusted correlates of HIV testing included female gender, higher education, more frequent health-care visits, inconsistent condom use, and perceived access to HIV testing and to high-quality medical services. In addition, people with stigmatizing attitudes toward people living with HIV had 35% lower odds of testing (adjusted odds ratio [AOR]=0.65; 95% CI, 0.50-0.85), and people with poor self-reported health status were 30% less likely to test (AOR=0.70; 95% CI, 0.53-0.94). Of the 52% of participants who had never been tested, the key barriers to testing included fear of learning one's HIV status (52%), lack of perceived risk (43%), and fear of having to change sexual practices if positive (33%).
Knowledge of, Attitudes about, and Experiences with RHT

Only half (54%) of the participants had heard of RHT before being interviewed, but most (82%) were very much or extremely in favor of RHT once they had heard a brief explanation of the policy. There was limited experience with RHT among those sampled; only 15% of participants that tested said they had been tested by routine testing. A majority (60%) of respondents thought RHT would reduce HIV-related stigma, and more than half (55%) thought it would lead to decreased violence toward women. Eighty-nine percent of the respondents believed that RHT makes it easier for people to get tested, and 93% thought it would make it easier for people to gain access to ART. However, almost half (43%) believed that RHT might prevent people from going to the doctor because of fear of testing, and 14% thought the policy could actually increase violence against women. The study also looked at factors associated with having been specifically tested by RHT and found that individuals who were married and who had seen their doctor more often had higher odds of having received routine testing. In addition, respondents with stigmatizing attitudes toward people living with AIDS had 50% lower odds of receiving RHT.

Experiences with VCT versus RHT

Overall, testing experiences were similar for VCT and RHT. Over 90% of those who tested by either testing strategy had received both pre- and posttest counseling and returned to get their test results. The vast majority (93% VCT, 89% RHT) of those who had tested encouraged others to take the test as well. There were no substantial differences in negative testing outcomes between VCT and RHT. Although experiences with testing were generally positive, one striking finding was that two-thirds of interviewees (68% VCT and 65% RHT) who had been tested by either method felt that they could not refuse the HIV test. In addition, approximately 5% of respondents who had tested by either VCT or RHT said they had experienced a breach of confidentiality at the testing sites. Very few respondents (2% VCT and 3% RHT) regretted having been tested, and even fewer (2% VCT and 0% RHT) reported partner violence related to testing.

MORE RECENT FINDINGS

The results from the Physicians for Human Rights study show that there was widespread support for RHT in Botswana in late 2004. At the same time, concerns were raised about the quality of informed consent, confidentiality, gender-based violence, and people avoiding clinics for fear of getting tested for HIV. Since this study was conducted shortly after the implementation of the policy, it is important to review more recent data to better assess possible positive and negative impacts of this policy in Botswana. The following is a brief review of notable findings from subsequent studies.

Prevalence and Correlates of HIV Testing

In mid-2006, Cockcroft et al15 conducted a population-based study among 1,536 participants to determine whether RHT led to anticipated increases in HIV testing, to assess knowledge and views of routine testing, and to assess experiences with testing in government health facilities. They found that over half (55%) of respondents reported having an HIV test in the last 12 months. This compares to 48% reporting that they had ever tested in the PHR study. The correlates of testing were also similar to the PHR study and included female gender, higher education, more frequent health-care utilization, and perceived personal risk of HIV. In addition, people who were in favor of routine testing had nearly three times the odds of being tested for HIV.
Awareness and Support of RHT

Awareness of, experiences with, and support of RHT increased during the first few years after the roll-out of the RHT policy. Compared with the PHR study in 2004, there was increased awareness of RHT in the Cockcroft et al study in that 79% of participants had heard of RHT. There was also persistent support for routine testing, with 94% in favor or strongly in favor of RHT. Finally, there was increased experience with routine testing: of 55% of respondents who reported having an HIV test in the last year, half said they had tested via RHT, up from 15% in the PHR study just 18 months earlier.

Uptake of Testing and Treatment

Data from two studies conducted by the Botswana MOH reported significant increases in testing and treatment uptake following the implementation of RHT. Two years after the policy was introduced, Steen et al reviewed aggregated data submitted to the MOH from 31 public hospitals and primary care facilities (608 clinics and health posts). The authors found that the rate of RHT increased substantially between 2004 and 2006, from 36/1,000 people tested by RHT in 2004 to 104/1,000 in 2006. In addition, the proportion of people opting out decreased from 11% in 2005 to 7% in early 2006. Finally, people were being diagnosed at earlier stages of disease. The proportion of people testing positive with CD4 counts less than 100 cells/mm$^3$ decreased from 49% in 2003 to 34% in early 2006.

In another study, Creek et al used data from antenatal clinic (ANC) logbooks to evaluate the impact of RHT on ANC and PMTCT programs. The logbooks were reviewed before (control period) and after (intervention period) routine testing training was implemented for staff at four clinics in Francistown (Botswana’s second largest city). Aggregate data from the regional hospital and the national PMTCT program were also used to examine the impact of the nationwide introduction of routine testing on the PMTCT program. The authors found that the proportion of pregnant women from ANCs in Francistown being tested increased from 76% in 2003, prior to the implementation of RHT, to 95% in late 2004. The proportion tested that learned of their status also increased from 72% to 82% in that same time frame. The regional data showed that the percentage of all HIV-positive women who knew their status at the time of delivery increased from 47% in 2003 (before RHT) to 78% in 2004.

In terms of PMTCT uptake, Creek et al reported that nearly two years after the RHT policy was introduced, almost 80% of pregnant HIV-positive women were receiving PMTCT interventions, compared to 37% in 2003. This is the highest proportion of women receiving PMTCT anywhere in Africa. Similarly, there was a four-fold increase in ART uptake. In January 2004, there were 17,500 individuals on ART, compared with 84,900 in March 2007. These data are promising, but it is important to emphasize that we cannot necessarily infer a causal connection between routine testing and treatment uptake, because there were likely many factors that contributed to the high treatment uptake in Botswana during this period.

Clinic Avoidance for Fear of Testing

One of the concerns raised about RHT is that people might avoid going to clinics for fear of being tested for HIV. Although this has not been directly evaluated in any study, available evidence suggests that most people are continuing to visit government health facilities. In Cockcroft’s study, 76% of participants reported that they visited a government health facility in the previous year. We do not know whether fear of HIV testing played a role in preventing the other 24% from going to clinics. Routine testing also does not appear to be associated with decreased use of prenatal care or the proportion receiving test results, according to the study by Creek et al discussed earlier.
ONGOING AREAS OF CONCERN

Although much of the initial data on RHT in Botswana appears promising, there are still ongoing concerns with the implementation of the policy, and there is a critical lack of data on certain key issues. Some key areas of concern include lower testing uptake for men, the potential for violence and discrimination against women, and issues related to confidentiality and informed consent.

Lower Testing Uptake among Men

Botswana’s RHT policy reaches more women than men, and national data by Steen et al16 show that men comprised less than one-third of those tested by RHT between January of 2004 and June of 2006. Not only are women more likely to use government health facilities compared with men, but once in clinics, women are also more likely than men to be offered testing and more likely to go on to be tested. In Cockcroft’s study, men were significantly less likely than women to have visited a government health facility (OR for men=0.59; 95% CI=0.45-0.76).15 Of those seen at clinics, only 42% of men were offered an HIV test, compared with 54% of women. Finally, men were more likely to opt out of testing when offered.15 These findings suggest that RHT may be missing out on key prevention and treatment opportunities for men in government health facilities, and that reaching men needs to be an ongoing target for intervention.

On the other hand, a 2005 study by Kessler et al18 found that women were less likely to be offered testing in one hospital setting. In their study, data were collected on all inpatients admitted to one medical team in Princess Marina Hospital in Gaborone during a six-month period. Out of 571 patients, 284 had an uncertain HIV status; and of those, 58% were offered and accepted testing, 2% refused, and 40% were not offered testing. Women had higher odds of not testing in this study (AOR=3.1; 95% CI=1.8-5.3). These findings suggest that strategies to better reach women will also be important in going forward.

Violence and Discrimination against Women

Because women likely comprise a majority of those tested by routine testing, there are concerns that this policy might lead to an increase in gender-based violence and discrimination. There is limited data on this issue, but preliminary data suggest that there does not appear to be an increase in violence against women tested by routine testing. Among 52 women tested by RHT in ANCs in the study by Creek et al, none reported domestic violence after disclosure.17 In the population-based study by Cockcroft et al, the authors found no association between having been tested over the previous 12 months and reporting partner violence.15 There are currently no further data on discrimination related to routine testing.

Confidentiality and Informed Consent

There are also ongoing concerns with practices related to confidentiality and informed consent in Botswana’s RHT policy. In Cockcroft’s study, 10% of participants who visited government health facilities were concerned that their health information was not kept confidential. In addition, up to 8% of participants may have been tested without their consent.15

LESSONS FROM BOTSWANA

These studies demonstrate that as of mid-2006, public awareness and approval of RHT in Botswana was high. In addition, Botswana’s routine testing program has probably contributed substantially to the gains in testing and treatment uptake that we have witnessed. These promising findings are tempered by ongoing concerns about informed consent, confidentiality, and gender-based violence.
and discrimination. There are still limited data on these issues, and more careful monitoring of the process will be critical to assess all positive and negative impacts of the policy. In view of the heterogeneous implementation of the RHT policy in Botswana, there are still several unanswered questions:

- What measures are necessary to ensure protection from violence and discrimination?

As Botswana continues to expand its RHT program and other countries adopt similar policies, consistent monitoring will help to ensure that both public health and human rights goals are met. In view of Botswana’s unique circumstances in terms of their high GDP, government commitment to combating HIV, and extensive health-care infrastructure, we would urge caution in generalizing this experience to other resource-limited settings without an extensive evaluation of local circumstances.

- Is an opt-out or an opt-in approach to provider-initiated testing more effective in increasing treatment uptake and in ensuring protection of human rights?

- What type of pretest information is adequate for true informed consent?

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EAR OF STIGMA AND OTHER forms of discrimination or abuse continue to deter people from being tested for HIV. Consequently, approaches to HIV testing (which provides the key to prevention, treatment, care, and support) need to include a range of protections for those being tested. In principle, provider-initiated testing and counseling (PITC) and routine HIV testing (RHT) include human rights safeguards through the inclusion of counseling, consent, and confidentiality. Yet these theoretical safeguards must, in practice, be implemented in a way that contributes to an overall reduction in stigma and discrimination, rather than further fueling HIV/AIDS-related human rights abuses. Given the close and complex relationship between HIV/AIDS and human rights, the scaling up of public health efforts with the aim of achieving universal access to care and treatment must include multipronged efforts to promote and protect the rights of the individual.

PITC

The World Health Organization (WHO) and the Joint United Nations Program on HIV/AIDS (UNAIDS) have adopted the following definitions of testing policies. Broadly, PITC denotes HIV testing initiated by health providers at health facilities. It includes diagnostic HIV testing, where patients are tested when they present with signs or symptoms that could be attributable to HIV; and HIV screening, where people attending health facilities...
who would benefit from knowing their HIV status are tested for HIV. In opt-out testing, patients are tested at the health center unless they explicitly refuse. In this process, which usually includes simplified pretest information, the default is to be tested. With an opt-in approach, testing is initiated by the provider, who offers an HIV test as a routine part of discussions with all patients in a given setting or those meeting certain criteria, but the client must specifically agree to the test, rather than having to refuse it. With both approaches, HIV testing is recommended as a standard component of medical care, and the purpose of testing “is to enable specific clinical decisions to be made and/or specific medical services to be offered that would not be possible without knowledge of the person’s HIV status.”

While the WHO/UNAIDS guidance on PITC recommends an opt-out approach, it acknowledges that an opt-in approach “merits consideration” in health facilities that serve highly vulnerable populations. The guidance also states that irrespective of which approach is taken, the end result should be the same: an informed decision by the patient to accept or decline the health-care provider’s recommendation of an HIV test.

The UNAIDS/WHO policy on HIV testing states that the use of RHT is ethically legitimate only when the “3 Cs” of consent, counseling, and confidentiality are actively practiced. The purpose of integrating ethical and legal values into the RHT process, as evidenced by the inclusion of the 3 Cs in the Botswana Ministry of Health (MOH) RHT guidelines, is to preserve human rights principles in HIV/AIDS care as in the treatment of all other diseases, in accordance with general WHO standards and/or professional medical standards. The most basic human rights to be considered in the context of RHT include the security of person, individual sovereignty, bodily integrity and autonomy, health and access to health care, privacy and information, and equality and nondiscrimination.

**From Policy to Practice in Botswana**

Botswana’s constitutional law and common law do recognize the right to privacy and confidentiality. The Constitution of Botswana, under Section 9, stipulates that except with his own consent, no person shall be subjected to the search of his person or his property or the entry by others on his premises.

The common law in Botswana consists of a combination of Roman Dutch law and English law, drawing heavily from the common law of South Africa. The right to privacy revolves around the ideas of “withdrawal,” “seclusion,” “being let alone,” “solitude, intimacy, anonymity, and reserve,” and “minimum interference with one’s own life.” Legal action can therefore be taken against any person who breaches this right, leading to monetary damages as compensation. The authority for this proposition is a South African case between a doctor and a patient, in which the doctor divulged information about his patient’s HIV status to another doctor while playing golf. The attendant doctor was adjudged by the court to be in breach of the right to privacy, and damages were consequently awarded.

The Botswana National Policy on HIV/AIDS recognizes the need for respect of human rights, privacy, and self-determination; expressly provides for counseling, consent, and confidentiality; and envisages
nondiscrimination in relation to HIV/AIDS. Provision of a “strengthened legal and ethical environment” constitutes the fifth goal under Botswana’s National Strategic Framework for HIV/AIDS. Toward this goal, the framework provides for creation of a supportive human rights–based environment conforming to international standards for the implementation of the National Response; integration of multisectoral strategies and identification of gaps in sectoral responses; information, education, and communication; nondiscrimination; care and support of vulnerable groups; and review and reform of laws and policies in keeping with human rights approaches.

Concerns Surrounding Routine HIV Testing

There is concern among people living with HIV, civil society organizations, and others that the practice of PITC including RHT is potentially coercive. Specifically, concerns revolve around the issue of inadequate consent and counseling, avoidance of clinics for fear of being tested, and increased testing-related domestic violence.

There is a strong argument in favor of providing real knowledge about HIV through counseling, which can guide and direct behavior change. In Botswana, the degree to which opt-out testing allows for pretest counseling and informed, voluntary, and specific consent is not clear, and there is a dearth of literature in this regard. In practice, it is unclear to what extent people understand that they have the ability to opt out, especially given the common power imbalances between health-care users and health-care providers. Conventional attitudes of fear, awe, respect, and deference toward health-care professionals, especially among less-educated and disadvantaged communities, make it likely that some patients will not opt out despite having reservations about testing. In resource-limited settings, where levels of education are typically suboptimal, there is a risk that informed consent can in practice be replaced by implied consent, thereby moving from a routine offer to a routine imposition of testing.

According to the WHO/UNAIDS guidance on PITC, positive outcomes “are most likely when HIV testing and counseling is confidential and is accompanied by counseling and informed consent, staff are adequately trained, the person undergoing the test is offered or referred to appropriate follow-up services and an adequate social, policy and legal framework is in place to prevent discrimination.” Yet despite this sensitive language, realities on the ground often play out quite differently. Denial, shame, stigma, fear, rejection, ostracism, marginalization, discrimination, criminalization, and other human rights abuses related to one’s HIV-positive status are still commonplace in many settings. Studies have found the presence of stigma and discrimination, which is particularly significant in the sector of health services, in settings around the world, including Latin America and the Caribbean, India, China and other parts of Asia, and several African and Eastern European states. A study in Botswana revealed that the HIV epidemic was often accompanied by stigma and discrimination that create the circumstances for spreading HIV. This study found considerable prevalence of HIV/AIDS-related stigma and discriminatory attitudes, with the degree of tolerance or intolerance varying with the
particular set of circumstances (e.g., whether the HIV-positive person was a family member or someone outside the family). The study concluded that the national information, education, and communication program needed to be strengthened in order to reach more people with HIV/AIDS education, and that programs aiming to promote more tolerant attitudes toward people living with HIV may be more effective if the human rights of those people were promoted and respected.

The social context is a primary consideration in any discussion on testing, especially because many people using public health facilities in the developing world tend to be socioeconomically disadvantaged. Botswana currently does not have any legislation specifically protecting the rights of people living with HIV or outlawing discrimination against them. Legislation designed to combat the spread of the virus has not kept pace with other anti-HIV/AIDS policies. Individual privacy is limited to some extent, for instance, through shared confidentiality policies, under which a person taking care of, living with, or otherwise coming into regular close contact with a patient must be informed about the patient’s medical condition if the patient is suffering from a communicable disease or has an infection that may be passed on if appropriate precautions are not taken. Unfair dismissal, refusal of employment, unfair treatment at the workplace, and other violations of human rights have not, up to now, attracted legislative intervention, despite calls for such intervention from civil society. In light of these gaps, there is a need to work toward the creation of a more supportive environment, which will include the requisite checks and balances accompanied by sufficient levels of information and education.

**Gender-Based Violence and Discrimination**

Gender inequality is ingrained in the social fabric of most societies, especially in the developing world, and Botswana is no exception. In a recent study by Physicians for Human Rights, the most basic finding was that deeply entrenched gender inequities perpetuate the HIV/AIDS pandemic in Botswana and Swaziland, the two countries with the highest HIV prevalence in the world. Legalized gender inequalities and discriminatory practices were stated to be the primary reasons why women continue to be disproportionately vulnerable to HIV/AIDS.

Because women likely comprise the majority of those tested for HIV, there have been concerns that RHT may result in increased violence and discrimination against women, but studies have not established a clear link. Women access health services more frequently and thus are subject to testing for HIV more often than men. Although this in itself is certainly not a negative factor, women may have more difficulty than men refusing a test, even when they are not psychologically ready to receive or accept a positive diagnosis. The violence and abuse faced by some women who are HIV-positive can further exacerbate the situation.

While preliminary data suggest that women in Botswana who test via RHT do not experience increased violence, the available data are limited both in nature and extent. However, this kind of information needs to be elicited from a greater variety of sources, including civil society organizations applying social
indicators like human rights standards. It should also be noted that most studies looking at this issue have been purely or largely quantitative in nature. These data are useful and appear to be promising; however, more qualitative studies are needed to capture the many nuances and complexities around issues like stigma and discrimination.

CONCLUSION

The lack of a clear and detailed law or policy on the process of RHT and the apparent vacuum that exists between policy and practice make further inquiry on implementation of RHT imperative. Systematic observation of RHT in practice, as well as in-depth interviews, may uncover more accurate information on patients’ experiences and feelings with regard to the testing process. As Rennie and Behets state:

Qualitative and quantitative social research are needed to shed light on issues surrounding the voluntariness associated with routine testing practices in the field, a task hampered by lingering uncertainties about the meaning of the term and its measurability . . . Until there is a greater body of evidence and conceptual clarity, it would be premature to assume that “voluntariness is at the heart” of routine HIV testing practices being implemented in resource-poor settings.

In 2007, the Botswana Network on Ethics, Law and HIV/AIDS (BONELA) conducted community-based dialogues with over 80 participants in four selected sites to assess human rights concerns related to RHT. Issues that arose included some confusion between routine and mandatory testing, with understanding of these concepts found to be inadequate. The quality of pre- and posttest counseling, the level of understanding of informed consent, and the observation of confidentiality were found to be significant concerns.

Some have expressed the view that more research is urgently needed to investigate whether the absence of informed consent and counseling affects people’s experiences of abuse or other negative outcomes as a result of testing HIV-positive. In Botswana, the adequacy of pretest counseling is questionable, because in practice, group counseling and simplified counseling measures have been adopted due to resource and time constraints. A 2006 study by the United States Agency for International Development, BONELA, and the POLICY Project clearly illustrates the need for exploration of how the 3 Cs are implemented in RHT.

The authors state that currently there is no data available in Botswana to evaluate how well staff has been trained to offer RHT, the manner in which HIV testing is offered, or the acceptance rates among patients in various clinical settings, other than PMTCT sites, for RHT.

The benefits of testing need to be weighed against the adverse consequences to the person being tested and to his/her family. In order to have maximum benefits, the policy of RHT should be analyzed in relation to its effectiveness, including cost-effectiveness, and should include the indicators of stigma, abandonment, violence, and other possible adverse outcomes of disclosure of one’s HIV status. The objectives of testing are important—in other words, it should be determined whether knowing one’s status necessarily translates into positive behavior change and the seeking out of care,
treatment, protection, and support. People should be empowered to make decisions that affect their lives, including those pertaining to their health care. What’s more, government and civil society should work toward creating an environment that protects and promotes human rights for all; this is the way that individuals will be allowed to take charge of their own destiny and in so doing, contribute to turning around the HIV epidemic in Botswana. It has been pointed out that the practice of RHT needs to be accompanied by aggressive training of health-care workers on policy, human rights, and public education to be successful. Moreover, research, monitoring, and evaluation of the RHT process need to be made more inclusive, through the integration of social indicators that paint a more comprehensive picture of people’s realities and experiences and take into account the nonhomogeneity of people—RHT should take place on a human rights and evidence-based foundation, against the backdrop of an enabling environment, and according to the specific contexts of different settings.

In Africa stigma has been identified as the key challenge to prevention and care efforts, and in Botswana stigma and discrimination are still widespread. Human rights protection and promotion are central to the response to HIV/AIDS and the achievement of universal access goals. The Declaration of Commitment on HIV/AIDS of the United Nations General Assembly Special Session on HIV/AIDS 2001 states that the realization of human rights and fundamental freedoms for all is essential in reducing vulnerability to HIV/AIDS. Although human rights should be the core element in the global HIV/AIDS struggle, human rights often constitutes the missing link.

In Botswana, RHT was introduced early in order to respond to the urgent needs arising from the HIV/AIDS crisis. Yet as HIV/AIDS prevention, treatment, care, and support efforts are scaled up elsewhere, issues around the implementation of PITC are becoming more complex. A cohesive and comprehensive response to HIV/AIDS also requires scaling up the protection and promotion of human rights within all HIV-related services. Research, policy, and program implementation and monitoring and evaluation also need to incorporate human rights considerations. This would include the creation of a supportive social, policy, and legal environment that protects individuals from all forms of stigma, discrimination, and violence so that increased funding and programmatic support could promote a comprehensive, human rights-based response.
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Couples HIV Counseling and Testing as an Entry Point to HIV Care

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HIV COUNSELING AND TESTING continues to be one of the most critically important interventions for both the prevention of HIV and the care of individuals living with HIV, their families, and their communities.1-4 HIV infection is largely asymptomatic and may not become symptomatic for up to 10 years.5 During the asymptomatic period, people living with HIV may not access prevention and care services if they do not know their HIV status, and may inadvertently transmit HIV to their sexual partners.6 Knowledge of one’s HIV status has been shown to modify sexual behavior in some high-risk groups. In a meta-analysis of 27 voluntary counseling and testing (VCT) studies, unprotected coitus and increased condom use among concordant HIV-positive and serodiscordant (i.e., one partner HIV-positive and the other HIV-negative) couples undergoing VCT decreased more than among those who were HIV-negative or did not undergo VCT.7 Counseling and testing appears to be most effective at reducing risk behaviors among HIV serodiscordant couples, since the HIV-negative partner is at high risk of HIV acquisition.4-8

HIV serodiscordance is common in sub-Saharan Africa, ranging from 3% to 20%,9-12 and most new HIV infections in this region occur in stable serodiscordant sexual partnerships.13-15 For example, in 2005 up to 80% of people living with HIV in Uganda did not know their HIV status because they either had not been tested for HIV or had been tested but did not receive their results.13 In addition, limited disclosure in sexual partnerships means that few partners know one another’s HIV status and are therefore not empowered to take risk reduction measures.16-18

There are a variety of proven models for the provision of HIV counseling and testing services, some of which may be used in combination. These include

- voluntary counseling and testing;
- routine diagnostic and clinical testing;
- prevention of mother-to-child transmission (PMCT);
- counseling and testing for adolescents/youth;
- family-based counseling and testing;
- couples HIV counseling and testing; and
- provider-initiated testing and counseling.

The focus of this chapter will be on couples HIV counseling and testing (CHCT) as an important entry point for HIV/AIDS care.
FAMILY-BASED APPROACHES TO COUNSELING AND TESTING

In the past, most models of HIV counseling and testing have tended to focus on individuals. A family-based approach to counseling and testing, as well as CHCT, are more recently developed interventions that target more than one individual in a household and couples and/or family members in particular. For instance, CHCT, in addition to providing HIV counseling and testing, can help build alliances between members of a presexual or sexual relationship. This model of counseling is aimed at empowering couples to make informed choices about HIV testing and to work together to cope with the implications of their test results.

Similarly, family-based counseling and testing empowers members of a particular household (sometimes including children) to receive HIV testing and counseling in a supportive, family-focused environment. This approach has been successfully used by many organizations to initiate antiretroviral therapy (ART), facilitate ART adherence, and reduce antiretroviral drug sharing by household members.

Both of these interventions are based on the belief that it is easier to transition HIV-tested couples and/or families from their initial counseling visit through to a broader referral network than when counseling and testing is done individually. A family-based approach can ease the process of disclosure to partners and family members and can help ensure that all those affected gain access to needed services.

Provider-initiated testing and counseling (PITC) is often used in conjunction with CHCT and is designed to integrate the routine provision of HIV counseling and testing services in a range of clinical settings. In this model, it is the health service provider that encourages and empowers their clients to undergo testing. This is in contrast to other counseling and testing interventions like VCT, in which clients seek out counseling and testing services voluntarily. In PITC, the client always has the right to opt out of taking the test.

The role of PITC in CHCT is to:

- provide the couple with the opportunity to get to know their results together so that they are better able to provide emotional support to one another and make informed choices based on their results;
- provide opportunities for couples to access immediate treatment (if warranted) and to make choices about future treatment options as well as other care and support services;
- facilitate identification of people that are eligible for ART; and
- help identify individuals in previously discordant relationships that have since seroconverted, so that they may access appropriate treatment, care, and support.

Deliberate steps need to be taken to ensure that the CHCT referral and HIV status disclosure process is properly managed and that follow-up measures are in place. If these additional steps are not included as part of the CHCT process, the counseling intervention alone will not be effective. The following sections outline some of the key benefits of CHCT as an entry point to HIV/AIDS care, treatment, and prevention services in resource-limited settings.

BENEFITS OF CHCT

The goal of CHCT is to empower couples to prevent the transmission of HIV and to help them provide care, support, and compassion for one another. Couples are also supported, when appropriate, to disclose their HIV status to their families as well as other members of their community. An additional benefit of CHCT is that when disclosure does occur, family and community support is actively sought and encouraged.

CHCT is appropriate for many types of couples, including presexual couples, dating or engaged couples, married or cohabitating couples,
polygamous couples, and reuniting couples.\textsuperscript{22} The benefits of providing CHCT within the context of HIV/AIDS programs are many. CHCT provides an opportunity to address opportunities for protection against infection for serodiscordant couples, and for the protection of current and future children. While transmission risk is highest in serodiscordant relationships, CHCT has been shown to greatly reduce rates of HIV transmission among serodiscordant couples.\textsuperscript{22}

CHCT also provides a safe environment for couples to discuss issues pertaining to risk reduction. By receiving information together, they are better equipped to make mutual, informed decisions. CHCT also helps couples identify appropriate additional services based on results, including care and support services like sexually transmitted infection management, ART initiation, and family planning.\textsuperscript{22}

CHCT as an Entry Point to HIV/AIDS Care
CHCT is a critical entry point to comprehensive HIV/AIDS care. Through CHCT, HIV care can be facilitated at the family, community, and institutional levels. The CHCT intervention is typically comprised of two sessions, the initial session and the second session. The initial session introduces the couple to CHCT and prepares them for their HIV test and the potential results (see Figure 1). The second session consists of additional counseling based on the couple's test results, discussion of risk reduction strategies, and, if one or both partners are found to be HIV-positive, referral to appropriate HIV-related services. The following sections highlight the importance of linking CHCT with different levels of care.

Family Level
Partners are provided with their HIV test results as part of the CHCT process. During the first and subsequent sessions, couples are empowered to discuss issues pertaining to risk reduction and to work out realistic risk reduction strategies based on their HIV status. This process can also help couples to consider the need for and benefits of both medical and psychosocial care and support. Acceptance of their HIV status allows the couple to openly discuss their status, either in a counselor-mediated or nonmediated environment, with close family members, including children, in an appropriate manner.\textsuperscript{23,24}

To facilitate the disclosure process, it is important that local and culturally age-appropriate role-playing scripts on methods of HIV status disclosure are provided during the counseling session. These scripts will help couples to initiate discussions with one another and with other family members and to prepare for any difficult questions or other issues that may come up during the disclosure process. Role-playing may sometimes be done with assistance from local folk storytellers or other HIV-tested couples who have previously disclosed their HIV status.

Community Level
CHCT enables the couple to mutually discuss their options for disclosure, especially regarding disclosure to extended family members, friends, and community members. CHCT also helps the couple cope with potential stigma and discrimination and can promote the couple's involvement in community initiatives through advocacy or involvement in community-based peer support groups. This level of community engagement is part of the referral process and can facilitate awareness of and access to other HIV care services. It should be noted that couples that are not ready or willing to disclose their HIV status to a wider network within their community are still eligible for referrals to other social services and support groups. However, these couples should be made aware that community disclosures can be an important tool for decreasing social stigmatization and for promoting couples'
confidence in accessing referral services. To help the couple identify services available in their community, the CHCT counselor should provide them with a standardized list of locally available HIV-related services.

**Institutional Level**

CHCT helps couples seek care and support from various health systems and organizations. The type of support sought may range from various forms of medical care to psychosocial support. In terms of medical care, CHCT provides couples with specific referrals to health-care providers for themselves and their family members, including children. Types of nonmedical referrals include professional and religious marriage counselors, social welfare support programs, NGO and charitable legal consultancies for will writing, life insurance and investment advice, and scholastic sponsorship programs for children. There is often a greater chance of compliance with these referrals in the context of CHCT due to the mutual agreements and understanding that is established between partners during the counseling session. Of equal importance, couples’ openness to HIV status disclosure can facilitate enrollment of children into HIV-related health services and other essential programs.

Establishing a referral process for a wide variety of HIV/AIDS service providers must be carefully planned and executed. In the context of a CHCT program, it is important that the people charged with establishing and/or strengthening...
the referral process possess the appropriate skill set. Maintaining contact with an ever-changing network of providers and establishing channels for follow-up can be extremely time consuming as well as challenging, even under the best conditions.

**CONCLUSION**

**Lessons Learned**
The following are some of the lessons culled from the experiences of CHCT providers in resource-limited settings:
- CHCT is a critical intervention for both prevention and care. It assists couples in making appropriate prevention and care choices for themselves and their families, especially children.
- CHCT facilitates disclosure by having partners learn their HIV serostatus together in a supportive environment.
- CHCT is a way to address the challenges and dynamics of HIV serodiscordance among couples.
- It is challenging to introduce CHCT in rural communities. Most people in these areas still prefer to test as individuals due to fear of stigma and discrimination.
- In the era of ART, CHCT provides an opportunity for members of HIV-positive couples as well as HIV-discordant couples to be the medical companion for their partner.

- CHCT can be integrated into various types of care, treatment, and prevention interventions.
- CHCT can serve as an entry point to care for the couple’s children, should they test positive for HIV or have other unmet needs.

**Recommendations**

There is need for various stakeholders, such as grassroots health organizations and medical research institutions, as well as policy and decision makers, to advocate for incorporation of CHCT into a range of HIV/AIDS prevention and care interventions. Such an approach is critical in facilitating disclosure among partners and in ensuring access to HIV care for other family members. Integration of CHCT into various programmatic interventions, such as PMTCT and home-based care, provides opportunities for couples to care for and support one another and their children and extended families. Integration may be achieved through the forging of referral linkages from a CHCT provider to other HIV-related programs and services within the community.

CHCT can also be used as a tool to address the challenges of stigma and discrimination in general and between couples and families in particular. This approach can be promoted through the provision of CHCT training to health providers and by facilitating subsequent referrals from such health providers.


21. Evering-Watley M. What counselor training assessments can inform us about the challenges of providing counseling and testing services to serodiscordant couples in sub-Saharan Africa. Presented at: 2006 Annual PEPFAR Implementers’ Meeting; June 12-15, 2006; Durban, South Africa.


PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV
Issues in Mother-to-Child Transmission of HIV: Breastfeeding Transmission

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In order to approach the low rates of mother-to-child HIV transmission seen in developed countries, the as-of-yet unresolved questions surrounding the risks and benefits of breastfeeding among HIV-positive mothers in resource-limited settings must be addressed. Yet there is no clear-cut, “one size fits all” solution. Despite its associated risk of HIV transmission, breastfeeding plays an important role in maintaining child health in many of the same settings that are severely affected by HIV and AIDS. The avoidance of breastfeeding can have profoundly negative effects on the health and survival of young children, leading to recurrent respiratory infections, gastrointestinal diseases, otitis media, atopic dermatitis, and malnutrition.1-4 These negative impacts are especially felt among the most economically disadvantaged populations. In this chapter, we will discuss the role of breastfeeding in the transmission of HIV from mother to child, and we will present recent evidence regarding various methods to reduce the health risks associated with different infant feeding practices for infants born to women living with HIV.

Routes and Risks of Mother-to-Child Transmission

More than 90% of HIV infections in children are attributed to mother-to-child transmission of HIV (MTCT). In the absence of any intervention, MTCT rates can vary from 15% to 30% without breastfeeding and can reach 30% to 45% with prolonged breastfeeding, depending on population and regional differences.5 Women at greatest risk of transmitting HIV to their children are those with a high HIV viral load, which is often associated with immunosuppression and clinical disease progression.6

Transmission can take place during pregnancy, labor or delivery and during breastfeeding, and can therefore affect the fetus, newborn, infants, and young children (Figure 1). The risk of MTCT varies among individuals and populations and can be attributed to a variety of maternal, obstetrical, fetal, neonatal, and viral factors, as well as infant feeding methods.7 Maternal risk of transmitting HIV to the infant is determined by her immunological status, clinical staging, sexual behavior, and nutritional status, all of which affect HIV viral dynamics. Risk of MTCT during labor and delivery is also potentially
influenced by the presence of ascending infections due to longer duration (more than four hours) of membrane rupture, exposure to maternal blood during intrapartum hemorrhage and certain obstetric procedures, invasive fetal monitoring, and mode of delivery. Intrauterine risk of transmission is influenced by fetal immaturity, genetic susceptibility, multiple pregnancy, and aggressive suctioning in the neonate could also increase neonatal vulnerability to HIV transmission through ingested contaminated maternal fluids and breast milk.

**RISKS AND BENEFITS OF BREASTFEEDING**

A meta-analysis conducted by the World Health Organization (WHO) in 2000 confirmed that breastfeeding is associated with reduced infant mortality in developing countries (the analysis did not look at HIV status). The analysis found that in infants who were not breastfed, the risk of dying was 4 to 6 times higher in infants under 4 months compared with those who were breastfed; the risk of death decreased with increasing age. A 2003 *Lancet* child survival series paper asserted that among the numerous basic interventions available to prevent the more than 10 million deaths occurring annually among children under 5 years of age in developing countries, breastfeeding was the most efficacious, estimated to prevent 13% of child deaths. Breastfeeding was found to be superior to several basic public health interventions including clean water, sanitation, and personal hygiene; Hib and measles vaccines; and vitamin A and zinc supplementation. Furthermore, secondary data analysis from a multicenter, randomized, controlled trial of vitamin A supplementation in three developing countries showed that nonbreastfed infants had a 10 times higher mortality risk compared to predominantly breastfed infants by 6 months of age. It should also be emphasized that breastfeeding is critical to health throughout the human lifecycle, as its imprint is discernible throughout childhood and into adulthood.
Providing appropriate counseling to HIV-positive women enables them to make infant feeding choices that are best suited to their circumstances. Breastfeeding is the optimal form of infant feeding for at least six months, and ideally for up to two years, but it also can transmit HIV to the infant. Avoidance of breastfeeding and use of replacement feeding (most often commercially obtained infant formula or other breast milk substitutes such as cow’s or goat’s milk) carries no risk of transmitting HIV but does put the infant at risk of exposure to harmful agents. These agents may be present in weaning foods (e.g., black tea without sugar or milk, rice water, maize porridge) and can also be present in the water used to make the formula. Risks of slowed growth, malnutrition, diarrhea, hospitalizations, and death are all associated with the use of formula in developing countries. The main factor determining which form of infant feeding is most suitable is the capacity of the mother and/or other caregivers to prepare the formula hygienically.

Role of Breastfeeding in HIV Transmission

There is absolutely no doubt that breastfeeding contributes a substantial proportion of the overall transmission of HIV-1 from the mother to the infant. The exact proportion of transmission attributable to breastfeeding varies according to a number of different factors (e.g., maternal CD4 count, duration and type of breastfeeding), which will be discussed in more detail later in this chapter. The only randomized controlled trial to assess breastfeeding transmission, undertaken in Nairobi, Kenya, by Nduati and colleagues in 2000, found the proportion of HIV transmission attributable to breastfeeding to be 44%. This same study also found an MTCT rate of 36.7% over 24 months in breastfeeding women, compared to an MTCT rate of 20.5% in those who formula fed. There were no ARVs available in Nairobi at the time; therefore, these results reflect a natural history of the disease. The most simple interpretation of these data, which does not include a consideration of other risk factors involved in the transfer of HIV from mother to infant, is that transmission attributable only to breastfeeding is roughly 16.2%.

The findings from a nonrandomized trial in Durban, South Africa, conducted during roughly the same period, gave almost identical results: an MTCT rate of 35.9% in breastfeeding women and 19.4% in those who formula fed. There have been a number of other studies from West Africa, South Africa, Kenya, Malawi, and Uganda, among other places, that have confirmed these findings. In a meta-analysis of individual patient data from 4,085 infants born to HIV-1-infected women in high-prevalence, developing countries, the main findings on MTCT were similar to those in the Durban study, although the rates of transmission were expressed differently: 8.9 transmissions per 100 child-years of breastfeeding. An important result from this meta-analysis, at variance with other reports suggesting higher MTCT rates during the early weeks after birth, was that the rate of transmission was found to be constant throughout the 18-month breastfeeding period; in other words, transmission was observed to continue steadily as long as breastfeeding continued. Thus, a more practical expression of these findings, based on the meta-analysis results, is that HIV transmission occurs at a constant of about 0.74% for every month of breastfeeding.

Breastfeeding versus Formula Feeding

A rising tide of new information from published and ongoing studies throughout sub-Saharan Africa has focused attention on the hazards of avoiding breastfeeding altogether or stopping breastfeeding too early for HIV-exposed infants. The harmful effects of breastfeeding avoidance have mostly...
and health system investments in promoting and supporting the wider use of formula and the curtailment of breastfeeding among women living with HIV, there is questionable, if any, benefit in switching away from breastfeeding.

In Botswana, one of the more economically advantaged African countries, a catastrophic outbreak of diarrhea occurred during early 2006 and resulted in many fatalities that were ascribed to the use of infant formula. The government had started providing free formula to HIV-positive mothers in 1999 as part of its MTCT prevention program. The largest risk factor for these deaths was found to be “not breastfeeding” (OR 50.0; 95% CI, 4.5-100). The PEPI (Post-Exposure Prophylaxis to the Infant) trial in Malawi, in which three prophylactic ARV regimens are being tested in breastfeeding infants, has shown an increased incidence of diarrhea and associated mortality soon after discontinuing breastfeeding, compared to a historical control with continued breastfeeding. The Kisumu Breastfeeding study (KiBS) in Kenya, and the Breastfeeding, Antiretrovirals and Nutrition (BAN) study in Malawi, which are testing the effects of maternal combination antiretroviral therapy (ART) on breastfeeding transmission of HIV, have also reported growth faltering, increased incidence of diarrhea, and more

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**Table 1. Risk Factors for Postnatal HIV-1 Transmission**

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Breast Milk Factors</th>
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<tbody>
<tr>
<td>▪ Younger maternal age, lower parity</td>
<td>▪ Plasma and breast milk viral load</td>
</tr>
<tr>
<td>▪ Maternal seroconversion during lactation</td>
<td>▪ Duration of breastfeeding</td>
</tr>
<tr>
<td>▪ Material immune status (CD4)</td>
<td>▪ Breast health:</td>
</tr>
<tr>
<td></td>
<td>▪ Mastitis (clinical and subclinical)</td>
</tr>
<tr>
<td></td>
<td>▪ Breast abscess</td>
</tr>
<tr>
<td></td>
<td>▪ Cracked nipples</td>
</tr>
<tr>
<td>Infant Factors</td>
<td>Viral Factors</td>
</tr>
<tr>
<td>▪ Infant health (oral thrush, prematurity)</td>
<td>▪ Plasma viral load</td>
</tr>
<tr>
<td>▪ Pattern infant feeding (exclusive versus mixed)</td>
<td>▪ Viral clade-C</td>
</tr>
</tbody>
</table>

been seen among HIV-uninfected infants. This group demands serious attention as prevention of mother-to-child transmission (PMTCT) programs continue to reduce the incidence of perinatally-acquired pediatric HIV infections and increase the proportion of HIV-exposed, uninfected infants. A randomized controlled trial in Botswana showed that formula feeding did reduce MTCT as expected, but that replacement feeding increased infectious-disease mortality by 7 months of age. At 18 months, more breastfed babies had become HIV-infected, but more formula-fed infants had died; the combined index of HIV transmission and mortality (i.e., HIV-free survival) was therefore similar between the group assigned to formula and the group in the breastfeeding arm. Similarly, in a study from Zambia, early cessation (at 4 months) of breastfeeding revealed no advantage over continued breastfeeding for longer periods. The 24-month HIV-free survival in the group of infants who ceased breastfeeding at 4 months was similar to the group of infants who continued breastfeeding (83% vs. 81%). In a study from Côte d’Ivoire, women were allowed to choose either formula feeding from birth or exclusive breastfeeding from birth. The HIV-free survival rate was similar in the two groups in the second year of life. These studies demonstrate that despite the financial, social,
hospitalizations following cessation of breastfeeding at about six months of age. In a study in Kampala, Uganda, serious gastroenteritis followed breastfeeding cessation during a trial on passive immunization with immunoglobulins to prevent breastfeeding transmission.  

There is evidence of significant benefit for continued breastfeeding of HIV-infected infants from two studies, one from South Africa and the other from Zambia. In the Zambian study, conducted among 153 HIV-infected infants, the mortality at 12 months was found to be higher in the group that stopped breastfeeding at 4 months (57%), compared with the group that continued breastfeeding (29% [P<.01]).

**PREVENTION OF BREASTFEEDING TRANSMISSION**

The factors that increase the risk of breastfeeding transmission of HIV are given in Table 1. Measures that can be used to reduce these risks are listed in Table 2, the most important of which are the management of pregnant women with low CD4 counts, the promotion of “exclusive breastfeeding” and avoidance of “mixed breastfeeding,” the use of ARVs for the lactating mother, and strengthening

<table>
<thead>
<tr>
<th>Table 2. Prevention of HIV-1 Transmission from Breastfeeding</th>
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<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
</tr>
<tr>
<td>- Prevention of HIV infection in women of childbearing age</td>
</tr>
<tr>
<td>- Prevention of unintended pregnancies (contraception, termination of pregnancies)</td>
</tr>
<tr>
<td><strong>Infant Feeding Options</strong></td>
</tr>
<tr>
<td>- Exclusive breastfeeding for six months</td>
</tr>
<tr>
<td>- Exclusive breastfeeding with early cessation</td>
</tr>
<tr>
<td>- Measures to reduce mastitis and breast milk stasis</td>
</tr>
<tr>
<td>- Measures to improve breastfeeding practice and breast health</td>
</tr>
<tr>
<td>- Treatment of breast milk (heat, antivirals)</td>
</tr>
<tr>
<td>- Breast milk banks</td>
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<tr>
<td>- Wet-nursing by HIV-uninfected women</td>
</tr>
<tr>
<td><strong>Immunophylaxis</strong></td>
</tr>
<tr>
<td>- Passive: specific antibodies, immune globulins</td>
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<tr>
<td>- Active: vaccination at birth</td>
</tr>
<tr>
<td><strong>Chemophylaxis</strong></td>
</tr>
<tr>
<td>- Antiretrovirals (ARVs) to infant or mother or both through breastfeeding</td>
</tr>
<tr>
<td>- Effective ARV regimens for all HIV-positive pregnant women, and combination antiretroviral therapy for those with advanced immunosuppression</td>
</tr>
<tr>
<td><strong>Policy Options</strong></td>
</tr>
<tr>
<td>- Enforce the “International Code of Ethics for Marketing of Breast Milk Substitutes”</td>
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<tr>
<td>- Implement the “Baby-Friendly Hospital Initiative”</td>
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<tr>
<td>- Replace budgetary outlays on “Free Formula” with investments in improved health services, community outreach programs, job creation, income generation schemes, and so forth</td>
</tr>
<tr>
<td>- Stringent selection, suitable training, continuous mentorship, regular monitoring, fair remuneration, and an identifiable career pathway</td>
</tr>
<tr>
<td>- Optimized counseling according to the text and spirit of WHO Guidelines</td>
</tr>
</tbody>
</table>

of existing global policies on breastfeeding that include measures to improve breastfeeding practice and breast health. These policies should continue to promote breastfeeding for six months or longer for women who are HIV-negative or whose HIV status is unknown. In addition, these policies should ensure initial and ongoing counseling for HIV-positive women regarding guidance on infant feeding choice or change in practice based on affordability, feasibility, acceptability, sustainability and safety (AFASS) of replacement feeding.

There is convincing evidence that the type of breastfeeding influences rates of HIV transmission. “Exclusive breastfeeding,” defined as providing the infant with breast milk and prescribed medicine but no water, other liquids, or food, has been associated with markedly lower HIV transmission rates; “mixed breastfeeding” or “nonexclusive breastfeeding” carries the highest risk of transmission. A Durban study in 1999 showed that the MTCT at six months in exclusively breastfeeding mothers (19.4%) was similar to that in mothers who were formula feeding (19.4%) and considerably lower than in those who were mixed breastfeeding (26.1%).  This study provided the first evidence indicating that the type of breastfeeding promoted by WHO and others as optimal for infant growth and development well before the arrival of HIV is also optimal for HIV-positive mothers. However, the evidence from this study was not enough to spur a change in policy, as the study had set out to do a vitamin A trial and not specifically assess the value of “exclusive breastfeeding” among HIV-positive mothers. In addition, the mothers had only breastfed exclusively for three months, rather than the maximum period of six months.  

The same group behind the Durban study recently completed a much more carefully designed study involving 2,722 mothers and infants.  

In the more recent study, roughly half of the women were HIV-positive, all the women were vigorously encouraged to breastfeed exclusively, and there was a rigorous determination of the breastfeeding pattern. There were two important outcomes from this study related to breastfeeding: (1) the health promotion intervention was successful in changing women’s behavior from “mixed” to “exclusive” breastfeeding (from about 6% of the women who breastfed exclusively before the intervention to 66% after) and (2) the rate of HIV transmission from 4 weeks to 6 months in the exclusively breastfed group of infants was found to be 4%. The rate of HIV transmission among breastfed infants who also received solids (homemade cereals and porridges) anytime after birth was 10 times higher than the rate among those who exclusively breastfed. The rate of HIV transmission among those who formula fed and breastfed interchangeably was twice as high as for exclusive breastfeeding.  

A study in Zimbabwe observed HIV transmission rates among infants who were exclusively breastfed (EBF; the infant consumed only breast milk and no other liquids, milks or solid foods except vitamins or prescribed medicines, according to mothers’ reports at all three study timepoints, or at two of three timepoints), infants who were predominantly breastfed (PBF; the infant’s predominant source of nourishment was breast milk, but nonmilk liquids, such as water, tea, juice, and cooking oil, were also consumed according to mothers’ reports at all three study timepoints, or at two of three timepoints), infants who were mixed breastfed (MBF; the infant consumed breast milk and either nonhuman milks, such as infant formula or cows’ milk, or solid or semisolid foods or both, according to mothers’ reports at one or more timepoints). Transmission rates between 6 weeks

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*Breastfeeding can be “exclusive” for up to six months, as mother’s milk is sufficient to provide all the nutrients necessary for infant growth during this period. After six months, other foods must be introduced to meet the needs of the growing child.*
and 6 months were reported to be 1.3% in the EBF group; early mixed breastfeeding was associated with a 4- to 2.5-fold higher risk of transmission between 6 months and 18 months, respectively.31 There was a dose effect: lesser degrees of “exclusivity” among infants who were predominantly breastfed were associated with higher rates of HIV transmission.

Research projects in Uganda, Côte d’Ivoire, and Zambia have confirmed that reductions in HIV transmission are possible through exclusive breastfeeding.22,32,33 Furthermore, recent studies on exclusive breastfeeding among infants born to HIV-positive mothers in South Africa, Malawi, and Zambia, and among infants born to women from the general population, have shown that exclusive breastfeeding is associated with improved infant survival.11,22,34,35

Antiretroviral Drugs during Pregnancy and Postpartum

There is overwhelming evidence that ARVs are highly efficacious in preventing the transmission of HIV from mother to child. ARVs can be effective either as a long-term treatment or short-term prophylaxis in pregnant women with established chronic HIV infection or as prophylaxis to infants after exposure to HIV. Since the world’s first clinical trial (Pediatric AIDS Clinical Trials Group [PACTG 076]) in Europe and the United States in 1994 investigating the use of zidovudine (ZDV) from 14 weeks into pregnancy for the mother to 6 weeks post-delivery for the infant, together with breastfeeding avoidance, no other clinical trial using a single agent has achieved a similar rate of efficacy (67%) in reducing MTCT.6 Two other studies in developed countries highlighted the role of combination drugs as opposed to single drugs in achieving a five-fold reduction in MTCT.27,28 The efficacy and safety findings from these groundbreaking studies have contributed to policy changes in the United States as well as other developed countries.39 The adoption of these combination ARV regimens has resulted in a dramatic and sustained reduction of MTCT rates of less than 2% in these settings.40

There were several initial challenges to implementing the long and complex PACTG 076 regimen in developing countries. A key challenge was that of addressing breastfeeding transmission of HIV. As a result, a series of 16 more practical, safe, and effective short-course regimens were subsequently evaluated in developing countries (Tables 3 and 4). Regimens evaluated included those with shorter courses of nucleoside reverse transcriptase inhibitors (NRTIs), such as ZDV, alone or in combination with other drugs; non-nucleoside reverse transcriptase inhibitors (NNRTIs) alone, such as nevirapine (NVP); and others in which NVP was combined with NRTIs (e.g., ZDV, lamivudine [3TC]). These regimens were evaluated over varying durations and given during the antepartum, intrapartum, and postpartum periods. The common goal of each study was to achieve the highest reduction in MTCT using the most cost-effective and practical regimen. Results from the trials in nonbreastfeeding populations using shorter regimens of ZDV alone or in combination with NVP achieved perinatal transmission rates of less than 10%.21,41-45

A second generation of studies in breastfeeding populations using NVP alone or in combination with ZDV or 3TC recorded transmission rates of between 2% and 20%.46-55 The single-dose NVP (sdNVP) regimen was found to reduce transmission by 42% to a rate of 12% at 6 weeks.47 Because of the cost-effectiveness and simplicity of the single-dose regimen, it has been recommended by WHO as the minimal regimen to be provided in developing countries when there is no access to ART or combination ARVs for MTCT prophylaxis.56 The efficacy of sdNVP is maintained into the second year of life.57 The Thailand Perinatal HIV Prevention Trial-2 (PHPT-2) study using ZDV alone from 28 weeks in pregnancy, or ZDV in combination
### Table 3. Options for Antiretroviral Prophylaxis for Prevention of Mother-to-Child Transmission in Nonbreastfeeding Populations and Transmission Rates

<table>
<thead>
<tr>
<th>Antepartum (weeks)</th>
<th>Antiretrovirals (ARVs)</th>
<th>Intrapartum ARVs</th>
<th>Postpartum ARVs and Transmission Rates (%)</th>
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<tbody>
<tr>
<td></td>
<td>&lt;14</td>
<td>14–28</td>
<td>28–34</td>
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<tr>
<td>Thailand PHPT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
<td></td>
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<tr>
<td>Thailand CDC-1999&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>Thailand PHPT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>PACTG076&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>Thailand PHPT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>Botswana (HARVARD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>Thailand PHPT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>Florida CDC-2004&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>Thailand Ministry&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>Thailand PHPT-2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
<td></td>
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<tr>
<td>Thailand PHPT-2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<tr>
<td>France ANRS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
<td></td>
<td></td>
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<tr>
<td>PACTG316&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV</td>
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<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> = Antiretroviral prophylaxis for mother only
<sup>b</sup> = Antiretroviral prophylaxis for infant only

**Notes:**
- PI = protease inhibitor; ZDV = zidovudine; 3TC = lamivudine; NVP = nevirapine
- Transmission rates may vary depending on the specific regimen and population.

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**Table Notes:**
- Data compiled from various studies and guidelines published between 1997 and 2005.
- Transmission rates are generally lower in breastfeeding populations due to the protective effects of breastfeeding.
- The use of antiretroviral prophylaxis is a critical component in reducing vertical transmission of HIV.

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**Reference:**
- From The Ground Up: Establishing a Framework for Success
Table 4. Options for Antiretroviral Prophylaxis for Prevention of Mother-to-Child Transmission in Breastfeeding Populations and Transmission Rates

<table>
<thead>
<tr>
<th>Antepartum (weeks)</th>
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<th>Intrapartum ARVs</th>
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<td>&lt;14</td>
<td>14–28</td>
<td>28–34</td>
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<tr>
<td>Malawi (NVAZ)</td>
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<td>HIVNET 012</td>
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<tr>
<td>South Africa (PEP)</td>
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<tr>
<td>Ivory Coast ANRS</td>
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<td>Zimbabwe</td>
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<tr>
<td>Ivory Coast CDC</td>
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<td>Malawi (NVAZ)</td>
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<td>Zimbabwe</td>
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<td>Malawi (NVAZ)</td>
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<td>South Africa (PEP)</td>
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<td>PETRA</td>
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<td>Malawi (NVAZ)</td>
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<td>SAINT</td>
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<tr>
<td>HIVNET 012</td>
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</tbody>
</table>

ZDV = zidovudine; 3TC = lamivudine; NVP = nevirapine; ddl = didanosine; m = mother; i = infant

= Antiretroviral prophylaxis for mother only
= Antiretroviral prophylaxis for infant only
= Antiretroviral prophylaxis for mother and infant

continued on next page
Table 4. Options for Antiretroviral Prophylaxis for Prevention of Mother-to-Child Transmission in Breastfeeding Populations and Transmission Rates (cont.)

<table>
<thead>
<tr>
<th>Antepartum (weeks)</th>
<th>Antiretrovirals (ARVs)</th>
<th>Intrapartum ARVs</th>
<th>Postpartum ARVs and Transmission Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiretrovirals (ARVs)</td>
<td></td>
<td>1 week (w)</td>
</tr>
<tr>
<td>&lt;14</td>
<td></td>
<td>ZDV</td>
<td>ZDV+3TC</td>
</tr>
<tr>
<td>14–28</td>
<td></td>
<td></td>
<td>ZDV+3TC</td>
</tr>
<tr>
<td>28–34</td>
<td></td>
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<td>ZDV+3TC+3TC</td>
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<tr>
<td>≥34–36</td>
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<td></td>
<td>ZDV+3TC+3TC</td>
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<td>Labor</td>
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<td>ZDV+3TC+3TC</td>
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<tr>
<td>1 week (w)</td>
<td></td>
<td></td>
<td>ZDV+3TC</td>
</tr>
<tr>
<td>4w</td>
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<td>ZDV+3TC</td>
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<tr>
<td>6w</td>
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<td>ZDV+3TC</td>
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<tr>
<td>2mo</td>
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<td>ZDV+3TC</td>
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<td>6mo</td>
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<td>ZDV+3TC</td>
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<tr>
<td>8w–24mo</td>
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<td></td>
<td>ZDV+3TC</td>
</tr>
<tr>
<td>15mo–24mo</td>
<td></td>
<td></td>
<td>ZDV+3TC</td>
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</tbody>
</table>

SAINT53     ZDV ZDV+3TC     9.3
Botswana (HARVARD)53    ZDV ZDV+NVP ZDV+NVP ZDV     9.1
PETRA52     ZDV+3TC ZDV+3TC     8.9 18.1
Ivory Coast ANRS52    ZDV ZDV+NVP ZDV+NVP     6.5
PETRA52    ZDV+3TC  ZDV+3TC     5.7 14.9
Tanzania (MITRA)52    ZDV+3TC ZDV+3TC ZDV+3TC  3TC  5.1
Ivory Coast ANRS52    ZDV+3TC ZDV+3TC+NVP ZDV+NVP     4.7
Botswana (HARVARD)52    ZDV ZDV+NVP ZDV+NVP ZDV     4.3
Botswana (HARVARD)52    ZDV ZDV ZDV+NVP ZDV     3.7
Uganda, Rwanda58 (SIMBA) | ZDV+ddl | ZDV+ddl ZDV+ddl (m) | NVP | 2.4 |
Uganda, Rwanda58 (SIMBA) | ZDV+ddl | ZDV+ddl ZDV+ddl (m) | 3TC |      |
Uganda, Rwanda58 (SIMBA) | ZDV+ddl | ZDV+ddl ZDV+ddl (m) | 3TC |      |

ZDV = zidovudine; 3TC = lamivudine; NVP = nevirapine; ddI = didanosine; m = mother; i = infant

= Antiretroviral prophylaxis for mother only
= Antiretroviral prophylaxis for infant only
= Antiretroviral prophylaxis for mother and infant
Prevention of Mother-to-Child Transmission of HIV

This therapeutic indication for the mother may translate into a prophylactic tool for the breastfeeding baby.

It has been well established in developed countries that maternal combination ART will reduce MTCT to about 2% or less. To date, there is no firm evidence that prophylactic maternal ART in women with CD4 counts above 200 cells/mm³ can reduce breastfeeding transmission, given the persistence of HIV viral reservoirs in breast milk cells despite ART, differences in mammary penetration of ARVs into the breasts, and likely fluctuations in availability of these drugs to the breastfeeding infant. However, there has been preliminary evidence that maternal ART for treatment-eligible women may reduce postnatal HIV transmission, based on program data from Botswana, Mozambique, and Uganda.

Potential (Unproved) Prophylactic Measures

There are a number of studies under way that are addressing the prophylactic role of HIV vaccines and passive immunoprophylaxis with HIV antibodies administered to breastfeeding infants to minimize transmission through this route. ARV prophylaxis given to breastfeeding infants is being investigated at a number of sites in Africa.

Breastfeeding, HIV, and Policy Changes

The studies cited in this chapter have allowed for improved and more accurate infant feeding counseling for women, allowing them to make informed choices about feeding methods for their infants that are appropriate to their circumstances. Key recommendations resulting from these findings are included in this section.

National policies on HIV and infant feeding should be framed and implemented according to the best available and most appropriate...
scientific evidence and global policies on breastfeeding should be reinforced (see “Policy Options” in Table 2). In most developing countries the prevention of breastfeeding transmission of HIV requires a boosting of health services and the health infrastructure; this is critical since only a fraction of the mothers and infants who are eligible for HIV prevention and treatment services currently receive them. Key requirements for the scale-up of PMTCT services include improvements to and maintenance of health facilities; reasonable access to health care; community acceptance of state and other programs; recruitment, training, and retention of appropriate health professionals and health workers; and investments in large-scale (roads, transport, employment opportunities) and small-scale (clinics, equipment, clean water) infrastructure.63

Counselors need to be updated on the risks of HIV transmission if women choose breastfeeding. They may need to be retrained to accurately represent the risks according to the duration of breastfeeding to HIV-positive pregnant women in order to allow them to make the best choice based on a personal evaluation of risks. Women should be supported antenatally in making their infant feeding choice, as well as postnatally in sustaining or changing their choice.

HIV-positive women, as is the case for all women, should be afforded the right to choose the infant feeding option that is most appropriate for them. This can only be ascertained after effective counseling and in accordance with WHO guidelines that stress that replacement feeding is recommended only when it meets the AFASS criteria (acceptable, feasible, affordable, sustainable, and safe).64 The following recommendations (based on the views of investigators of the Durban study11) take into account the basic rights of all women and evidence from related studies mentioned previously and others cited here:

- National policies on infant feeding need to be regularly reviewed.
- Careful recruitment of counselors to assess literacy, basic mathematical skills, and potential for acquiring counseling skills, together with training according to the latest WHO guidelines on infant feeding, are critical to improving “exclusive breastfeeding” rates.
- Antenatal counseling sessions—three sessions in the first two weeks postnatally and two weekly counseling sessions thereafter—can help to achieve high exclusive breastfeeding rates.11
- Counselors need to be updated on the risks of HIV transmission for women who exclusively breastfeed for six months and should be retrained to represent these risks accurately to HIV-positive pregnant women, thus empowering their clients to make the best choice based on a personal risk evaluation. This particularly relates to women whose CD4 counts are greater than 200 cells/mm³. Counselors need to be similarly briefed on the risks of nonbreastfeeding with respect to infant survival (i.e., increased early mortality risk).
- Policy and budgets can be revised to promote and support exclusive breastfeeding as a child survival intervention, knowing that it is achievable and carries less risk of transmission than mixed feeding. This action would improve survival in both HIV-exposed infants when the mother chooses to breastfeed and also in the larger HIV-uninfected and unexposed infant population.
- Policies on free provision of infant formula within clinics for the purposes of PMTCT should be reviewed in light of the latest evidence.65

The following additional notes on infant feeding choice should be considered:

- Some HIV-positive women are able to safely use replacement feeding as part of a PMTCT program. However, this is generally the case only in more developed, urban environments where there is dependable access to clean water. Programmatic data, largely anecdotal
and unpublished in the peer-reviewed literature, does report the safe use of infant formula with minimal impact on diarrheal incidence, malnutrition, and death. Similarly, some women in rural or even poor urban settings can perform safe replacement feeding in spite of conditions that are far short of the recommended AFASS criteria.

- Modeling papers suggest that the use of formula by HIV-positive women to prevent MTCT may carry a lower risk of contamination and concomitant morbidity and mortality in some settings as compared to others. The threshold-determining settings that are “safe” for formula use can be defined by the infant mortality rate criteria.66

- Data indicate high risks of postnatal transmission associated with mixed feeding, which is likely to be a direct consequence of free formula provision. Unless very substantial support systems are in place both within the health sector and in communities to promote and support exclusive replacement feeding, the hazards of mixed feeding will persist.

- Some HIV-positive women are likely to choose a free formula option even when they live in circumstances that are nonsupportive and mitigate the benefits of safe and exclusive formula feeding. These women may be likely to mix-feed because of local pressures and expectations, or to prepare and feed their infants in a dangerous manner by incorrect reconstitution of powder resulting in over- or underconcentrated feeds that lead to obesity or failure to thrive, respectively. Incorrect reconstitution could frequently occur as a result of use of an inaccurate or nonspecific powder scoop for measure or feeding bottle of a variable volumetric measure or lack of training on preparation of formula feeds.

- Some HIV-positive women are likely to choose the free formula option because of a perceived financial benefit. If the woman chooses not to exclusively formula feed, then she may not be able to access support for exclusive breastfeeding and will almost certainly end up mix-feeding her infant. Support for “exclusive breastfeeding” should include trained peer counselors who would (1) provide antenatal and postnatal education, (2) increase confidence in women that breast milk is safest for an infant, (3) ensure proper attachment to breast such that the infant can effectively suckle, (4) help resolve difficulties with breastfeeding, and (5) educate on breast care.

** Summary **

The policy implications of this new information on HIV and infant feeding are partly clear but also require further research to establish the options for feeding after six months. For the present, the following recommendations proposed in a 2007 WHO consensus statement on infant feeding are suggested:

- The most appropriate infant feeding option for an HIV-positive mother should continue to depend on her individual circumstances, including her health status and the local situation, but should take greater consideration of the health services available and the counseling and support she is likely to receive.

- Exclusive breastfeeding is recommended for HIV-positive women for the first six months unless replacement feeding meets AFASS criteria for them and their infants before that time.

- When replacement feeding meets AFASS criteria, avoidance of all breastfeeding by HIV-positive women is recommended.

- At six months, if replacement feeding still does not meet AFASS criteria, then continuation of breastfeeding with additional complementary foods is recommended, while the mother and baby continue to be regularly assessed. All breastfeeding should stop once a nutritionally
adequate and safe diet without breast milk can be provided.

• Whatever the feeding decision, health services should follow up with all HIV-exposed infants and continue to offer infant feeding counseling and support, particularly at key points when feeding decisions may be reconsidered, such as the time of early infant diagnosis and at six months of age.

• Breastfeeding mothers of infants and young children who are known to be HIV-positive should be strongly encouraged to continue breastfeeding.

• Governments and other stakeholders should revitalize breastfeeding protection, promotion, and support in the general population. They should also actively support HIV-positive mothers who choose to exclusively breastfeed, and take measures to make replacement feeding safer for HIV-positive women who choose that option.

• Research findings regarding interventions found to reduce breastfeeding transmission of HIV before and after weaning should be rapidly integrated into public health services.

• Likewise, research findings that improve the safe and hygienic preparation of replacement foods should be rapidly integrated.

• National programs should provide all HIV-exposed infants and their mothers with a full package of child survival and reproductive health services as follows:

  • For the majority of women who are HIV-positive, live in developing countries, and choose to breastfeed: access to the most effective and cost-efficient ARV regimen that reduces perinatal transmission of HIV; exclusive breastfeeding for six months; reassessment of AFASS criteria at six months, and continued breastfeeding if justified by these guidelines; optimal use of local resources for complementary feeding after weaning; access to community and clinical services for routine child immunization, cotrimoxazole prophylaxis, treatment of common childhood diseases, and ART.

  • For a minority of women who are HIV-positive, live in developing countries, and choose not to breastfeed: access to the most effective and cost-efficient ARV regimen that reduces perinatal transmission of HIV; replacement feeding in place of breastfeeding if AFASS criteria are met; support for improving household hygiene and safe preparation of formula feeding; optimal use of local resources for complementary feeding after exclusive formula feeding; access to community and clinical services for routine child immunization, cotrimoxazole prophylaxis, treatment of common childhood diseases, and ART prevention and treatment care.


64. WHO, UNAIDS, UNICEF. HIV and infant feeding counseling: a training course. 
Overview of Prevention of Mother-to-Child Transmission of HIV

Isaac Adewolea and Solomon Sagayb

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MOTHER-TO-CHILD TRANSMISSION (MTCT) of HIV is a particularly challenging public-health issue in developing countries. This is especially true in sub-Saharan Africa, where the HIV disease burden is greatest among women1,2 and cultural norms put pressure on women to reproduce and to breastfeed their children for long periods of time. Unfortunately, high rates of reproduction and long-term breastfeeding in high-HIV-prevalence settings are fueling the growing pediatric HIV epidemic in sub-Saharan Africa and elsewhere.2,3

Pregnancy, childbirth, and breastfeeding are responsible for the majority of more than 500,000 pediatric HIV infections occurring annually worldwide, over 90% of which occur in developing countries.4,5 Globally, more than 1,400 children under the age of 15 continue to become infected with HIV every day, and children still account for more than 12% of all new infections. Without appropriate care and treatment, more than half of newly infected children will die before their second birthday.6

The exact timing of MTCT varies, but it is estimated that in breastfeeding populations, 60% of infections occur in utero and during labor, whereas 40% occur during breastfeeding.7,4 In the pre–anti-retroviral therapy (ART) era, the risk of MTCT of HIV was estimated to range from 15% to 30% in nonbreastfeeding populations and from 20% to 40% in breastfeeding populations.5,6

The administration of zidovudine (AZT) to the HIV-positive pregnant woman during pregnancy, labor, and delivery marked a new beginning in the quest to terminate the link between reproduction and pediatric HIV infection. The landmark Pediatric AIDS Clinical Trials Group 076 study demonstrated a 67% reduction in MTCT of HIV in an essentially nonbreastfeeding population of HIV-positive pregnant women who had a CD4 lymphocyte count of equal to or greater than 200 cells/mm³ and who did not have a prior history of ART administration.9 That study paved the way for numerous other studies designed to eliminate HIV transmission from an infected mother to her baby. In addition, the success of the AZT trial provided support to the idea that an intervention for the prevention of mother-to-child transmission (PMTCT) was a viable public-health strategy.

In 2001, a United Nations General Assembly Special Session (UNGASS) was held on HIV/AIDS...
to review and assess the current state of the AIDS pandemic. Key components of the UNGASS declaration relating to the reduction of MTCT were (1) to reduce the proportion of infants infected with HIV by 20% by 2005 and by 50% by 2010; (2) to ensure that 80% of pregnant women accessing antenatal care (ANC) have access to information, counseling, and other HIV-prevention services; (3) to increase the availability of and access to effective treatment to reduce MTCT of HIV for HIV-positive women and their infants; (4) to increase the availability of and access to effective interventions for HIV-positive women, including voluntary and confidential counseling and testing, treatment (especially ART), and, where appropriate, breast-milk substitutes; and (5) to ensure the provision of a continuum of care for women, their partners, and their children.10

The 2003 Joint United Nations Program on HIV/AIDS (UNAIDS) progress report on the 2001 UNGASS declaration indicated that by the end of December 2002, 88% of countries globally, and 91% of countries in sub-Saharan Africa, had national PMTCT policies in place.11 However, many countries with severe HIV epidemics were falling well short of goals to increase access to PMTCT services, including antiretroviral (ARV) prophylaxis, for pregnant women visiting public health facilities. According to the 2003 report, in 14 of the 17 countries surveyed in sub-Saharan Africa, less than 10% of pregnant women visiting public facilities were receiving ARV prophylaxis for PMTCT.11

While the situation has improved somewhat since 2003, a large proportion of HIV-infected women still do not have access to specific interventions for PMTCT. According to the 2006 UNAIDS Report on the Global AIDS Pandemic, just under 8% of pregnant women globally and 6% in sub-Saharan Africa in 2005 were offered services for PMTCT of HIV.12

This ongoing gap in services indicates that a comprehensive and integrated approach to preventing HIV infection in women, infants, and young children is urgently required. Interventions focusing on HIV-positive pregnant women need to be complemented by interventions that address primary prevention of HIV infection, particularly in women of childbearing age and their partners, and prevention of unintended pregnancies among HIV-positive women.

In developed countries, a combination of public-health strategies consisting of routine counseling and testing (with an opt-out approach), combination ART, elective cesarean delivery, and use of formula feeding has helped reduce MTCT of HIV to less than 2%.13-16 These dramatic reductions in MTCT have yet to be replicated in developing countries due to a variety of factors, including fragile health-care systems, poverty, lack of political commitment, limited uptake of HIV testing, stigma and discrimination, and inadequate human resources. Yet the overwhelming contribution of MTCT to pediatric HIV infection makes it imperative to establish prevention programs at all levels of care (e.g., facility, local, regional, national).

The following are the four prongs of PMTCT17:
- Prevention of primary HIV infection
- Prevention of pregnancy in the HIV-positive woman
- Specific interventions in pregnancy, labor, and delivery
- Care of the woman, as well as of her partner and children, after delivery

Although examples of successful PMTCT strategies in resource-limited settings are still few and far between, there are reports from some countries that clearly demonstrate how success in PMTCT can be achieved in settings where resources are scarce.18-20
VULNERABILITY OF WOMEN AND FETUSES TO HIV INFECTION

Women in developing countries where the male-to-female ratio is less than one are particularly susceptible to HIV infection. This susceptibility is due to a variety of factors. For instance, rates of HIV transmission are reported to be two to three times higher for male-to-female transmission than for female-to-male transmission.\(^{21-23}\) A complex combination of factors—ranging from the biology of the virus, to the anatomy of the female genital tract, to sociocultural traditions—has increased women’s vulnerability to the virus.\(^{24}\) Research has shown that the sperm and the ovum lack CD4 receptors and therefore cannot be infected by HIV. This implies that at fertilization, the resulting zygote does not contain the HIV genome. In most HIV-positive women, HIV does not cross the placenta from mother to fetus; instead, the placenta acts as a physical barrier that shields the developing fetus from viruses circulating in the mother’s blood.\(^{25}\) The protection offered by this placental barrier may break down, however, if the mother has a viral, bacterial, or parasitic placental infection during pregnancy; the mother seroconverts during the pregnancy and, as a result, there is a brief spike in viral load; or the mother has severe immune deficiency resulting from HIV infection. Thus, various health conditions in the pregnant woman, such as untreated placental infections (particularly malaria), recent HIV infection, and advanced HIV disease, have been cited as risk factors for MTCT.\(^{26}\)

Data from polymerase chain reaction (PCR) studies have confirmed the rarity of MTCT in early pregnancy.\(^{27}\) Clinical studies of children born to HIV-positive mothers present two distinct syndromes of acquired infection in the uterus: a smaller group of severely ill babies, suggesting early intrauterine infection,\(^{28}\) and a larger group of apparently healthy babies who develop features of HIV infection after birth, suggesting infection later in the pregnancy or around the time of delivery.\(^{29}\) After delivery, breastfeeding is a key route of MTCT of HIV.\(^{30}\)

EPIDEMIOLOGY OF PEDIATRIC HIV

MTCT of HIV represents an especially tragic dimension of HIV/AIDS, particularly in resource-limited settings where the fragility and poor funding of health-care systems hamper both care and prevention efforts. In these settings, MTCT contributes to over 90% of pediatric HIV infections.\(^{31}\) At the end of 2007, 2.3 million children were estimated to be living with HIV.\(^{31}\) The dramatic impact of HIV among children is best captured by data suggesting that at least one-third of HIV-infected children in developing countries will die within their first year of life.\(^{33}\) Thus, MTCT has become a critical child health issue in sub-Saharan Africa, with HIV infection contributing to significant childhood morbidity and mortality. The impact of HIV has also undermined the effectiveness of longstanding programs such as routine immunization and management of diarrheal diseases and malnutrition, which before the arrival of HIV had helped to significantly reduce childhood mortality in developing countries.

MTCT of HIV can be greatly reduced by expanding high-quality antenatal and obstetric care, voluntary counseling and testing (VCT) services, ARV drug therapy for pregnant women living with HIV, and the use of breast-milk substitutes or practice of exclusive breastfeeding. PMTCT programs can have an additional public-health impact by reaching HIV-negative women with health information, skills training, and support to prevent them from becoming infected.

SEXUAL AND REPRODUCTIVE HEALTH AND RIGHTS OF WOMEN LIVING WITH HIV

Sexual and reproductive health and rights (SRHR) issues have become a central theme at many HIV/AIDS meetings in recent times. It is popularly
believed that success in the control of HIV and AIDS cannot be achieved without addressing the SRHR issues that influence both the acquisition and prevention of HIV infection.

The HIV pandemic has converted the long-standing sexual, economic, and cultural subordination of women in many parts of the world into a death sentence. It is impossible to mitigate the impact of HIV among women without first looking at the SRHR issues that leave them vulnerable to infection. Foremost among the SRHR issues related to HIV is the right to life. This basic right is being denied to women who, due to their subordination, are routinely exposed to HIV and are often left powerless to protect themselves from infection and/or prevent HIV-related illness or death. The following quotes illustrate the feelings of helplessness that many women, especially those in resource-limited settings, experience in the face of HIV infection.

The women tell us they see their husbands with the wives of men who have died of AIDS. And they ask, “What can we do?” If we say no, they’ll say, “Pack up and go.” But if we do, where do we go?

—Miria Matembe, member of the Ugandan parliament

We fear what our husbands may bring home.

—Ugandan woman

As in the case of birth control pills, men will suspect women who want to use condoms of servicing other men.

—Ugandan woman

Clearly, an effective, woman-controlled method of contraception and infection prevention, such as an anti-HIV microbicide, is urgently needed.

Women living with HIV suffer further denials of human rights through being deprived of the right to bear children and the right to freedom of reproductive choice. In health-care settings, even in middle-income countries, discrimination and serious violations of the SRHR of HIV-positive women, such as sterilization without consent, are reported to be common. The following quotes illustrate the tragic reality of HIV-positive women who are denied the right to live a healthy and normal life.

I am still hoping to have a child . . . I have been told that it is totally selfish, that I have no right to inflict the potential for suffering on an as yet unborn child. Who says I have no right? If I am lucky enough to fall pregnant, my child will be loved and wanted. Will that be further reason for rejection by society? I hope not.

—Zimbabwean woman

To be alone and dying yet trying to care for one’s own HIV-positive child is a tragedy, the dimensions of which few of us can truly comprehend.

—Catherine Hankins, Canada

Furthermore, the mother’s right to privacy is stripped from her when her own HIV status becomes known because of the illness of her child, when she is denounced as being “responsible” for having transmitted HIV infection to an unborn child, or when she is rejected by her husband because she is living with HIV.

Women have routinely been denied the right to health and even the right to access health-care services, further increasing their vulnerability to HIV. In addition, they have been denied the right of access to education and to economic independence. Ensuring access to education for women and girls and increasing opportunities for women to achieve economic independence represent a few strategies that can lead to the greater emancipation of women, thereby reducing their vulnerability to HIV.

In the wake of interventions to prevent MTCT, little consideration was initially given to the enhancement of the mother’s health. The focus
was on ensuring an HIV-free baby, often through interventions that put the mother’s health and her future treatment options in jeopardy. However, with sustained advocacy, national governments and the international community have mobilized more resources to fund comprehensive PMTCT programs that address primary HIV prevention in young women, SRHRs of HIV-positive women, core prevention of MTCT of HIV, and the treatment, care, and support of the mother, her partner, and her family. These key issues have been reinforced in recent years by the New York Call to Commitment and the Abuja Call to Action. Yet despite these advances, implementing comprehensive PMTCT programs continues to be a major challenge in developing countries, which are more severely affected by the HIV pandemic and where human rights abuses are more widespread.

PREPREGNANCY CARE
Prepregnancy care is an excellent opportunity for primary HIV prevention and PMTCT. Such care provides an opportunity for couples testing and counseling, couple education, partner disclosure of serostatus, and promotion of adherence to interventions and follow-up. In many resource-limited settings, prepregnancy care is underutilized, and access to such care varies greatly.

Pre-conception Counseling and Management
Pre-conception counseling for women who are contemplating pregnancy substantially optimizes the outcome of pregnancies complicated by chronic maternal illness. Such counseling ensures highly informed, up-to-date decision making on the part of women living with a chronic illness.

With the advent of potent ARV medications, HIV-positive patients are living longer, healthier lives and HIV infection is slowly becoming a manageable chronic illness. Many HIV-affected couples desire to have children and their main challenge is to reproduce without transmitting infection to their HIV-negative partners (in serodiscordant settings) or to their infants. Many HIV-positive women have reported that pregnancy and childbirth is a way to regain their sense of womanhood and sexuality, making childbearing a high personal priority. Some have also cited raising children as a way to give purpose to their life.

In the context of HIV, patients or couples may present for prepregnancy care with one or more of the following concerns:

- How to achieve conception safely
- Fear of HIV transmission to partner and/or baby
- Impact of pregnancy on progression of HIV disease
- Impact of HIV/AIDS on pregnancy
- Safety of ARV medications during pregnancy
- Absence of menstruation and infertility (due to wasting syndrome)

In these cases, the patients’ HIV disease must be controlled before initiating attempts to become pregnant. Available evidence also emphasizes the improbability of conception when the body mass index is below 17.5 (very underweight). In the case of serodiscordant couples, there are a number of options to consider depending on the availability of PMTCT and other reproductive health services. In a serodiscordant couple consisting of an HIV-positive woman and an HIV-negative male partner, self-administered artificial insemination with the partner’s sperm can eliminate the risk of HIV transmission. If the woman is HIV-negative and her male partner is HIV-positive, referral to a specialist center with relevant experience is warranted to eliminate the risk of HIV transmission. Semprini et al have advocated a technique of artificial intrauterine insemination of HIV-negative women with processed semen.
from HIV-positive male partners. The group reported 200 pregnancies after 1,000 insemination attempts in 350 couples, with no cases of female HIV seroconversion either before or after delivery. As of 2002, Semprini et al reported no seroconversions during 2,000 inseminations of 800 women.50

In sub-Saharan African countries such as Nigeria, a few assisted conception centers with relevant technology to do sperm washing are appearing in the private sector; issues of cost and accessibility of this technology continue to be major challenges. In more developed countries, HIV-serodiscordant couples routinely seek reproductive assistance, yet despite access to improved technologies, these couples often consider or practice unsafe measures to achieve pregnancy.51 In developing countries, where such assistance is not within reach, health-care providers must go to great lengths to counsel serodiscordant couples on their unique reproductive issues and options.

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### Box 1. Suggested Steps in Pre-conception Care of Couples in the Context of HIV

| 1. **Pretest counseling, HIV testing, disclosure of serostatus, and posttest counseling** |
| 2. **Discussion of safe sex** |
| 3. **Pre-conception couples counseling:** |
| ■ Discussion of safer conception techniques |
| ■ Discussion of risk of HIV transmission to partner and baby |
| ■ Discussion of current and future health of infected partner(s) |
| ■ Discussion of options for infant feeding |
| ■ Discussion of critical need for adherence to interventions |
| 4. **Evaluation for presence of an active AIDS-defining illness** |
| 5. **CD4 lymphocyte count and/or HIV RNA viral load** |
| 6. **For patients receiving ART, check:** |
| ■ HIV RNA level |
| ■ ART regimen for teratogenic drugs |
| ■ Adequate therapy for at least one year with appropriate follow-up (i.e., stable viral load and/or CD4 count) |
| 7. **Routine investigations** |
| ■ Pap smear |
| ■ Full blood count including platelets |
| ■ Liver function tests |
| ■ Hepatitis virus screening |
| ■ Screen for sexually transmitted infections |
| o Syphilis |
| o Gonorrhea |
| o Chlamydia |
| o Trichomoniasis |
| ■ Screen for tuberculosis |
| ■ Investigate infertile couples as appropriate |
| 8. **Referral for complementary care as appropriate** |

*Source: Adapted from Thornton et al.*
To assist couples affected by HIV in making appropriate reproductive choices, women and their partners should be provided with realistic MTCT rates applicable to their specific circumstances and the interventions available to them, such as those provided by the UNAIDS Reference Group for Estimates, Modeling and Projection. Additionally, the greater availability of rapid testing now makes it possible for women to be tested for HIV and receive their results at the first prenatal visit.

Diagnosis of HIV infection during pregnancy often marks the beginning of a period of crisis for a woman and her family that requires methodical, compassionate, well-informed counseling and support. It is also important to ensure that women identified as HIV negative receive support to prevent infection. Prevention of HIV infection is especially critical during the course of pregnancy and breastfeeding, as the high viral load resulting from seroconversion is believed to be associated with MTCT; however, seroconversion during pregnancy has not been reported to increase vertical transmission rates. A pregnant woman whose HIV status remains unknown should receive further counseling during subsequent antenatal visits and should be made aware that testing is available.

After the initial evaluation, HIV-positive pregnant women should be counseled on the following topics as appropriate: condom use for prevention of sexual transmission of HIV and other sexually transmitted infections (STIs); the risk of HIV transmission to the fetus/neonate and how to prevent it; the risks and benefits of ARV prophylaxis as part of PMTCT strategy; the risks of perinatal transmission of hepatitis B and C virus and how these risks can be reduced; the risks of perinatal syphilis transmission and the need for treatment of syphilis, gonorrhea, and chlamydia to reduce the risk of HIV transmission to infant or partner; the impact of drug use or abuse on fetal development, including drug withdrawal syndrome and drug interactions; the implications of different modes of delivery in reducing the risk of HIV transmission, including the benefits and adverse effects of cesarean section; and instruction on infant feeding.

**CARE DURING PREGNANCY**

**Antenatal Care of Women Living with HIV**

In addition to the basic services recommended for all pregnant women, HIV-positive women require additional obstetric and medical care to address their specific needs (see Boxes 2, 3, and 4). Several countries have developed national protocols for ANC services provided to HIV-positive women by modifying relevant World Health Organization (WHO) guidelines so that they are appropriate to local conditions. The Nigerian national guidelines for the implementation of PMTCT are one such example.

Determining a woman’s HIV status is the first step in providing appropriate treatment, care, and support services, including access to ARV prophylaxis. Evidence from both developed and developing countries indicates that the uptake of HIV testing increases when it is routinely discussed and offered and where it is well integrated into prenatal care. Additionally, the greater availability of rapid testing now makes it possible for women to be tested for HIV and receive their results at the first prenatal visit.
Box 2. Essential Quality Antenatal Care Services

Quality antenatal care for all women, regardless of their HIV status, should include the following:

- Health education and information on condom use and dual protection
- Malaria prevention and case management, including the use of insecticide-treated nets and intermittent preventative treatment
- Delivery and family planning assistance
- HIV/AIDS-related services, including HIV testing and counseling, PMTCT, counseling on optimal infant feeding, and early diagnosis and treatment of STIs
- Nutritional counseling and support
- Advice on rest, care-seeking, self-care, and hygiene
- Psychosocial support, including referral for women who have experienced violence or women with substance abuse issues (injecting or other illicit drug use)
- Physical examination and obstetric history
- Birth planning, including counseling on skilled birth attendance (should involve companions such as husband or partner and parents)
- Infant-feeding counseling
- Emergency preparedness counseling
- Tetanus vaccination
- Iron and folate supplementation
- Deworming
- Syphilis screening and management of STIs
- Discussion of universal precautions
- Routine offer of HIV testing and counseling, using rapid tests

Source: WHO HIV/AIDS Department.54

Box 3. Additional Antenatal Care Services for Women Living with HIV

Women living with HIV should receive the following antenatal care services, in addition to the essential services listed in Box 2:

- Counseling and support on safer sex practices (including condom use)
- Couples counseling and partner testing, if requested
- Documentation of history of prior ARV prophylaxis for PMTCT or prior/ongoing ART
- Clinical evaluation, including clinical staging of HIV disease
- Immunologic assessment (CD4 count), where available
- Discussion of known and unknown risks and benefits of ART in pregnancy and ARV prophylaxis for PMTCT
- Initiation of ART for women who meet local criteria or initiation of ARV prophylaxis for PMTCT
- Cotrimoxazole prophylaxis
- Tuberculosis risk assessment and referral
- Infant-feeding counseling and support
- Psychosocial support
- Supportive care, including adherence support

Source: WHO HIV/AIDS Department.54
Prevention of Opportunistic Infections
 Preventing OIs can reduce rates of illness and death among HIV-positive pregnant women. These interventions may reduce the risk of adverse pregnancy outcomes, such as preterm labor and delivery, which can increase the risk of MTCT.59,60

Counseling and support on basic hygiene, safe drinking water, and malaria prevention are critical in preventing OIs in most high-HIV-prevalence countries. Where CD4 counts are available, WHO recommends that all HIV-positive individuals with CD4 counts below 350 cells/mm³ should take cotrimoxazole prophylaxis regardless of whether or not symptoms are present. In addition, those with stage III and IV disease should take cotrimoxazole regardless of CD4 count. Where CD4 counts are not available, cotrimoxazole prophylaxis should be taken by all those with mild, advanced, or severe symptoms of HIV disease (i.e., WHO stage II, III, or IV disease). In resource-limited settings with a high prevalence of HIV and malaria, WHO endorses giving cotrimoxazole to everyone who tests HIV positive and continuing this therapy indefinitely.61

Cotrimoxazole is also recommended for all HIV-positive pregnant women regardless of their stage of pregnancy, with therapy to be continued during breastfeeding. Women living with HIV who reside in a malaria-endemic region should take cotrimoxazole rather than sulfadoxine/pyrimethamine-based intermittent presumptive therapy for malaria.61 Prophylaxis for other common conditions should be given according to local guidelines.

Assessment and Management of HIV-Related Illnesses
 Because HIV-related illnesses can increase the risk of MTCT, pregnant women should be routinely monitored for signs or symptoms of progressive HIV disease. A multidisciplinary approach involving the obstetrician, HIV physician, nutritionist, and midwife is advocated in the management of HIV-related illnesses (e.g., malaria, recurrent vaginal candidiasis, tuberculosis, urinary tract infections, and respiratory infections) in pregnant women.62

Psychosocial and Community Support
 Since pregnancy can be a time of unique stress, health-care workers may consider assessing the amount of support a woman is receiving from family and friends. Women living with HIV usually have additional concerns related to their own health, their child’s health, confidentiality, disclosure to partners, and the possibility that their HIV status might be disclosed to other people. To provide additional support beyond the health-care setting, referrals to support groups for people living with HIV should be made where these programs are available. Strategies that recruit and train previous PMTCT clients as counselors and field officers have also been successful in providing additional support to HIV-positive mothers and their families.63

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**Box 4. Additional Antenatal Care Services for HIV-Negative Women**

Women who are HIV-negative should receive the following antenatal care services, in addition to the essential services listed in Box 2:

- Counseling to consider retesting late in pregnancy
- Counseling and support on safer sex practices (including condom use)
- Couples counseling and partner testing, if requested

Source: WHO HIV/AIDS Department.54
HIV TESTING STRATEGIES

Provider-initiated rapid HIV testing and counseling is now the recommended approach to HIV testing in ANC and labor ward settings globally. This approach to testing and counseling should be accompanied by a recommended package of basic HIV-related prevention, treatment, care, and support services (see Boxes 2, 3, and 4), which should be available in the same facility where the HIV test is performed or through local referral. Rapid HIV antibody tests are highly sensitive, specific, and simple to use, and they do not require sophisticated laboratory services, running water, or electricity. Accurate results can be available within a much shorter time than for the traditional Enzyme-Linked ImmunoSorbent Assay (ELISA). The advantages of using rapid HIV tests for provider-initiated HIV testing and counseling—particularly for health facilities where laboratory services are weak—are included in the following:

- Visibility of the test and quick turnaround increases confidence in results and avoids clerical errors.
- Testing can occur outside laboratory settings.
- Testing does not require specialized equipment.
- Testing can be carried out in primary health facilities by appropriately trained nonlaboratory personnel, including counselors.
- Rapid turnaround gives the ability to deliver necessary interventions in a timely manner.

It is important to note that despite the relative ease of use of rapid tests, trained laboratory supervisors are still required for supervision and quality assurance, including quality control for testing and biosafety.

HIV testing and counseling as early as possible during pregnancy enable pregnant women to benefit from prevention, treatment, and care and to access interventions for reducing HIV transmission to their infants. HIV testing should therefore be offered to all pregnant women during the first (booking) visit.

Even in health facilities that offer comprehensive PMTCT services, many women may still fail to access HIV testing prior to labor. A study in one such center in northern Nigeria found that over one-third of pregnant women presented at the time of labor without having previously accessed antenatal HIV testing and counseling. Although ARV prophylaxis for PMTCT is most effective when given during pregnancy, labor, and the early postpartum period, it has also been shown to be effective when started at the time of labor or in the infant shortly after birth. Therefore, HIV testing and counseling should be offered to all women of unknown HIV status in labor or, if this is not feasible, as soon as possible after delivery.

If an HIV test has not been performed prior to delivery, HIV testing and counseling should also be offered to women in the postpartum period, preferably as soon as is feasible. Doing so enables them to receive HIV-related services for themselves and the infant, including initiation of postexposure ARV prophylaxis for the infant, as well as to receive infant-feeding counseling and support.

DELIVERY OPTIONS

The protective role of cesarean section before labor and before rupture of membranes was demonstrated in a randomized clinical trial in Europe and in a meta-analysis incorporating European and North American data prior to the widespread use of combination therapy in pregnancy for PMTCT. In these studies, cesarean section after labor and/or after ruptured membranes was, however, associated with a risk of HIV transmission similar to that associated with vaginal delivery. Subsequent observational data demonstrated very low rates of MTCT in women on combination ART with undetectable viral loads who delivered vaginally. These data have provided a basis for the current recommendation of elective cesarean section for HIV-
positive women, irrespective of therapy, who have viral loads greater than 1,000 copies/mL near the time of delivery.70

Elective cesarean delivery should not be routinely provided for women on ART who have HIV RNA levels below 1,000 copies/mL, unless they choose this procedure after thorough counseling regarding the uncertain benefits and known risks. If the decision is made to perform prelabor cesarean delivery to prevent HIV transmission, it should be done at 38 weeks, gestation, as determined by the best clinical estimate.70

It is important to note that there is an increased risk of maternal morbidity among HIV-positive women undergoing cesarean section.71 In a retrospective study of 401 HIV-1-infected women undergoing scheduled cesarean delivery specifically for prevention of HIV-1 transmission in Paris, France, incidence of fever in the mother after delivery was greater for those undergoing the cesarean section than for those delivering vaginally. In a multivariate analysis adjusted for maternal CD4 count and antepartum hemorrhage, the relative risk of any postpartum complication was 1.85 (95% CI, 1.00-3.39) after elective cesarean delivery and 4.17 (95% CI, 2.32-7.49) after emergency cesarean delivery, as compared with that for women delivering vaginally. Febrile morbidity was increased among women with low CD4 counts.72

Among women with ruptured membranes before delivery, increased duration of ruptured membranes is associated with an increased risk of MTCT.73 Obstetric procedures, such as fetal scalp monitoring, episiotomy, and instrumental deliveries (such as forceps or ventouse), can also increase MTCT rates. Therefore, artificial rupture of membranes and invasive obstetric procedures must be avoided unless absolutely necessary. Partograms should be used as a management tool to avoid prolonged labor.

**POSTNATAL CARE AND CARE OF THE NEWBORN INFANT**

In addition to the standard postpartum care provided for all mothers, HIV-positive mothers may require additional care and support in one or more of the following areas:

- Review for signs and symptoms of postpartum infection
- Care for the genital area and basic hygiene in the disposal of sanitary towels
- Wound healing
- Treatment and prophylaxis for OIs
- Infant-feeding counseling and support
- Care of the breasts
- Malaria prophylaxis
- Evaluation for ARV eligibility
- Adherence counseling
- Access to safe drinking water
- Nutritional care and support
- Family planning counseling and support
- Screening for cervical dysplasia

Family planning counseling sessions should include the development of risk-reduction strategies with the mother to decrease the risk of HIV transmission to an uninfected partner and the risk of STI acquisition; condom use should be emphasized throughout the period of breastfeeding. Where such counseling services are not available together in one facility, referrals to other facilities should be offered as needed.

The association between breastfeeding and maternal disease progression and death has important implications for public-health policy. Two studies in Kenya and South Africa looking at breastfeeding and mortality among women infected with HIV-1 produced conflicting results.74,75 However, a more recent report did not associate breastfeeding with increased maternal mortality when appropriate care was available.76

The current preponderance of evidence regarding the association of breastfeeding and maternal
in health infrastructure and human capacity are needed in order for PMTCT to become a routine component of maternal and child health care in all resource-limited settings.

The widely published efficacy and cost-effectiveness studies of the perinatal nevirapine-based regimen for PMTCT, as well as the subsequent donation of nevirapine by Boehringer Ingelheim and of Determine rapid test kits by Abbott, gave way to several large-scale PMTCT interventions in developing countries. The main objective stated by these programs was to contribute to the reduction of infant mortality through implementation of a comprehensive package that aims at reducing the transmission of HIV from mothers to their babies. Yet while most PMTCT programs have focused on providing ARV prophylaxis to prevent transmission of HIV to infants, it is also important to recognize that women who are diagnosed with HIV through antenatal screening have a wide variety of other needs related to their HIV-positive status. Their children and other family members also need support, as many partners are HIV-positive or at risk of infection, and even uninfected children are at a high risk of mortality due to their mother’s illness. These considerations fueled international support for the original 2001 UNGASS declaration that promoted the

### Box 5. Essential Care Services for HIV-Exposed Infants

- ARV prophylaxis
- Routine immunization
- Cotrimoxazole prophylaxis starting at six weeks
- Early diagnosis of HIV infection (virological tests)
- Diagnosis of HIV infection around 15–18 months (HIV serology)
- Continued infant-feeding counseling and support
- Growth monitoring and support
- Screening for and management of tuberculosis
- Prevention and treatment of malaria
- Nutrition care and support
- Psychosocial care and support
- ART
- Symptom management and palliative care if needed

Source: WHO HIV/AIDS Department.
provision of treatment, care, and support for women living with HIV, their children, and their families as the fourth prong of PMTCT interventions.10

More recently, several opportunities have arisen to support the expansion of PMTCT services. A number of multilateral and bilateral organizations are committing more funds to the fight against HIV/AIDS in developing countries. The Global Fund to Fight AIDS, Tuberculosis and Malaria; the President’s Emergency Plan for AIDS Relief (PEPFAR); the World Bank; the Bill & Melinda Gates Foundation; and a number of other partners have all recently provided funds for expansion of PMTCT programs in the most affected countries.

Several countries in Latin American and the Caribbean—most notably Brazil—have already succeeded in providing PMTCT services to the majority of pregnant women attending antenatal clinics.84 Thailand has also been successful in providing widespread access to PMTCT since 1999.85 Botswana leads the way in the provision of PMTCT in sub-Saharan Africa; PMTCT services are provided in all of the country’s public facilities through the Maternal Child Health / Family Planning system, which serves over 95% of pregnant women.86 Other countries are also beginning to make progress: as of December 2005, 80% of districts in Cameroon had begun offering PMTCT interventions,87 and other countries in sub-Saharan Africa, such as Uganda and Nigeria, had blueprints in place for countrywide expansion of PMTCT services.81,82 These plans provide a framework for the involvement of all stakeholders—all tiers of government, development partners, the private for-profit sector, civil society, faith-based organizations, groups of people living with HIV, and communities—in national efforts to scale up the PMTCT programs. For example, during fiscal years 2004 to 2006, the PEPFAR program supported PMTCT services for women during more than six million pregnancies through a number of strategic partnerships. These services provided ARV prophylaxis for 533,700 HIV-positive pregnant women, averting an estimated 101,500 infant HIV infections, at approximately 4,863 service outlets.88

In summary, the long-term goal of any national PMTCT program is to institutionalize PMTCT services and ensure universal access to PMTCT for all pregnant women attending antenatal care, all pregnant women coming to deliver at maternity centers, and all HIV-exposed infants.

INTEGRATION OF PMTCT SERVICES WITH REPRODUCTIVE HEALTH

Whereas a great deal of emphasis has been placed on the third component of the UNGASS declaration—focusing mainly on ARV-based interventions—much less attention has been focused on preventing unintended pregnancy in HIV-positive women. Yet this approach is not only beneficial in itself but could also be as effective as ARV regimens in preventing MTCT of HIV.89 It is practical to integrate family planning services into existing PMTCT programs in settings such as sub-Saharan Africa, where HIV seroprevalence and rates of unintended pregnancies are high. Contraception is the best-kept secret in HIV prevention and should be considered as a valuable HIV-prevention intervention.90 The need for increased access to contraception among women living with HIV is great. Of the 20 million HIV-positive women worldwide, 25% have an unmet need for contraception; this translates into an estimated five million HIV-positive women in need of contraception.91 In order for the UNGASS goals to be realized, there must be a greater emphasis on the prevention of unwanted pregnancies among HIV-positive women. Even moderate reductions (6%-12%) in pregnancies among women living with HIV would yield equivalent reductions in infant HIV infections.91-93

A model developed by Family Health International and applied to a hypothetical
types of chemoprophylaxis available for reducing the risks of transmission to her child; and (3) if she is pregnant, she should be offered the opportunity to obtain ART. Postpartum contraception should then be offered, if available.95

Ethical Issues in PMTCT Service Provision

PMTCT programs entail serious ethical challenges. These challenges are amplified in developing countries where operational and infrastructural constraints often prevent the provision of optimal care. Areas where challenges are routinely encountered include counseling and testing modalities and strategies for disclosure (especially in serodiscordant unions), a woman’s right to terminate an unwanted pregnancy, selection of ARVs, selection of mode of delivery, use of breast-milk substitutes, and patients’ ability to pay for services.96-99

Although it is a pregnant woman’s absolute right to choose, on the basis of full information, whether to take advantage of some or all of the PMTCT interventions available to her, there is a need to balance this right against the rights of her unborn child. The population in sub-Saharan Africa demonstrated that increasing contraceptive use among sexually active women who wish to avoid pregnancy would be approximately 25% more cost-effective than increasing access to PMTCT services in preventing vertical HIV transmission (US$663 vs. US$857 per HIV-positive birth averted). This model also suggested that if the same amount of money were to be invested in increased use of contraceptives as for PMTCT, use of contraceptives would prevent approximately 30% more HIV-positive births than a traditional PMTCT strategy (30 vs. 23 HIV-positive births averted).91 These findings suggest that contraceptive services are at least as important as traditional PMTCT programs for preventing HIV and therefore deserve more financial and political support.

At least three family planning options should be available to HIV-positive women who are identified at testing and counseling sites: (1) if a women does not wish to become pregnant, she should be referred to a family planning program; (2) if she wishes to become pregnant, she should be educated about the availability of prenatal services and the

Source: International Center for AIDS Care and Treatment Programs.94

THE MTCT-PLUS INITIATIVE

In 2000, THE MTCT-PLUS INITIATIVE was conceptualized in response to a call to action at the Durban International HIV Conference. Before that time, programs for the prevention of mother-to-child transmission (PMTCT) of HIV did not provide care and treatment to HIV-infected pregnant women and mothers. If the children were spared HIV infection, then ultimately their mothers would die without treatment. The MTCT-Plus Initiative, recognizing the important roles that women play in their families and communities, built on PMTCT programs to include comprehensive treatment services for women throughout pregnancy and postpartum.

Source: International Center for AIDS Care and Treatment Programs.94
controversial issue in a PMTCT setting is whether the pregnant woman has the right to refuse PMTCT services, since her baby should have the right to receive HIV-prevention services. This is particularly relevant in countries such as South Africa, where the Patients’ Rights Charter allows a patient to refuse treatment. In the United States, judicial pronouncement has forced perinatal interventions in cases where parents have refused treatment.

Informing sex partners is another extremely complicated issue. Part of pre- and posttest counseling involves informing patients of the need to disclose their HIV status to their partners. The healthcare worker is advised to persuade the patient to self-disclose or to consent to disclosure. Pre- and posttest counseling and referral to a counseling service should also be offered to the partner.

As mentioned earlier in this chapter, the provision of ARV prophylaxis to the mother for PMTCT was often at the detriment of the mother’s own health, since the initial emphasis of these interventions was on preventing vertical transmission of HIV to the infant, not preserving the long-term health of the mother. The introduction of the MTCT-Plus Initiative (see sidebar), as well as other family-based approaches to PMTCT, has eliminated this dilemma to a great degree. Determination of maternal CD4 count has now become a standard of care, and mothers in developing countries who qualify for treatment are being offered combination ART for their personal health.

**CONCLUSION**

A major challenge for the next decade is to bridge the current gap in PMTCT coverage and effectiveness between more-developed and less-developed countries. Confronting this challenge will require a unique global collaboration of governments, public-health professionals, pharmaceutical companies, and nongovernmental organizations. Although the challenge is great, the public-health benefits of this endeavor will extend beyond HIV prevention to improvements in the overall health care and life of women and their children worldwide. Adoption of an ethical framework that rests on the pillars of the right to health and life could help narrow the current divide and help promote truly universal access to PMTCT services.
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A Review of Clinical Efficacy Trials and Guidelines for the Prevention of Mother-to-Child Transmission of HIV during Pregnancy, Labor, and Delivery

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This chapter will highlight major findings from pivotal clinical trials that have led to the evolving mother-to-child transmission (MTCT) prevention guidelines over the past 10 to 15 years. The trials are generally presented in chronological order but are also grouped by type of intervention (single-antiretroviral [ARV] regimen, single-dose nevirapine [sdNVP], breastfeeding MTCT intervention, etc.). Smaller observational studies, phase I/II studies of perinatal ARV interventions, and ARV drug resistance that emerges with the use of ARVs for MTCT prevention will not be covered in this chapter. Areas of controversy and of ongoing study will be highlighted.

When evaluating and comparing results of MTCT prevention trials, it is particularly important to consider maternal disease stages (as low CD4 cell counts and high HIV-1 RNA levels are associated with MTCT), the duration of antepartum intervention, whether (and for how long) the infants received postexposure prophylaxis, at what age the infant HIV-1 infection status is being reported, what proportion of study infants are breastfeeding versus formula feeding, adherence to study interventions, and mortality and completeness of follow-up. Please see other chapters in this publication for information on the routes and risk of MTCT, obstetric interventions for preventing MTCT, information regarding breastfeeding-related MTCT, and drug resistance following ARV use for MTCT prevention.

EARLY STUDIES USING SHORT-COURSE ZIDOVUDINE

The landmark PACTG 076 study, published in 1994, ushered in the era of effective interventions for the prevention of mother-to-child transmission of HIV-1. In this randomized, placebo-controlled trial, Connor et al demonstrated that short-course zidovudine (ZDV) alone led to a 67.5% decrease (from 25.5% to 8.3%) in the rate of MTCT among formula-feeding infants in the United States and France. The ZDV regimen in this trial consisted of maternal oral ZDV started as early as the 14th week of gestation (and given for a median of 11 weeks), intravenous ZDV during labor, and infant oral ZDV for six weeks.

The efficacy of ZDV alone for preventing MTCT was confirmed in two subsequent placebo-controlled clinical trials using a less-intensive
ZDV regimen (ZDV starting at approximately 36 weeks of gestation and during labor) than in PACTG 076. MTCT was decreased by 50% (from 18.9% to 9.4%) in a trial in Thailand among formula-feeding infants and by 44% (at four weeks of infant age) in a study in Côte d’Ivoire among breastfeeding infants. In a different placebo-controlled trial (DITRAME) among breastfeeding participants conducted in Côte d’Ivoire, in which mothers also took one week of ZDV postpartum, MTCT at six months was 18.0% in the ZDV arm compared with 27.5% in the placebo arm (P=.027). However, when data from these two different Côte d’Ivoire studies were combined, efficacy at 24 months of infant age was only 26% (cumulative risk of HIV-1 infection 22.5% in the ZDV arm compared with 30.2% in the placebo arm). This unfortunate “erosion” of some (but not all) of the protective efficacy of MTCT prevention regimens is due to breastfeeding-related MTCT, and has been seen in several studies conducted in breastfeeding populations.

A subsequent study conducted in Thailand (PHPT) randomized formula-feeding mother-infant pairs to one of four different ZDV regimens of different durations (starting in the mother at either 28 or 35 weeks’ gestation, and given to the infant for either three days or six weeks). This study found that MTCT rates were higher (10.5%) in the arm receiving the shortest courses of maternal and infant ZDV than in the arm receiving the longest courses of maternal and infant ZDV (4.1%, P=.004). The study also demonstrated that although overall MTCT rates did not differ significantly between the other three arms, rates of antepartum MTCT were significantly higher among the two pooled arms in which mothers started ZDV at 35 weeks (5.1%) rather than 28 weeks (1.6%) (P<.001). This suggests that a considerable amount of in utero transmission occurs between 28 and 35 weeks’ gestation.

SINGLE-DOSE NVP

The widespread implementation of short-course ZDV for MTCT prevention in resource-limited settings has been limited by the need to identify and initiate treatment in HIV-positive women by 34 weeks’ gestation, and to a lesser extent by the cost of ZDV. In this context, the HIVNET 012 trial made another seminal contribution to our body of knowledge by demonstrating that one dose of NVP taken by the mother during labor and one by the infant when 48-72 hours old was able to reduce MTCT by 42% at six to eight weeks of age in a breastfeeding population compared to intrapartum ZDV and one week of infant ZDV (from 20.0% to 11.8%). Interestingly, the protection conferred by sdNVP was not markedly affected by breastfeeding-related transmission: at 18 months of age, estimated transmission in the sdNVP arm was 15.7% compared with 25.8% in the ZDV arm, yielding a 10.1% absolute reduction in MTCT or a 41% reduction in relative risk of MTCT at 18 months.

Several other studies have evaluated the utility of sdNVP in various programmatically simple combinations for preventing MTCT. The SAINT study, conducted in South Africa among both breastfeeding (42%) and formula-feeding (58%) mother-infant pairs, randomized participants to receive either of the following treatments: (1) two doses of maternal NVP (during labor and again at 24-48 hours postpartum), with one dose of NVP to the infant, or (2) ZDV plus lamivudine (3TC) given to the mother during labor, and to both the mother and infant for seven days postpartum. Estimated infant infection rates through eight weeks of age were 9.3% in the ZDV plus 3TC arm and 12.3% in the NVP group (P=.11), with transmission rates among formula-fed-only infants somewhat lower (6.9% and 10.6%, respectively). The second dose of maternal NVP may not confer much additional MTCT protection but might be associated with higher rates of NVP resistance development.
Two additional concurrent randomized trials in Malawi among a population of breastfeeding women who did not take any antenatal ARV drugs tested the efficacy of a different approach using sdNVP. In both studies, infants were randomized to receive either one dose of NVP alone or one dose of NVP with seven days of ZDV.11,12 The first trial enrolled women who did not receive any intrapartum intervention, as they presented within two hours of delivery11; the overall rate of MTCT at six to eight weeks was 27% lower in the NVP plus ZDV group (15.3%) than in the NVP-only group (20.9%) ($P=0.03$). The second trial enrolled mothers who received a single dose of NVP during labor12; estimated MTCT at six to eight weeks was 14.1% in the infant NVP-only group and 16.3% in the NVP plus ZDV group ($P=0.36$). In sum, these two parallel randomized trials suggested that one week of infant ZDV plus infant sdNVP is better at preventing MTCT than infant sdNVP alone if the mother did not receive any NVP during labor, but that infant ZDV does not add significant protection if the mother did receive NVP during labor.

**SINGLE-DOSE NVP IN COMBINATION WITH OTHER ARV DRUGS**

As the cost of ZDV declined and the availability and uptake of voluntary counseling and testing during pregnancy improved somewhat, additional studies evaluated whether or not sdNVP provided additional efficacy when short-course (including antenatal) ZDV regimens were used. Two open-label, nonrandomized studies suggested that the addition of sdNVP to short-course ZDV (starting at 34-36 weeks’ gestation in Thailand and at 36-38 weeks in Côte d’Ivoire) led to greater protection against MTCT than did ZDV alone, compared to historical controls.13,14

Two other studies—randomized placebo-controlled trials—studied the efficacy of sdNVP in addition to short-course ZDV. The first, PHPT-2, was conducted in Thailand among formula-feeding women who all received ZDV starting at 28 weeks of gestation.15 Participants were randomized to one of three intervention arms: (1) a placebo to both the mother (during labor) and the infant, (2) one dose of NVP to the mother with a placebo to the infant, or (3) one dose of NVP to both the mother and the infant. HIV-1 transmission was significantly higher in the placebo-placebo arm (6.3%), which stopped enrolling participants early as a consequence. The final transmission rate in the NVP-NVP arm (1.9%) was not significantly inferior to that in the NVP-placebo arm (2.8%), with both of these rates being remarkably low, and at least in part attributable to lack of breastfeeding.15

The Botswana Mashi study provided ZDV starting at 34 weeks’ gestation and for at least one month after birth to all study participants and some combination of sdNVP. Twelve hundred mother-infant pairs were randomized to receive either sdNVP (as in HIVNET 012) or maternal and infant placebo in addition to the ZDV.16,17 Mother-infant pairs were also randomized in a 1:1 ratio (2x2 factorial design) to either formula feed or breastfeed for six months, with six months of infant prophylactic ZDV. When the Thai PHPT-2 results were made public in 2002, the Mashi study design was changed to provide a dose of NVP to all infants, for ethical reasons, but women continued to be randomized to either sdNVP treatment or a placebo.16 In the revised study period, the one-month HIV-1 MTCT rates were 4.3% in the NVP-NVP arm and 3.7% in the placebo arm—low rates in a group in which 50% of women breastfed. The Mashi study16 and the two concurrent Malawi studies11,12 described above suggest (but were not designed to prove) that maternal sdNVP does not prevent additional infections among breastfeeding infants who receive at least one week of ZDV plus a dose of NVP.
The PACTG 316 trial, conducted in the United States, Europe, and the Bahamas among formula-feeding women and infants, also compared the efficacy of a single dose of NVP versus a placebo to mother and infant.18 However, in this study, mothers and infants received NVP or a placebo in addition to local standard, nonstudy ARV drugs; 77% of women took combinations of two or more ARV drugs antepartum.19 Transmission rates in this formula-feeding population were again very low, and did not differ by sdNVP receipt status (1.4% in the NVP arm and 1.6% in the placebo arm by six months of infant age).18 An observational study—DITRAME Plus—conducted in Côte d’Ivoire among women (66% breastfeeding) who took ZDV and 3TC from 32 weeks’ gestation and one dose of NVP during labor (with infants receiving sdNVP and one week of ZDV) found an HIV-1 MTCT rate of 4.7% at four to six weeks of age19 (this rate did not differ significantly from the historical rate of 6.5% among women taking short-course ZDV and sdNVP at the same site). Although a discussion of drug resistance following ARV drug use for the prevention of MTCT is beyond the scope of this chapter (see chapter entitled “Drug Resistance Following the Use of Antiretrovirals for Prevention of Mother-to-Child Transmission of HIV: Prevalence and Implications for Treatment Response” in this section), the PETRA20 and DITRAME Plus21 studies demonstrated that following antepartum treatment with ZDV and 3TC to prevent MTCT, the virus in 8.3% to 12% of women had developed the M184V mutation conferring 3TC resistance, which limits enthusiasm for the use of 3TC with only one other drug in this context (the PETRA study randomized pregnant HIV-1-infected women in South Africa, Uganda, and Tanzania to receive ZDV plus 3TC, given either antepartum, intrapartum, and postpartum; intrapartum and postpartum; or intrapartum alone—or a placebo for the first two years of the study—and found that in this population in which 74% of women breastfed, the antepartum/intrapartum/postpartum strategy was most effective at preventing MTCT when infection by six weeks was evaluated, but that by 18 months of age there was no significant overall difference in MTCT rates by randomized study arm22).

THREE-DRUG ANTIRETROVIRAL THERAPY

Combination, three-drug antiretroviral therapy (ART) can reduce the risk of MTCT to less than 2%,18,23-25 including in developing-country settings when breastfeeding transmission is not included,26 and has become the standard of care in settings in which it is safe and feasible. Three non-randomized studies in African breastfeeding populations of three-drug ARV combinations given daily during pregnancy to women who did and did not require ART for their own care showed four- to six-week HIV transmission rates as low as 1.2%-3.9%.27-29 These studies (DREAM, AMATA, KiBS) also continued the three-drug maternal regimens for up to six months postpartum during the breastfeeding period (see later in this chapter). It should be noted that to date, no randomized efficacy trials studying different three-drug combination regimens have been completed, although one such trial is currently under way in Botswana.

The studies outlined above have collectively demonstrated that ARV drugs administered during pregnancy and to infants can dramatically decrease HIV-1 MTCT, and that combination (two- or three-drug) ARV prophylaxis started in the antepartum period and given intrapartum and postpartum to infants is most effective.15,18,23,24 Three-drug combination regimens14,23-29 as well as short-course ZDV with sdNVP can reduce MTCT to less than 2% in a formula-feeding population.15 Even antepartum/intrapartum and intrapartum/postpartum ARV regimens can significantly reduce
infant ZDV (in addition to at least short-course ZDV to all mothers, combination ART to 6% of mothers, and various combinations of sdNVP, as described above).\textsuperscript{17} The seven-month infant HIV-1 infection rates were 5.6% in the formula arm and 9.0% in the breastfeeding arm ($P=.04$), but HIV-free survival at 18 months did not differ between arms (86.1% and 84.9%, respectively) due to significantly higher mortality in the formula arm.\textsuperscript{17} The incremental, breastfeeding-associated MTCT between one and seven months of age in the breastfeeding plus ZDV arm of the Mashi study was 4.4%; although it is impossible to determine whether infant ZDV prophylaxis during breastfeeding prevented any MTCT, and comparisons of absolute MTCT rates across studies must be made with caution, this LPT rate is similar to that seen among breastfeeding children in the absence of maternal and infant ARV drugs.\textsuperscript{31}

Results are available from two other non-controlled studies employing infant ARV prophylaxis during breastfeeding.\textsuperscript{32-34} The SIMBA study, conducted in Uganda and Rwanda, provided ZDV and didanosine to pregnant HIV-1-infected women from 36 weeks’ gestation through one week postpartum, and randomized infants to receive either daily 3TC or NVP from birth until six months or one month after the cessation of breastfeeding (maximum of seven months).\textsuperscript{34} The overall rate of MTCT by six months was 8%, but the rate of LPT (between four weeks and six months of age) was only 1.0% (with no difference between 3TC and NVP arms).\textsuperscript{34} It should be noted that the median duration of breastfeeding was only 15 weeks in the SIMBA study population, and maternal viral loads at delivery following antenatal ZDV plus didanosine were quite low ($2.7 \log_{10}$).\textsuperscript{34} In the MITRA study, mothers in Tanzania received ZDV and 3TC from 36 weeks’ gestation through labor and for one week postpartum, and infants received ZDV plus 3TC for one week and then 3TC alone through the

### ARV Drugs and Breastfeeding-Related MTCT: Infant Prophylaxis

The Mashi study, a 2x2 factorial design trial conducted in Botswana, included randomization of mother-infant pairs to six months of formula feeding (with one month of prophylactic infant ZDV) or six months of breastfeeding with six months of infant ZDV (in addition to at least short-course ZDV to all mothers, combination ART to 6% of mothers, and various combinations of sdNVP, as described above).\textsuperscript{17} The seven-month infant HIV-1 infection rates were 5.6% in the formula arm and 9.0% in the breastfeeding arm ($P=.04$), but HIV-free survival at 18 months did not differ between arms (86.1% and 84.9%, respectively) due to significantly higher mortality in the formula arm.\textsuperscript{17} The incremental, breastfeeding-associated MTCT between one and seven months of age in the breastfeeding plus ZDV arm of the Mashi study was 4.4%; although it is impossible to determine whether infant ZDV prophylaxis during breastfeeding prevented any MTCT, and comparisons of absolute MTCT rates across studies must be made with caution, this LPT rate is similar to that seen among breastfeeding children in the absence of maternal and infant ARV drugs.\textsuperscript{31}

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end of the breastfeeding period (for a maximum of six months). The cumulative MTCT rates were 3.8% at six weeks and 4.9% at six months (with 1.2% LPT), and the median duration of breastfeeding was also quite short (18 weeks). None of these studies of infant prophylaxis during breastfeeding had a “control” arm (of breastfeeding infants who do not receive prophylaxis), and the true efficacy (or lack thereof) of infant prophylaxis for preventing LPT cannot be determined. Results are available, however, from two recently published, randomized controlled clinical trials of infant prophylaxis with extended daily NVP dosing during breastfeeding. The Six-Week Extended-Dose Nevirapine (SWEN) study compared daily infant NVP dosing to six weeks of age to the standard sdNVP regimen in three combined trials in India, Ethiopia, and Uganda. At six weeks of age, SWEN infants had a 46% lower risk of HIV infection than sdNVP arm infants (2.53% vs. 5.27%; \(P < .01\)). However, for the primary endpoint of HIV transmission at six months of age, SWEN infants had a 20% lower risk than sdNVP infants (6.91% vs. 8.98%; \(P = .16\)), but this did not meet statistical significance. The risks of postnatal HIV transmission or death in the SWEN arm versus the sdNVP arm were 3.71% versus 6.81% (\(P < .01\)) at six weeks and 8.05% versus 11.58% (\(P = .03\)) at six months, respectively. The numbers of infants with serious adverse events were similar in each arm.

The Post-Exposure Prophylaxis of Infants (PEPI) trial was a three-arm, randomized controlled open-labeled trial in Malawi in which infants were randomized to sdNVP plus one week of daily ZDV (control). The control regimen was followed by extended daily NVP prophylaxis until 14 weeks of age, or extended daily prophylaxis with NVP plus ZDV until 14 weeks of age. At the primary endpoint of nine months of age, the HIV infection rate in infants who were HIV uninfected at birth was 10.6% in the control arm, 5.2% in the extended NVP arm (\(P < .001\)), and 6.4% in the extended NVP/ZDV arm (\(P = .002\)). The estimated protective efficacy of the extended NVP was 67% at six weeks, 67% at 14 weeks, 60% at six months, and 51% at nine months. There was no benefit from the addition of ZDV to the extended NVP regimen in terms of efficacy; there was, however, an increase in potentially related adverse events. Determination of whether the ZDV reduced the risk of development of NVP resistance in infants receiving NVP prophylaxis is under way.

Several ongoing studies (e.g., the Breastfeeding, Antiretrovirals, and Nutrition [BAN] study and the HIV Prevention Trials Network [HPTN] 046 study) are examining extended infant prophylaxis until six months of age with NVP to determine the safety and efficacy of a longer duration of NVP to provide greater coverage of the breastfeeding period.

**ARV Drugs and Breastfeeding-Related MTCT: Maternal Treatment**

Several ongoing randomized studies are also evaluating the efficacy of maternal combination ART in preventing breastfeeding-related MTCT among women who do not qualify for three-drug ART for their own health. The BAN study, which is being conducted in Malawi, has a six-arm, 2x3 factorial design with a randomization of women with CD4 cell counts of greater than or equal to 250 cells/mm\(^3\) to nutrition supplementation or no nutrition supplementation with three ARV intervention arms in each of these two groups. Women are randomized to either maternal three-drug ART (with ZDV, 3TC, and lopinavir/ritonavir) for six months, infant daily NVP for six months, or the background PMTCT regimen alone (which all women and infants received), consisting of a single dose of NVP, and ZDV plus 3TC for one week postpartum (as well as ZDV plus 3TC intrapartum).

The Kesho Bora study is being conducted at several African sites by the World Health
Organization (WHO). Women with CD4 counts of less than 200 cells/mm\(^3\) receive three-drug ART with ZDV plus 3TC plus NVP indefinitely. Women with CD4 counts of 200-500 cells/mm\(^3\) are randomized either to start three-drug ART with ZDV, 3TC, and lopinavir/ritonavir beginning between 28 and 36 weeks’ gestation through delivery and for six months postpartum, or to take ZDV beginning between 28 and 36 weeks’ gestation with sdNVP at the onset of labor, and a one-week tail of ZDV/3TC. Women with CD4 counts of greater than 500 cells/mm\(^3\) receive the same short-course ZDV, sdNVP, and one-week tail as women with lower CD4 counts. Both the BAN and Kesho Bora studies will provide insight into the efficacy and safety of maternal ART during the breastfeeding period in preventing LPT, and the Kesho Bora study will also evaluate the use of ART versus short-course ZDV plus sdNVP and ZDV/3TC tail for preventing the antepartum and intrapartum components of MTCT among women with higher CD4 counts.

The Mma Bana study, being conducted in Botswana, is the first randomized trial of different ART regimens in pregnant women to ever be conducted; pregnant women with CD4 counts greater than or equal to 200 cells/mm\(^3\) are randomized to receive either ZDV plus 3TC plus abacavir (Trizivir) or ZDV plus 3TC plus lopinavir/ritonavir starting in the second trimester and for six months during breastfeeding. Women with CD4 counts of less than 200 cells/mm\(^3\) who intend to breastfeed receive a regimen of ZDV plus 3TC plus NVP indefinitely.

Results are available from three non-randomized studies of maternal three-drug ART during pregnancy and breastfeeding.\(^{27-29}\) The DREAM study in Mozambique, Malawi, and Tanzania provided combination ART to all pregnant HIV-positive women regardless of CD4 count during pregnancy and continuing for six months after delivery. The reported cumulative rate of HIV infection at six months of age in breastfed infants was 2.2%.\(^{27}\) Similarly, in the AMATA trial in Rwanda, where all breastfeeding women received ART (AZT/3TC/NVP for those with CD4 counts less than 350 cells/mm\(^3\); AZT/3TC/efavirenz for those with CD4 counts greater than 350 cells/mm\(^3\)) during pregnancy from 26 weeks’ gestation and up until one month after breastfeeding cessation (maximum of seven months), the seven-month infection rate was 1.6% with six out of seven infections detected at birth.\(^{28}\)

The Kisumu, Kenya, KiBs study is following HIV-positive women taking three-drug ART from 34 weeks’ gestation to six months postpartum during breastfeeding (ZDV plus 3TC plus NVP indefinitely for women with CD4 counts of less than or equal to 250 cells/mm\(^3\), and ZDV plus 3TC plus nelﬁnavir for six months for women with CD4 counts greater than 250 cells/mm\(^3\)). Preliminary results showed a cumulative HIV infection rate of 5.0% at six months.\(^{29}\)

In the next one to two years, vital new information from several different randomized trials will be available regarding the safety and efficacy (to both mother and infant) of various ARV drug regimens in breastfeeding women with higher CD4 counts (generally greater than or equal to 200 cells/mm\(^3\)), as will observational information regarding breastfeeding women with lower CD4 counts (generally less than 200 cells/mm\(^3\)) on NVP-based ART.

**CURRENT GUIDELINES FOR THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV-1**

WHO\(^{37}\) and the U.S. Public Health Service (PHS) Task Force\(^{38}\) publish frequently updated guidelines on the management of HIV-positive pregnant women, focusing both on maternal health and MTCT prevention. Because these guidelines are
widely available and are regularly subject to change, only the key components of the WHO recommendations will be mentioned here, and the guidelines will not be covered in a comprehensive fashion. A brief discussion will be provided of some of the more important areas of controversy or uncertainty.

Maternal combination ART for pregnant women who need it for their own health both reduces maternal morbidity and mortality and comprises the most effective means of MTCT prevention, and should therefore be offered to pregnant women when indicated, whenever possible. The WHO criteria for initiating ART for pregnant women are very similar to those for nonpregnant women. In sum, combination ART for pregnant women is recommended for all women in WHO clinical stage 4, regardless of their CD4 counts; women in WHO clinical stage 3 whose CD4 counts are less than 350 cells/mm$^3$ (or whose CD4 counts are unavailable); and all women with CD4 counts of less than 200 cells/mm$^3$ (some experts suggest that ART should be considered for all pregnant women with CD4 counts of less than 350 cells/mm$^3$, regardless of clinical stage).

The WHO-recommended ARV regimen for pregnant women is ZDV plus 3TC plus NVP (generally initiated as soon as possible or as soon as is advisable for maternal health, and continued through labor and postpartum). ZDV should be included in the regimen when possible, but alternative nucleoside reverse transcriptase inhibitor (NRTI) drugs for use in pregnancy include abacavir and stavudine (the combination of stavudine and didanosine should be avoided in pregnancy). Lopinavir/ritonavir (rather than NVP) is an option for women with higher CD4 counts (discussed below), and is suggested by the U.S. PHS (although optimal dosing, including with the tablet formulation, is not known).

NVP is the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug of choice for ART in pregnancy, both because of fairly extensive clinical experience with its use in pregnant women (and therefore knowledge regarding its efficacy in reducing MTCT and its safety to the fetus) and because of the potential for teratogenicity with efavirenz (EFV). However, there are concerns about toxicity—primarily hepatitis and/or hypersensitivity reaction—in women starting NVP-containing ART with CD4 counts greater than 250 cells/mm$^3$. Several approaches to the treatment of pregnant women with CD4 counts greater than 250 cells/mm$^3$ exist, including use of a triple NRTI-based or protease-inhibitor-based regimen where possible, initiation of an NVP-containing regimen (particularly among women with CD4 counts closer to 250 cells/mm$^3$) with close clinical and (where available) transaminase monitoring in the first 12 weeks of therapy, or use of EFV rather than NVP in the second or third trimester of pregnancy (during the first trimester of pregnancy EFV should be used only if the potential benefit justifies the potential risk to the fetus).

For infants born to mothers taking antepartum combination ART, ZDV treatment for seven days is recommended (if the mother receives less than four weeks of antenatal ART, then four weeks rather than one week of infant ZDV should be given).

The recommended ARV regimen for preventing MTCT among women who do not have indications for (or who do not have access to) combination ART consists of ZDV from 28 weeks of pregnancy (or as soon as possible thereafter), ZDV plus 3TC plus sdNVP in labor, and ZDV plus 3TC for seven days postpartum for women (and for infants, sdNVP plus one week of ZDV). The intrapartum/postpartum maternal ZDV plus 3TC is recommended to reduce viral drug resistance that emerges following sdNVP exposure.$^{39}$ Omission of the maternal NVP dose can be considered for women who received at least four weeks of antepartum ZDV (if the maternal NVP dose is omitted, then intrapartum 3TC and postpartum ZDV plus 3TC are not needed, but the infant should receive sdNVP and four weeks rather than one week of ZDV). In some settings, it will not
be possible to deliver all these ARV components, and women and infants should receive as much of the recommended regimen as is possible (e.g., ZDV with sdNVP alone, or even sdNVP alone, if that is all that is possible).

**UNANSWERED QUESTIONS**

Many important questions remain unanswered in the field of MTCT prevention:

1. Importantly, the best approach to preventing breastfeeding-related MTCT of HIV-1 (including making formula-feeding or weaning safer) in different settings (and a reliable algorithm for determining which approach is recommended for an individual woman) is not known.

2. The optimal ARV regimen in women with baseline CD4 counts in the 250-350 cells/mm³ range who cannot take protease inhibitors is uncertain.
   - There is a lack of data on the maternal safety of continuous NVP among women with CD4 counts in the 250-350 cells/mm³ range, although the level of concern is great enough that this should be avoided when possible.
   - The safety of the fetus when EFV is taken in the second and third trimesters is not well studied.

3. The optimal ARV regimen in women with baseline CD4 counts above 350 cells/mm³ is unknown. The relative benefit (with regard to preventing MTCT) versus potential downsides (potentially higher rates of prematurity or other adverse infant outcomes, and of cost/complexity) of three-drug ART compared with the use of one or two ARVs remains unknown.

4. Pharmacokinetic data for many ARV drugs in pregnancy are insufficient (particularly for more recently approved ARVs), with a particular pharmacokinetic challenge arising for pregnant women requiring concomitant rifampicin-based tuberculosis therapy.

5. Some ongoing questions exist as to the safety of certain ARVs (or classes of ARVs) to the fetus or infant. For example, either contradictory or minimal data exist regarding the following topics:
   - Possible infant bone toxicity of in utero tenofovir exposure
   - Possible persistent sequelae of mitochondrial damage associated with in utero NRTI exposure
   - Premature delivery with combination ART, in particular protease inhibitors (which can carry grave consequences to the infant, particularly in resource-limited settings that have limited means for providing neonatal intensive-care medicine)
   - Possibly higher stillbirth rates in HIV-exposed infants (related to HIV exposure, early in utero HIV infection, ARV exposure, etc.)

However, these are all areas of great uncertainty, and these safety concerns may not be warranted. The risk-benefit ratio of perinatal ARV use, particularly among women with lower CD4 counts who are more likely to transmit HIV-1 perinatally, clearly favors ARV use but large, careful studies of child outcomes following perinatal ARV exposure would be helpful to determine which regimens maximize both safety and efficacy. Given some of these potential safety concerns, the results of randomized trials among less immunosuppressed women—comparing less intensive MTCT prevention regimens (sdNVP with or without short-course ZDV) to more intensive three-drug ART regimens—are particularly important, as the risk-benefit ratio of these strategies may be different in this population less at risk for transmitting HIV-1.
6. Questions remain regarding the best approach to preventing drug resistance from arising in the setting of highly abbreviated (and therefore much more feasible) MTCT prevention regimens (such as sdNVP), and the implications of this drug resistance for subsequent treatment response.

7. The optimal timing of ARV regimen initiation during pregnancy has not been well studied.

8. The role of elective cesarean sections among women with very low or undetectable HIV-1 RNA levels (and the safety of cesarean sections in resource-limited settings) is unclear.

9. Health delivery approaches that improve the availability and uptake of the best possible standard of care for MTCT prevention need to be tested.

10. Maternal health questions such as nutritional and/or micronutrient supplementation during pregnancy and breastfeeding, and the impact (if any) of brief ARV use for MTCT prevention (with cessation of ARVs postintervention among women who do not qualify for ART for their own health) are among the important, incompletely answered questions regarding the health of HIV-1-infected pregnant and postpartum women.

Despite gaps in our knowledge, we have many potent interventions already at our disposal for safely and effectively preventing MTCT and preserving and improving the health of mothers. We must do our utmost to use them.
REFERENCE LIST


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Special Considerations for the Administration of Combination Antiretroviral Therapy during Pregnancy

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The standard of care for the prevention of mother-to-child HIV transmission (PMTCT) in North America and Europe is combination antiretroviral therapy (ART), regardless of maternal disease status.\textsuperscript{1} This standard has so far not been attainable in resource-limited settings due to limited feasibility and high cost. In these settings, the World Health Organization (WHO) recommends that HIV-positive women be screened for ART eligibility early in the course of pregnancy, and then triaged to ART or another PMTCT regimen according to the maternal disease status based on CD4 cell count and WHO stage. ART is only initiated in pregnant women who meet the regular adult criteria for treatment eligibility.\textsuperscript{2} In this chapter, we highlight special considerations for the administration of ART in pregnancy, including when to initiate therapy, selection of appropriate drug regimens, drug toxicities, and complications associated with advanced HIV disease.

**PREGNANCY AND CD4 CELL COUNT**

Pregnancy is associated with physiological changes that may alter hematologic and immunologic parameters. The effect of pregnancy on CD4 cell count, however, is believed to be marginal; as a result, absolute CD4 cell count is still recommended by WHO as a criterion for ART eligibility.\textsuperscript{2} Although recent work has advocated use of CD4 percentage as a more reliable marker for immunosuppression during pregnancy,\textsuperscript{4} the convention remains unchanged.

Based on cross-sectional CD4 data from a pregnant population in Zambia (unpublished data, N. Chintu), almost 20\% of all pregnant women qualify for ART (i.e., meet the criterion of a CD4 cell count <200 cells/mm\textsuperscript{3}) and the majority of these women will have WHO stage I or II HIV disease. To capture all ART-eligible pregnant women, CD4 testing must become a routine part of PMTCT programs, and countries should make access to comprehensive HIV care—which includes CD4 testing—a priority. In many settings, women will have difficulty returning several times to the clinic and efforts should be made to reduce the number of clinic visits required. For instance, blood for the CD4 cell count can be drawn on the same day the patient is diagnosed with HIV.

Recent data from the European Collaborative Study from 240 HIV-positive pregnant women who commenced ART showed that the majority of
women who were started on a nevirapine (NVP)-based regimen achieved viral load suppression by 15 weeks.\(^5\) Because many women in resource-limited settings may have uncertain due dates or no access to ultrasound-confirmed dating, it is generally agreed that ART should be started as soon as possible in pregnant women identified as eligible for therapy. Given the multiple logistical challenges in resource-limited settings, such as off-site lab testing, delays in getting lab results, and difficulties in getting patients to return to collect results, doing as much as possible while women are actually at the clinic is preferable. In addition, postpartum women who are eligible for ART but did not start therapy while pregnant should immediately start therapy to reduce the chances of mother-to-child HIV transmission during breastfeeding.

**INITIATING COMBINATION ANTIRETROVIRAL THERAPY DURING PREGNANCY**

Many studies have shown that increased maternal viral load, low maternal CD4 cell count, vaginal birth, and breastfeeding are the most significant risk factors for perinatal transmission of HIV.\(^6\) In recent years, perinatal transmission of HIV has been virtually eliminated in the United States, Europe, and other high-resource settings by ensuring high service coverage and by offering combination ART to all pregnant HIV-positive women. With ART having the potential to decrease perinatal HIV transmission to less than 5% during pregnancy and breastfeeding, initiation of ART during pregnancy for all eligible women in the most affected countries is an essential step toward eradicating pediatric AIDS.

WHO has recommended the following criteria for the initiation of combination ART in pregnant women in resource-limited settings:\(^2\):

- All pregnant women having WHO stage IV HIV disease
- All pregnant women with a CD4 cell count <200 cells/mm\(^3\)
- WHO stage III and CD4 cell count <350 cells/mm\(^3\) or just WHO stage III if CD4 cell count is not available

WHO has not made strong recommendations for initiation of ART in pregnant women with a CD4 cell count between 200 and 350 cells/mm\(^3\). Based on data from the Zambia Exclusive Breastfeeding Study, 31% of perinatal infections occurred in infants born to women with a baseline CD4 cell count between 200 and less than 350 cells/mm\(^3\). If taken together with women whose CD4 cell counts were less than 200 cells/mm\(^3\), 82% of postnatal infections and 84% of maternal deaths occurred in this group. Additionally, infants born to women who had a CD4 cell count of less than 350 cells/mm\(^3\) (even if the infants were not HIV-infected) had substantially higher mortality rates than infants born to mothers with a CD4 cell count greater than 350 cells/mm\(^3\) (unpublished data, D. Thea).

**ART REGIMENS FOR PREGNANT WOMEN**

**Women with CD4 Cell Counts <250 cells/mm\(^3\)**

The most common regimen for women with a CD4 count less than 250 cells/mm\(^3\) is zidovudine (AZT) + lamivudine (3TC) + NVP. WHO and the U.S. Public Health Service recommend that first-line regimens include AZT (300 mg/day) based on extensive data in pregnancy.\(^9\)

Anemia remains a concern as a side effect of AZT, especially in women who may be anemic before initiating ART. Despite this concern, 97% of HIV-positive pregnant women at baseline in a cross-sectional analysis in Lusaka, Zambia, were
not anemic (defined as having an Hb <10 g/dL); the median Hb was 10.2 g/dL (unpublished data, N. Chintu). Stavudine (d4T) may be used instead of AZT in the presence of significant anemia. We recommend starting AZT on any woman who has an Hb greater than 8 g/dL.

**Women with CD4 Cell Counts >250 cells/mm³**

Women with CD4 cell counts greater than 250 cells/mm³ have been shown to be at a higher risk of hepatotoxicity when started on an NVP-containing regimen; therefore, the authors recommend distinguishing between pregnant women with a lower (≤250 cells/mm³) versus a higher CD4 cell count, when choosing regimens for the initiation of ART. The NRTI backbone should be either AZT + 3TC or d4T + 3TC.

There are several different options for initiating ART in pregnant women with CD4 cell counts greater than 250 cells/mm³. These include the following:

- Continue an NVP-based regimen and repeat liver function tests after the first week and then every 2-4 weeks for the first 12 weeks. This option has a disadvantage in that some sites may not have ready access to liver function tests. However, an advantage to this option is that most countries have AZT/3TC/NVP combinations readily available; it also reserves protease inhibitors (PIs) for second-line therapy.
- Give an efavirenz (EFV)-based regimen if the woman is in her second or third trimester.
- Administer a regimen based on AZT, 3TC, and a PI. This may hinder selection of a second-line regimen in the future since PIs are usually reserved for cases of treatment failure. However, a future second-line regimen could include a non-nucleoside reverse transcriptase inhibitor (NNRTI) such as EFV or NVP if the CD4 count has decreased to below 250 cells/mm³. Use of PIs in pregnant women with high CD4 cell counts can also cause severe nausea and vomiting.
- Give a triple nucleoside-based regimen such as AZT, 3TC, and abacavir. A potential drawback is that this may not be as potent as other regimens, which is particularly relevant for women with high viral loads.

Interestingly, in the European Collaborative Study, ART-naive pregnant women who were initiated on a PI-based therapeutic regimen needed on average 1.4 times longer to achieve viral load suppression than women initiated on an NVP-based regimen.

**SECOND-LINE ART REGIMENS FOR PREGNANT WOMEN**

Switching ART regimens due to treatment failure during pregnancy is likely to be uncommon since most women will either start ART during pregnancy or become pregnant while on their current ART regimen. However, if a patient is determined to be

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**Box 1. Case Study: Switching to a Second-Line Regimen during Pregnancy**

A 32-year-old woman being followed in the ART clinic is on a regimen consisting of AZT + 3TC + NVP. She was initiated on ART before her pregnancy when her CD4 count was 180 cells/mm³. During her pregnancy, her CD4 count is rechecked and found to be 100 cells/mm³. At that point, a viral load is ordered. Her viral load is found to be 30,000 copies/mL at 36 weeks. The clinician decides that the patient is failing her therapy and that she should be switched to emtricitabine and tenofovir plus a PI. After delivery, she continues on her PI-based regimen and her infant tests HIV-negative at six weeks by polymerase chain reaction.
failing therapy during pregnancy—as indicated by a dropping CD4 count, a new opportunistic infection, or a rising viral load—it is imperative that her ART regimen be switched to maximize her health and minimize the risk of perinatal HIV transmission. All antiretrovirals will need to be switched if it is determined that the patient is failing therapy. The choice of second-line nucleoside reverse transcriptase inhibitor (NRTI) backbone depends on which regimens were used for first-line regimens. If the first-line regimen contained AZT + 3TC, the second-line regimen can either contain a backbone of emtricitabine + tenofovir (TDF) or didanosine (ddI) + abacavir (ABC). A PI would then complement this regimen such as lopinavir/ritonavir, nelfinavir, or saquinavir. If the first-line regimen included d4T and 3TC, then the second-line regimen could contain AZT + ddI + a PI or TDF + a PI. An increasing number of developed countries are using lopinavir/ritonavir in second-line regimens based primarily on the demonstrated potency of these regimens. Despite the absence of substantial data on the use of lopinavir/ritonavir in pregnancy, it is currently the PI most commonly given to pregnant women because of its low associated risk of side effects. The case study in Box 1 provides an example of the management of a pregnant woman found to be failing her first-line regimen during pregnancy.

**ART SIDE EFFECTS AND DRUG TOXICITIES**

First-line antiretroviral drugs are fairly well tolerated in pregnant women. For the most part, side effects are uncommon, relatively mild, and often transient. However, there are a few important considerations.

NVP has been associated with two rare but potentially severe side effects: rash and hepatotoxicity. Both usually occur in the first three months of therapy and appear more common in women with CD4 counts greater than 250 cells/mm³.7 Incorporation of a two-week lead-in period for NVP—where 200 mg is administered once daily rather than twice daily—is believed to reduce these risks.10

When combined with other first-line antiretrovirals, d4T is considered safe and effective. However, stavudine must not be prescribed with ddI during pregnancy due to significantly elevated risks for lactic acidosis and pancreatitis. Given the potential severity of either diagnosis, particularly in settings where diagnostic tests may not be readily accessible, this combination should be avoided.

Consideration should also be given to the specific side effects of each medication in the context of the pregnancy. One common side effect of AZT is nausea. If a patient has a condition that may be exacerbated by these side effects (e.g., hyperemesis gravidarum), care should be taken to avoid AZT or to be aggressive about treating symptoms.

Due to its tolerability, effectiveness, and low pill burden, TDF has been incorporated into first-line drug regimens in many countries. Although the drug has been categorized by the U.S. Food and Drug Administration (FDA) as "B" (i.e., animal evidence reveals no harm to the fetus), its chronic use in pregnancy has not been well studied. TDF has been associated with decreased bone mineral density among children and as a result, theoretical concerns have been raised that the drug may impair fetal bone development. At this time, WHO has not recommended TDF as a first-line regimen and it is therefore listed among the second-line regimens in this chapter.5

EFV has been associated with neural tube defects in animal studies and in a few cases among humans. For this reason, the drug has been designated as category “D” (i.e., positive evidence for fetal malformations) by the FDA. However, when choices for second-line antiretroviral drugs are limited, EFV may be considered in the second or third trimester, long after organogenesis. This option is particularly important in settings where...
ADVERSE OUTCOMES ASSOCIATED WITH HIV INFECTION AND ART IN PREGNANCY

Preterm Birth and Low Infant Birth Weight
HIV infection has been associated with higher rates of preterm birth and low birth weight (LBW) when compared to the general antenatal population. A large observational cohort in the United States found that HIV infection was associated with a nearly twofold risk in preterm birth. In Kenya, HIV infection was associated with a threefold risk for delivering an LBW infant. Other studies have described similar phenomena. Among HIV-positive women, those with severe immunosuppression appear to be at the greatest risk.

At present it is unclear whether the use of ART increases the likelihood of preterm birth or LBW infants among HIV-positive pregnant women. In Europe, cohort studies have demonstrated up to a fourfold increase in risk for preterm delivery among women using PIs. However, most studies from the United States and Latin America have not demonstrated this association. Because of the limited availability of ART in Africa for the past decade, few studies are available for this region. In one such analysis, investigators from Côte d’Ivoire did note a two- to threefold increase in LBW infants when ART was used compared to short-course PMTCT regimens, but this did not specifically look at PI-based regimens.

Stillbirth
HIV infection has been associated with an increased risk for fetal death in a number of studies. Separate case-control studies in Kenya, for example, demonstrated a nearly threefold risk for stillbirth among HIV-positive women. These results were supported by a large meta-analysis examining the same issue; across 31 studies, stillbirth was nearly four times as likely in HIV-positive pregnant women when compared to HIV-negative pregnant women. More recent work in African countries has suggested that this effect may be mediated by immunosuppression (i.e., lower CD4 counts), suggesting that ART may improve these birth outcomes. However, more investigation is needed.

Fetal Malformations
Few antiretrovirals have been associated with fetal malformations, yet cases have been reported with the use of EFV in the first trimester of pregnancy. In population-based studies and pregnancy registries, none of the commonly used antiretroviral drugs have been associated with birth defects. Despite these findings, surveillance should continue as services expand rapidly in HIV-high-prevalence settings.

Other Obstetrical Complications
Suy and colleagues identified HIV infection as a risk factor for the development of pre-eclampsia. Risk appeared to be highest—over fivefold when compared to HIV-negative women—among women on ART before conception. Risk was not associated with any specific drug regimens; however, others have hypothesized a theoretical link between pre-eclampsia and PIs. Certain antiretroviral drugs, in
particular PIs, had been linked to increased odds of gestational diabetes.\textsuperscript{32,33} More recent data, however, suggest no association.\textsuperscript{34,35}

In summary, HIV infection has been independently associated with a number of adverse pregnancy outcomes. In some cases, these outcomes may be related to the use of antiretrovirals, although risk appears to be highest among patients receiving long-term therapy. Despite these concerns, it is important to initiate ART during pregnancy for all eligible women, either for maternal treatment or for PMTCT, since the benefits of such therapy convincingly outweigh any potential risks identified thus far.

**HIV-RELATED COMPLICATIONS IN PREGNANCY**

**Pneumonia**

Pneumonia in pregnancy is associated with greater morbidity and mortality than in nonpregnant women. Pregnant women living with HIV are at higher risk of acquiring pneumonias (such as *Staphylococcus*, *Mycoplasma*, *Mycobacterium*, and *Pneumocystis carinii* pneumonia [PCP]). For example, one U.S. study found an overall mortality rate among pregnant women infected with PCP of 50% (n=22).\textsuperscript{36} Even slight changes in oxygenation can adversely affect the fetus, and women who have pregnancies complicated by pneumonia are more likely to have LBW and premature infants. While the impact of PCP and other pneumonias on maternal morbidity and mortality as well as pregnancy outcomes in African countries is considered to be significant, there are no currently available data on the incidence of PCP among HIV-positive women in this region.

Symptoms of pneumonia in pregnancy include fever, cough, and dyspnea. The evaluation of pregnant women with signs of pneumonia should include a thorough history, a chest exam, and a chest X-ray (the woman should be draped with a lead shield to protect her abdomen before having an X-ray).

Treatment recommendations for PCP are trimethoprim/sulfamethoxazole at 15 mg/kg/day intravenously or orally for 21 days.\textsuperscript{36} If the patient is severely immunocompromised (CD4 <200 cells/mm\(^3\)), oral prednisone or intravenous methylprednisolone can be initiated before starting trimethoprim/sulfamethoxazole. Once diagnosed, patients will need to stay on lifelong PCP prophylaxis.

Any HIV-positive pregnant woman should receive PCP prophylaxis if her CD4 cell count is less than 350 cells/mm\(^3\).\textsuperscript{37}

**Tuberculosis**

Pregnancy is not a risk factor for the development of tuberculosis (TB). HIV-positive pregnant women do not need to receive isoniazid prophylaxis simply because they are pregnant. However, like pneumonia, TB can cause even higher morbidity and mortality in pregnancy because of the reduction in pulmonary reserves. TB can also be hard to diagnose, and clinicians may not be as aggressive in attempting to diagnose or in treating pregnant women with suspected TB.

Pregnant women with suspected TB (i.e., experiencing cough for more than two weeks, fever, or weight loss) should undergo a sputum test and chest X-ray and should be treated aggressively if found to be infected with TB. HIV-positive pregnant women who are not on ART can receive the same nationally approved anti-TB regimen given to nonpregnant women. If a pregnant woman is receiving ART, it is most likely an NVP-containing regimen. Many TB regimens in Africa are rifampicin based, which makes the selection of antiretrovirals for women receiving rifampicin challenging because rifampicin decreases the therapeutic levels of NVP, leading to decreased effectiveness.\textsuperscript{38} Rifampicin also interacts with many PIs,\textsuperscript{39} decreasing their blood serum concentrations. Choices of
antiretroviral drugs for pregnant women who are receiving anti-TB therapy are as follows:

- An EFV-based ART regimen (if TB is diagnosed in the second or third trimester).
- Rifabutin substituted for rifampicin. This can be given with NVP; however, rifabutin is not widely available in many countries.
- A triple-drug NRTI regimen, such as AZT + 3TC + ABC or TDF; this regimen may not be as potent as other regimens.
- Another option is to give a boosted PI with anti-TB therapy; however, this may cause untolerable side effects such as nausea and diarrhea.

Isoniazid, ethambutol, pyrazinamide, and rifampicin are all safe for use in pregnancy. Streptomycin is teratogenic and should not be given in pregnancy.

**Malaria**

Malaria is endemic to sub-Saharan Africa and HIV infection may affect a pregnant woman’s ability to mount an appropriate immune response to *Plasmodium falciparum*. Studies have shown that pregnant women coinfected with HIV and malaria have higher risks of placental malaria and parasitemia. The standard of care in many malaria-endemic areas is intermittent presumptive therapy (IPT) with sulfadoxine-pyrimethamine (S-P). It is crucial that health-care providers be aware of whether a pregnant woman on ART is also receiving IPT; for this reason, administration of IPT to pregnant women should always be well documented. Both S-P and NVP can cause liver and skin toxicity, and S-P and AZT can both cause anemia. If anemia is seen as a side effect in patients receiving both S-P and AZT, it may be difficult to distinguish which drug is responsible. Therefore, staggering the administration of IPT with the administration of ART may be something to consider.

Women taking cotrimoxazole prophylaxis do not require IPT because cotrimoxazole prophylaxis provides sufficient protection against malaria. However, these women should be advised to sleep under mosquito nets for additional protection.

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**Box 2. Case Study: Pregnant Woman with Kaposi’s Sarcoma**

A 26-year-old woman is seen in October with a CD4 count of 288 cells/mm³. She presents to the ART clinic three months later at 32 weeks gestation, at which time she is diagnosed with KS, placing her at WHO HIV disease stage IV. At this time, she complains of breathlessness, fatigue, and odynophagia. Fetal movements are present. Her oral/pharynx examination shows subcutaneous and cutaneous KS nodules on the face, arms, thighs and legs, conjunctiva, and eyelids. She also has KS lesions on the tongue and hard palate with questionable lung involvement. Chest has bronchial breath sounds.

The patient is started on an ART regimen consisting of d4T, 3TC, and high-dose lopinavir/ritonavir (4 capsules twice daily) as well as septrin and hematins (her Hb was <10.0 g/dL). An ultrasound is performed that is suggestive of oligohydramnios, and the symphysial fundal height is 27/40 but the U/S estimate is 32/40 weeks gestation. Chest X-ray is not suggestive of lung involvement but close follow-up is required to rule it out.

The patient is referred to a tertiary center for chemotherapy and is given steroids; she delivers two weeks after starting ART. Chemotherapy is started after delivery.

The patient develops a fever three weeks after commencing chemotherapy and is treated for early sepsis. Liposomal doxorubicin is given in cycles and the patient’s general condition starts improving. Septrin prophylaxis is given to the infant, and at six weeks, PCR testing is done on the infant, who is found to be HIV-uninfected. The patient is closely followed at a general health clinic and shows marked improvement. After six months on antiretrovirals, she is asymptomatic with the KS lesions resolving and no further facial edema.
**Kaposi’s Sarcoma**

Common treatments for systemic Kaposi’s sarcoma (KS) are chemotherapeutic agents such as (paclitaxel), doxorubicin, interferon-alpha 2, alitretinoin, and vinblastine; none of these can be safely given in pregnancy. For cases of disseminated KS in pregnancy, the benefits of treating the mother with a teratogenic agent versus preserving the health of the fetus should be weighed. Antenatal steroids should be given to the mother if the decision is made to deliver the infant before 34 weeks in order to start maternal therapy. After delivery, the mother can be given the appropriate agents. The case study in Box 2 provides an example of a patient who was diagnosed with KS during pregnancy and subsequently treated.

**SPECIAL CONSIDERATIONS**

**ART in Early Pregnancy**

At each routine visit, women who are on ART should be asked what, if any, method of contraception they are using. ART clinics are an ideal place to promote contraception for women who do not wish to become pregnant. Women should also be asked when their last menstrual period was in order to detect any possibility that they may be pregnant.

Many of the commonly used antiretroviral drugs are not known to be teratogenic; however, it is usually best to avoid initiating ART during the first trimester. If a woman who is already on ART becomes pregnant, it is recommended that she continue therapy since the risks of discontinuing ART outweigh any known risks to the fetus.

**ART and Breastfeeding**

Pregnant women who are placed on ART during pregnancy for their own health usually continue on ART postpartum. In many countries, these women will choose to breastfeed. Currently WHO does not explicitly recommend that women on ART continue to breastfeed, but an increasing body of evidence suggests that women on ART have a reduced risk of transmitting HIV to their infants postpartum. Results of multiple studies from Rwanda, Tanzania, and Zambia on breastfeeding and transmission rates all demonstrate very low rates of postpartum mother-to-child transmission among women on ART. In the study from Rwanda, 572 pregnant women were enrolled, of whom 224 chose breastfeeding while on ART (which were mostly NRTI-based regimens). Only six infants became infected with HIV, all of whom were infected at birth. A second study done in Tanzania followed women who started ART at 34 weeks gestation (earlier if they needed ART for their own health) or through six months of breastfeeding. Women were counseled to stop breastfeeding at six months postpartum. Of the 441 infants included in the analysis, 4.1% were infected at birth and 5% at six months of age, showing little transmission during breastfeeding.

**CONCLUSION**

Treating eligible pregnant women with ART has many benefits beyond the improved health of the mother. Using a CD4 cell count cutoff for starting ART that continues for a lifetime should be highly considered for both maternal and infant benefits. Treating pregnant women can be complicated, and new data are constantly emerging which will enable us to treat these patients more effectively.


Drug Resistance Following the Use of Antiretrovirals for Prevention of Mother-to-Child Transmission of HIV: Prevalence and Implications for Treatment Response

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The likelihood of developing detectable HIV-1 drug resistance depends upon numerous factors. First, even a single mutation in the HIV-1 reverse transcriptase gene is sufficient to cause high-level resistance to nevirapine (NVP) or lamivudine (3TC) (e.g., K103N or Y181C with nevirapine, or M184V with 3TC). NVP has been detected in maternal blood for up to three weeks following ingestion of a single dose, and this long half-life essentially creates a lengthy period of monotherapy that predisposes to the development of NVP resistance. Higher HIV-1 RNA level and lower CD4 count at the time of drug exposure during pregnancy are associated with the development of drug resistance following mono- and dual-drug use for prevention of mother-to-child transmission (PMTCT). HIV-1 subtype may also be associated with emergence of drug-resistant virus: NVP resistance following single-dose (sd) NVP exposure arises more frequently with subtype C than with D, and less with subtype A. Potent combination regimens that fully suppress maternal viral load and/or use of antiretroviral drugs with a high resistance barrier will minimize the development of resistance in mothers and in infected babies. However, these combination regimens are not yet widely available for PMTCT, and in many settings, sdNVP remains the most feasible option.

Two additional factors to consider when evaluating drug resistance results post-PMTCT are the timing of measurement of drug resistance in relation to the timing of the intervention (drug resistance tends to “fade” from detection over time, in the absence of ongoing selection pressure for the resistant virus strains) and the assay used to test for drug resistance (e.g., standard licensed technique vs. highly sensitive research assay such as allele-specific polymerase chain reaction [PCR]). Current standard genotyping sequencing assays (such as Viroseq) can detect subpopulations of drug-resistant virus that comprise 10%–20% or more of the overall virus population. Highly sensitive assays, such as allele-specific PCR or TyHRT yeast assays, can detect viral variants that comprise 1% or less of circulating virus. The clinical implications of the presence of very small populations of resistant virus have yet to be fully elucidated.
DRUG RESISTANCE FOLLOWING 
ZIDOVUDINE AND 3TC FOR PMTCT

Clinically significant drug resistance arises relatively infrequently following antiretroviral prophylaxis with short-course zidovudine (ZDV) during pregnancy.\(^4\)\(^,\)\(^1\)\(^1\)\(^,\)\(^1\)\(^2\) For example, in the Pediatric AIDS Clinical Trials Group 076 study, maternal samples from 96 women (with high median CD4 count of greater than 550 cells/mm\(^3\)) were tested for the presence of minor (K70R) and major (T215Y/F) ZDV drug resistance mutations; only one of 39 developed the former, and none of 42 women developed the latter (clinically significant) drug resistance mutations.\(^1\)\(^1\) Pregnant women in the Thai Perinatal HIV Prevention Clinical Trial (PHPT-2) study started ZDV at 28 weeks gestation, and the majority also received sdNVP; 4.6% (12 of 256) developed one or more important ZDV resistance mutations when tested at a median of 12 days postpartum.\(^1\)\(^3\) Drug resistance mutations were detected in a higher proportion (25%) of Women and Infants Transmission Study participants after receipt of antepartum ZDV, and the emergence of drug resistance was associated with higher viral load and lower CD4 count.\(^4\)

Drug resistance of 3TC arises with greater frequency following use of 3TC in combination with ZDV during pregnancy. New 3TC resistance in this context is associated with the duration of 3TC exposure. For example, when pregnant women in a French cohort added 3TC to ZDV at 32 weeks gestation, 39% had 3TC resistance at six weeks postpartum.\(^5\) Longer exposure to 3TC was associated with greater risk of resistance: 3TC resistance was detected in 50% (37 of 74) of women who received at least two months of 3TC, 20% (14 of 70) who received one to two months, and none of 12 who received less than one month of 3TC.\(^5\) Among participants in the sub-Saharan Africa PETRA trial who took ZDV/3TC starting at 36 weeks gestation and for one week postpartum, 12% (six out of 50) of women were found to have 3TC resistance at one week after delivery.\(^1\)\(^4\) In the DITRAME Plus study in Côte d’Ivoire, women took ZDV/3TC starting at 32 weeks gestation and one dose of NVP intrapartum; 8.3% of women had 3TC resistance at four weeks postpartum, and 3TC resistance was again associated with duration of ZDV/3TC exposure.\(^1\)\(^5\) In a smaller study in Thailand, none of 32 women tested at six weeks postpartum was found to have 3TC-resistant virus following antepartum exposure to ZDV/3TC from 34 weeks gestation.\(^1\)\(^6\) Similarly, none of 37 women who received ZDV/3TC for one week after delivery in the South African Intrapartum Nevirapine Trial\(^2\)\(^\text{7}\) or of 42 women who received ZDV/3TC for four to seven days postpartum in the Treatment Options Preservation Study (TOPS)\(^1\)\(^8\) had detectable ZDV or 3TC mutations at four to six weeks after delivery using standard resistance assays.

SINGLE-DOSE NVP 
AND DRUG RESISTANCE 
USING STANDARD ASSAYS

Drug resistance that emerges after the use of NVP—particularly sdNVP—arises frequently both in women and in HIV-1-infected infants exposed to sdNVP and has engendered the most concern related to resistance and PMTCT regimens.

Several studies conducted in Africa using standard genotyping assays have examined the prevalence of maternal NVP resistance mutations following ingestion of only sdNVP (without other antiretrovirals) and found it to be present in 25%–75% of women.\(^6\)\(^,\)\(^7\)\(^,\)\(^1\)\(^8\)\(^-\)\(^2\)\(^2\) NVP resistance emerges with somewhat lower frequency when other antiretroviral drugs are used in combination with sdNVP for PMTCT. For example, when sdNVP was given in combination with short-course ZDV, NVP resistance was detected in 45% of women in Botswana,\(^2\)\(^3\) in 33% in Côte d’Ivoire,\(^2\)\(^4\) and in 18% in Thailand.\(^2\)\(^5\) The use of NVP-containing three-drug
antiretroviral therapy (ART) during pregnancy further attenuates (to the 10%–15% range) but does not entirely eliminate the selection of NVP drug resistance,\textsuperscript{26,27} which can certainly also emerge in the context of suboptimal adherence.

A strategy for reducing NVP resistance that was employed with success in South Africa’s TOPS was the use of a four- or seven-day postpartum maternal “tail” of ZDV/3TC following sdNVP (among mothers who did not receive any other antiretroviral drugs).\textsuperscript{18} This approach was associated with a significant reduction in the prevalence of NVP resistance among women, from 57% with sdNVP alone to 13% with the addition of four days of ZDV/3TC and 9% with an additional seven days of ZDV/3TC.\textsuperscript{18} These findings prompted the inclusion of intrapartum ZDV/3TC and a seven-day “tail” of maternal postpartum ZDV/3TC among women who took intrapartum sdNVP (with or without short-course ZDV during pregnancy) to reduce the emergence of NVP resistance among mothers.\textsuperscript{28}

Another study has demonstrated that among mothers with CD4 greater than 200 cells/mm\textsuperscript{3} who take ZDV from 32 weeks gestation plus sdNVP, the addition of a single dose of tenofovir/emtricitabine also significantly reduces the rate of maternal NVP resistance (from 30% without tenofovir/emtricitabine to 14% with the drug) among women with viral load greater than 2,000 copies/mL and genotypes available (\textit{P}=.001).\textsuperscript{29} Other similar “tail” strategies are currently under study.

**SINGLE-DOSE NVP AND DRUG RESISTANCE USING HIGHLY SENSITIVE ASSAYS**

Many recent studies have evaluated the presence of minor resistant variants in women following sdNVP ingestion, some of them studying the persistence of these variants over time. These studies have demonstrated that some level of NVP-resistant virus is present in the majority of women, and that many women without detectable NVP resistance using standard assays harbor some degree of resistance when highly sensitive assays are used.\textsuperscript{30–32} For example, among 9 women with NVP resistance at 6–8 weeks but not at 12–24 months postpartum by standard genotyping, 3 women had K103N using the highly sensitive LigAmp technique.\textsuperscript{33} Johnson et al found the NVP resistance-conferring K103N mutation in 16 (40%) of 40 women (who did not have resistant virus at this time by conventional sequencing) at 6–36 weeks postpartum, using real-time PCR-based methods.\textsuperscript{31} In another, smaller study in 22 women, using allele-specific PCR, 5 of 7 women who did not have non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance by standard sequencing at 2 months postpartum had NVP resistance detected by allele-specific PCR.\textsuperscript{32}

NVP resistance is known to “fade” from detection with increasing time since sdNVP exposure when standard resistance assays are used.\textsuperscript{3,20,34} Resistance is also detected with decreasing frequency over time when more sensitive resistance assays are employed. In a study of 144 women who took sdNVP in the HIV Network for Prevention Trial 012 study in Uganda, K103N resistant variants were estimated to persist at low levels in 41.7% of women at six to eight weeks, 12.4% at two years, 8.1% at three years, and 0.9% at four and five years postpartum (using the LigAmp technique).\textsuperscript{35} The mean percentage of virus that harbored the K103N mutation among women with detectable K103N was 1.2% at two years and 0.8% at three years.\textsuperscript{35} Persistence of resistance in this study was independently associated with HIV-1 subtype (more frequent with subtype D than with subtype A) and with higher pre-sdNVP viral load.\textsuperscript{35}

A different study sought minor variants with the K103N mutation both in plasma and in cell-associated virus (peripheral white blood cells) over time.\textsuperscript{8} The investigators used allele-specific PCR and tested samples from 67 women from South Africa.
They found plasma virus with K103N in 87% of women at 6 weeks, 39% at 6 months, and 11% at 12 months, but detected K103N in cell-associated virus among 52% of women at 6 weeks but only 4% at 12 months post-exposure. These K103N variants comprised small proportions of the overall circulating plasma HIV-1 population, particularly with increasing time postpartum: the median relative frequency of viral mutants in plasma was 11% at 6 weeks, 6% at 3 months, 1% at 7 months, and 0.7% at 12 months.4

The most important question is whether these low proportions of circulating or archived NNRTI-resistant virus that persist for months or even years following sdNVP exposure affect virologic and immunologic responses to subsequent NNRTI-based ART, as well as responses to sdNVP for PMTCT in the future.

**DRUG RESISTANCE AND SUBSEQUENT RESPONSE TO NVP-CONTAINING ART**

Over the past several years, evidence has emerged that prior sdNVP exposure may compromise subsequent response to NNRTI-based ART among women but that this deleterious effect may be concentrated among women who start ART relatively early following sdNVP ingestion. The first study to report on this was a substudy of PHPT-2, conducted in Thailand.13 In this study, women started ZDV at 28 weeks gestation and were randomized to receive either sdNVP or placebo during labor. Enrollment to the maternal placebo group was halted after the first interim analysis showed higher MTCT rates in the placebo arm. NVP-containing ART subsequently became available to women in the study with CD4 <250 cells/mm3, and 269 women were followed for virologic and immunologic responses to ART—48 with prior placebo and 221 with prior sdNVP receipt. The median time between delivery and ART initiation was 14.9 months in the placebo group and 6.1 months in the sdNVP group (P<.001), although pre-ART baseline CD4 and HIV-1 RNA were comparable in these groups (which introduces the possibility that the placebo recipients who started ART in this study experienced slower disease progression). Six months after ART initiation, 68% of the placebo group and 49% of the sdNVP group had HIV-1 RNA <50 copies/mL (P=.03), although the proportions with HIV-1 RNA <400 copies/mL did not differ significantly between groups (85% and 76%, respectively).25 When the analysis was restricted to women who delivered before the placebo arm stopped enrolling (i.e., contemporaneously enrolled women), there was no longer a significant difference in proportions suppressing HIV-1 RNA to less than 50 copies/mL (although a trend existed). The investigators did not find statistically significant differences in virologic response among women starting ART within versus longer than 6 months postpartum. Results from this study did not change after 18 months of follow-up of women on ART.36

The next major study to report data in response to NNRTI-containing ART following sdNVP exposure was the “Mashi Plus” study from Botswana.37 This study had a similar design. In the “parent” Mashi study, women started ZDV at 34 weeks gestation and were randomized to receive either sdNVP or placebo during labor. Enrollment to the maternal placebo group was halted after the first interim analysis showed higher MTCT rates in the placebo arm. NVP-containing ART subsequently became available to women in the study with CD4 <250 cells/mm3 or an AIDS-defining illness. Two hundred eighteen women who started ART (with NVP, generally in combination with ZDV and 3TC) postpartum were included in the first analysis. Overall, 5.0% of 106 women who had previously taken placebo versus 18.4% of 112 with prior sdNVP exposure experienced virologic failure by 6 months on treatment (P=.002). However, the treatment response among sdNVP-exposed
and sdNVP-unexposed women was equally good among the subset of 158 women who started ART at least 6 months postpartum (7.8% of placebo and 12.0% of sdNVP recipients experienced virologic failure after 6 months on ART, \(P=.39\)). Among the 60 women who started ART within 6 months of delivery, 41.7% of the sdNVP recipients versus none of the placebo recipients experienced virologic failure on treatment \((P<.001)\). These findings did not change qualitatively with increasing time on ART. However, only 96 women had follow-up data through 24 months on ART, and these—and additional—Mashi Plus study participants are still being followed to determine the longevity of virologic suppression on NVP-containing ART in the sdNVP and placebo groups. Maternal CD4 cell response and suppression of HIV-1 RNA to <50 copies/mL did not differ by sdNVP exposure status. Only 30 HIV-infected infants—15 with prior exposure to both maternal and infant sdNVP and 15 sdNVP-unexposed infants—were included in a similar analysis in the Mashi Plus study. The virologic failure rates by 6 months on NVP, ZDV, and 3TC were much higher (76.9%) in the sdNVP-exposed infants compared with the non-NVP-exposed infants (9.1%) by 6 months on ART \((P<.001)\). These are the first data on this topic in infants, albeit in a small group.

HIV-positive women with recent pregnancy tend to be healthier than the general population of HIV-positive women presenting for care in most settings. As a consequence, it is challenging to find women with and without prior sdNVP exposure who are comparable in key characteristics such as CD4 and HIV-1 RNA, and thus difficult to control for these (and other potential unmeasured) confounding health characteristics. Therefore, these two double-blind placebo-controlled PMTCT trials (PHPT-2 and Mashi Plus), in which NVP-based ART became available after study initiation, provide the most rigorous data to date on this topic. Other studies have nevertheless added important information on this topic. Collectively, they suggest that women who start NNRTI-based ART more remotely following sdNVP exposure can experience immunologic and virologic outcomes that are comparable to those in non-sdNVP-exposed women.

The Nevirapine Resistance Study (“NEVEREST”) from South Africa includes HIV-1 RNA response to ART (with NVP, 3TC, and stavudine) among 65 women who took sdNVP 18–36 months (median 25 months) previously, and 40 HIV-positive women who gave birth in the same time frame (median 19 months earlier) but who had never received sdNVP. Both baseline median CD4 count and HIV-1 RNA trended toward being higher in the non-sdNVP-exposed women. At 24 weeks on treatment, 100% of 48 sdNVP-exposed women and 74% of 23 unexposed women had HIV-1 RNA less than 50 copies/mL \((P=.007)\), and the CD4 count did not differ. The fact that the sdNVP-exposed women actually had higher rates of virologic suppression than the nonexposed women raises the possibility that they were healthier in some unmeasured way. Nevertheless, this study added data to support the efficacy of NVP-containing ART among women who received sdNVP at least 18 months previously.

One other study, conducted in Zimbabwe, also evaluated virologic response to NVP-containing ART among 20 women with prior exposure to sdNVP and 33 women with prior exposure to short-course ZDV; similar proportions (45% and 50%, respectively) had HIV-1 RNA less than 50 copies/mL at 48 weeks after ART initiation. Interestingly, a study among 247 HIV-positive postpartum women in Côte d’Ivoire who started NNRTI-based ART following exposure to varying degrees of antiretroviral use for PMTCT found in multivariate analysis that postpartum 3TC resistance mutations and baseline CD4 less than 200 cells/mm\(^3\) were associated with virologic
failure on subsequent ART, but that exposure to sdNVP was not significantly associated with virologic failure.40

Several other studies have evaluated immunologic (but not virologic) outcomes on NVP-based ART among women with prior sdNVP exposure. A Zambian treatment program found that clinical failure and mortality on NVP-containing ART did not differ among 751 women with and 5,989 women without prior sdNVP exposure, respectively, and CD4 count increase did not differ by sdNVP exposure status in the subsets of women with complete CD4 data.41 However, as might be expected, baseline CD4 count was lower (143 cells/mm³) and World Health Organization (WHO) stage higher in the non-sdNVP-exposed women than in the exposed women (170 cells/mm³, P<.001). The investigators did describe a trend toward lower CD4 increase on ART among women starting treatment within six months (150 cells/mm³) versus those starting treatment six or more months following sdNVP exposure (219 cells/mm³, P=.06).41 A smaller study from Côte d’Ivoire among 64 women with (median 19 months previously) and 63 women without prior sdNVP exposure and with CD4 outcomes available did not observe differences in CD4 count increase on ART (the sdNVP-exposed women had received either short-course ZDV or ZDV/3TC in addition to sdNVP, and virologic outcomes were not available).42

**CONCLUSION**

In summary, sdNVP (alone or in combination with one or two other drugs) selects for NVP-resistant virus in a large proportion of women and HIV-infected infants. Available data suggest that sdNVP taken with short-course ZDV for PMTCT (and perhaps sdNVP alone) does not compromise virologic, immunologic, and clinical responses to subsequent NVP-containing ART among women who start ART at least six months after sdNVP ingestion, although one important study42 did report lower rates of virologic suppression to less than 50 copies/mL among sdNVP-exposed women, with no association with time from exposure.

Several important questions remain. Approaches to decreasing the rate of NVP resistance following sdNVP (e.g., by giving additional intrapartum and postpartum antiretroviral drugs) are needed and are under study, as are other effective, safe, and simple PMTCT interventions that might obviate the use of sdNVP. The longevity of viral suppression on ART among women with prior sdNVP exposure needs further elucidation. Additional studies that incorporate HIV-1 RNA monitoring are important, given the relatively low sensitivity of CD4 or clinical responses for virologic failure. More data regarding ART response among women who take sdNVP alone or with antiretroviral drugs other than ZDV are needed, as are studies that evaluate the optimal ART regimen for sdNVP-exposed women. Finally, data regarding infant ART outcomes among infants who become HIV-infected despite sdNVP use are urgently needed.

In the meantime, while sdNVP still plays an important role in PMTCT in settings where it is the only currently feasible option, every effort should be made to provide ART to pregnant women with advanced HIV disease; this will improve maternal health, decrease MTCT, and avoid sdNVP use in the women who are at greatest risk for developing drug resistance.
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The Evolution of Prevention of Mother-to-Child Transmission: From Simple to More Complex Regimens

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ESPITE THE DEVELOPMENT OF highly efficacious interventions for the prevention of mother-to-child transmission (PMTCT) of HIV in developed countries, the full benefits of such interventions have yet to be realized in the most affected regions of the world, where the number of infants perinatally infected with HIV continues to rise. This increase is due in part to the still rising number of HIV infections among women of childbearing age.¹

According to the World Health Organization (WHO) and the Joint United Nations Program on HIV/AIDS (UNAIDS), in 2007, only one-third of HIV-positive pregnant women worldwide received any intervention to prevent transmission of HIV to their infants.¹ While the number of women having access to PMTCT services continues to grow, the use of the simplest PMTCT intervention—single-dose nevirapine (sdNVP) at delivery—is still limited not only by its feasibility, affordability, or required logistics, but also by a lack of political leadership and commitment at various levels. These barriers must be overcome if pregnant women are to have greater access to essential information, antenatal care, counseling, and testing. Women living with HIV also require additional forms of support in order to overcome fear of their disease and the discrimination and stigma attached to it.

This chapter provides a scientific overview of the successive breakthroughs in PMTCT research that have led to the current recommendations in high-, middle-, and low-income countries.² The evolution of PMTCT interventions are described, with a focus on the increasing use of complex regimens. First, we discuss the efficacy of various PMTCT interventions, as well as safety considerations for the mother and child regarding use of antiretroviral drugs (ARVs) during pregnancy. This will be followed by a brief summary of the dilemma posed by the selection of HIV-resistance mutations following the prophylactic use of ARVs. Finally, we discuss the obstacles to be overcome when using such regimens in resource-limited settings. The formidable challenges represented by HIV transmission through breastfeeding are covered elsewhere in this text.
TIMING OF MOTHER-TO-CHILD TRANSMISSION OF HIV: RISK FACTORS AND INITIAL PREVENTION STUDIES

Early cohort studies performed in the 1980s showed that mother-to-child transmission (MTCT) of HIV could occur during pregnancy, labor, and delivery, as well as during breastfeeding.\(^3\),\(^4\) In Africa, where most women breastfeed their infants, transmission rates varied from 25% to 43%.\(^5\),\(^6\) In contrast, in high-income countries, where formula was provided to most babies, rates were much lower, ranging from 13% to 25%.\(^7\)\,-\(^12\)

The exact timing of transmission was estimated retrospectively by studying the kinetics of viral markers after the birth of the infants and was confirmed by observing the preventive effects of variously timed interventions. Infants found to be HIV infected at birth were conventionally assumed to have been infected during pregnancy (in utero), whereas infants found to be HIV negative at birth who later turned out to be positive were presumed to have been infected during labor and delivery (intrapartum) or through breastfeeding (postpartum).\(^13\)

Generally speaking, in the absence of preventive interventions, the risk of MTCT was estimated to be approximately 10% in utero, 15% intrapartum, and up to 15% postpartum, depending on the duration of breastfeeding.\(^4\)

In most studies during this period, high maternal viral load, together with advanced stage of the disease, impaired immunity, and intensity of exposure of the infant to HIV during delivery, was found to be associated with increased HIV transmission.\(^14\)\,-\(^18\) These observations on the timing and factors associated with transmission led to the eventual development of preventive interventions, which, in fewer than 10 years, virtually eliminated pediatric AIDS in high-income countries.

As soon as zidovudine (AZT)—the first ARV drug discovered—became available, its use during pregnancy to prevent HIV transmission from mother to child was envisioned. Its efficacy and safety were established in 1994 in the landmark Pediatric AIDS Clinical Trials Group (PACTG) 076 clinical trial.\(^19\) In this study, conducted in the United States and in France, women started taking oral AZT between 14 and 34 weeks gestation (median 28 weeks) and continued through to the end of the pregnancy. An AZT intravenous infusion was administered during labor, and oral AZT was given to the newborn for 6 weeks. All infants were formula fed, eliminating the risk of infection through breast milk. The trial was stopped at the first interim analysis, as the transmission rate in the placebo group was considerably higher than in the AZT group; all women and infants in the trial were then offered AZT. Final results demonstrated a 67.5% reduction of the transmission rate, from 22.6% in the placebo group to 7.6% in the AZT group.\(^20\) All subsequent studies confirmed the remarkable efficacy of ante-, intra-, and postpartum AZT prophylaxis for PMTCT.

Similarly, as a means to reduce fetal exposure to HIV during labor and delivery, the use of programmed cesarean section (C-section) to prevent intrapartum transmission was formally tested. In the European Mode of Delivery clinical trial, the rate of transmission in women randomized to deliver vaginally was 10.5%, whereas it was 1.8% in women who were randomized to deliver through elective C-sections.\(^21\) Interestingly, those women who were randomized to either group but who had an emergent C-section (i.e., performed after onset of labor) had a higher transmission rate of 8.8%.

In summary, these early landmark proof-of-concept studies demonstrated that MTCT of HIV could be prevented and that a combination of several methods would most likely reduce the risk of transmission even further.
TOWARD ERADICATION OF PEDIATRIC AIDS IN DEVELOPED COUNTRIES: INCREMENTAL CHANGES IN PRACTICE

In order to understand the evolution of perinatal HIV prevention in high-income countries, it may be helpful to recall that all along, since the initial discovery that HIV could be transmitted from an HIV-positive mother to her infant, there has been a constant interplay between actual medical care practices and research results. For example, as soon as it was reported that HIV could be transmitted through breast milk, clinicians in high-income countries started to advise HIV-positive women to give formula to their infants, even before formal recommendations were issued by the Centers for Disease Control and Prevention (CDC). It was only much later that the magnitude of postnatal transmission was established, partly through observational studies and clinical trials performed in Africa.

Following the release of the PACTG 076 results in 1994, counseling and testing of pregnant women, plus AZT prophylaxis begun during the second trimester, rapidly became the standard of care in high-income countries. Two years later, when the dramatic efficacy of combination antiretroviral therapy (ART; sometimes referred to as highly-active antiretroviral therapy or HAART) in controlling progression of HIV disease was established, an increasing proportion of HIV-positive pregnant women received more complex ARV regimens, at first for their own health, but later for the purpose of achieving lower MTCT rates. With these treatments, the MTCT rates seen in protocol 076 began to fall further.

PACTG 316, which started in 1997 and ended three years later, clearly exemplifies the interplay among clinical care, research, and policy in high-income countries. This study was designed as a randomized, placebo-controlled trial to test whether, in addition to various prophylaxis provided during pregnancy, a single dose of nevirapine (a potent ARV with a long half-life that is rapidly absorbed orally and then crosses the placenta) administered to women at delivery and to their infants within the first days of life could further reduce peripartum transmission. However, the trial was performed at a time when the HIV standard of care was rapidly evolving, with an increasing number of pregnant women receiving more complex ARV regimens as prescribed by their clinicians. In the final analysis of the trial, in addition to nevirapine or placebo, only 23% received AZT monotherapy, 28% received AZT plus lamivudine (3TC), and 49% received other combinations, most of them containing protease inhibitors. Moreover, one-third of the women delivered by elective C-section before onset of labor. Clinicians involved in the study had actually tailored maternal treatment during pregnancy to the women’s clinical and immunological status and to each clinician’s view of the “best” regimen available at the time. Largely as a consequence of this, PACTG 316 did not establish the efficacy of single-dose nevirapine in addition to the other prophylaxis, to prevent transmission, with observed transmission rates considerably lower than expected (1.4% in the nevirapine arm and 1.6% in the placebo arm). In all cases, the bedrock of intrapartum transmission had apparently been reached, and there was no further benefit to be expected from perinatal nevirapine.

Subsequent observational studies confirmed that use of potent ARV combinations during pregnancy, with or without elective C-section delivery, was associated with perinatal HIV transmission rates of 2% or less. Therefore, an increasing proportion of pregnant women, regardless of their immune status, started receiving potent ARV combinations during pregnancy, not for their own health but to minimize the risk of HIV transmission to their infants.
child. Virologically suppressive therapy during pregnancy, combined with elective C-section when viral replication is not fully controlled by the end of pregnancy, is now the base recommendation for PMTCT and care of HIV-positive pregnant women in high-income countries.28,29

PMTCT IN RESOURCE-LIMITED SETTINGS: AN INCREMENTAL, EVIDENCE-BASED APPROACH

While in high-income countries, the studies led to combined and complex PMTCT interventions, trials in developing countries were conducted to simplify and shorten PMTCT interventions in order to improve feasibility, safety, and adherence, while also reducing treatment cost and side effects. In Africa, a series of clinical trials of short-course ARV regimens were conducted in mostly breastfeeding populations, while in Asia, clinical trials evaluated simplified ARV regimens in the absence of breastfeeding. The results of these trials served as the basis for the WHO recommendations for PMTCT in resource-limited settings.2

African Studies in Mostly Breastfeeding Populations

The nevirapine HIV Network for Prevention Trial (HIVNET) 012 in Uganda was a major proof-of-concept trial in resource-limited settings.30 In this study, the simplest intervention was evaluated: a single dose of NVP to the mother during labor and to the infant within the first days of life to prevent transmission from occurring at the time of delivery. Between 1997 and 1999, HIV-positive pregnant women were randomized to receive either (1) sdNVP at onset of labor with sdNVP given to their infants within 72 hours of birth, or (2) repeated doses of AZT during labor, with repeated doses of AZT given to their infants during the first week of life. Virtually all infants were breastfed for a median duration of nine months. MTCT rates among women who had received AZT or sdNVP were, respectively, 10.3% or 8.1% at birth; 22.1% or 13.5% at 14-16 weeks; and 25.8% or 15.7% by 18 months. Single-dose nevirapine was associated with an overall 40% reduction of transmission up to 18 months.30

In Côte d’Ivoire, a CDC trial compared a short course of AZT from 36 weeks of pregnancy through labor to a placebo in a setting where more than 95% of the women breastfed their infants. A 38% reduction in transmission was observed in the AZT arm, with transmission rates at 16.5% in the AZT group versus 26.1% in the placebo group at three months after birth. A similarly short AZT regimen was tested in Burkina Faso and Côte d’Ivoire in the DITRAME-ANRS 049 trial.32 In this study, women received AZT from 36 to 38 weeks gestation until 7 days after delivery. As in the CDC study, a 37% transmission reduction was observed, with transmission rates of 16.8% in the AZT group versus 25.1% in the placebo group at three months of age. Another multicountry study—the UNAIDS-coordinated PETRA trial—evaluated shorter but more potent ARV interventions. This trial used various durations of a combination of AZT plus 3TC in South Africa, Tanzania, and Uganda.33 The rates of transmission at six weeks of age were 8.6% in women who started treatment at 36 weeks gestation and continued for one week postpartum, 10.8% in women who started treatment at onset of labor and continued for one week postpartum, and 17.7% in women who were treated during labor only (which was very similar to the 17.2% rate in the placebo arm).

The SAINT study followed, comparing the effectiveness of a regimen of AZT plus 3TC (similar to the longest PETRA arm) to sdNVP for the mother and child. The transmission rates in the two groups did not differ significantly at eight weeks of age: 9.3% in the AZT plus 3TC group versus 12.3% in the sdNVP group (P=.11).34
The DITRAME Plus study—a more recent study in Côte d’Ivoire, where half of the women were breastfeeding—reported that a regimen of AZT plus 3TC starting at 32 weeks of gestation, with sdNVP at onset of labor, could decrease the transmission to 4.7% at six weeks postpartum. This rate was significantly lower than with AZT alone starting at 36 weeks of gestation.35

Finally, the Mashi trial in Botswana tested the efficacy of sdNVP at onset of labor in addition to AZT initiated at 34 weeks of gestation, according to the mode of feeding.36,37 In the initial stage of the study, in formula-feeding mothers, the transmission rate by one month of age was 2.4% in the peripartum NVP (mother and infant) arm and 8.3% in the placebo arm. In the second phase of the study, the design was revised to compare peripartum NVP (mother and infant, or NVP-NVP) with neonatal NVP provided immediately after birth (neonates only, or placebo-NVP). The observed transmission rate in the placebo-NVP arm (3.7%) was found to not be inferior to the rate in the NVP-NVP arm (4.3%), thus raising the critical question of whether maternal NVP is necessary if the infant NVP dose is administered immediately after birth.

Asian Trials in Nonbreastfeeding Populations

In parallel with the short-course AZT trial in Côte d’Ivoire in breastfeeding women, the CDC was performing another trial in Bangkok, Thailand, comparing the same prophylactic regimen starting at 36 weeks of pregnancy versus a placebo in nonbreastfeeding mothers.38 The rates of MTCT were 9.4% in the AZT group versus 18.9% in the placebo group, indicating a 50.1% reduction in transmission.

Another study in Thailand, Perinatal HIV Prevention Trial (PHPT)-1, compared the efficacy of various durations of prophylactic AZT for PMTCT.39 The transmission rates were 10.5% in the shortest regimen (from 35 weeks of pregnancy and for 3 days in the neonates), 6.5% in the long-long regimen (from 28 weeks of pregnancy and for 6 weeks in the neonates), 4.7% in the long-short regimen, and 8.6% in the short-long regimen. This study demonstrated that AZT prophylaxis had to be initiated at the beginning of the third trimester of pregnancy in order to provide optimal PMTCT and that a longer treatment in the infant was only partially compensating for late initiation of maternal ARV prophylaxis.

A subsequent study in Thailand (PHPT-2) tested the efficacy of sdNVP given to women at onset of labor and to the infant two days after birth added to a standard AZT prophylaxis regimen starting at 28 weeks of pregnancy.40 In this study, three regimens were compared: standard AZT prophylactic regimen only, standard AZT plus sdNVP at onset of labor in the mothers, and standard AZT plus sdNVP at onset of labor in the mothers and sdNVP to the infants 48 hours after birth. The rate of transmission was significantly lower in the group in which both mother and infant received sdNVP (2.0%) and in the group in which only the mothers received sdNVP (2.8%), as compared with the group in which women had received the standard AZT treatment only (6.3%).

The lessons learned from all these studies are that in order to secure maximum efficacy in preventing in utero transmission, (1) ARV prophylaxis must be initiated at the beginning of the third trimester of pregnancy, (2) peripartum sdNVP is extremely efficacious at preventing intrapartum transmission, and (3) peripartum sdNVP associated with AZT monotherapy during pregnancy can lead to transmission rates as low as those obtained with the more aggressive ARV combinations used in high-income countries. Finally, these trials also showed that postnatal transmission associated with breastfeeding reduces, but does not abolish, the efficacy of these interventions over time and
that their benefit remains significant even after exposure to breastfeeding has ceased.

However, all of these simplified regimens lower, but do not completely suppress, viral replication. Therefore, depending on the ARV drugs used, the regimens may lead to the selection of HIV-resistance mutations, which, in turn, may affect the efficacy of ARVs when used for further PMTCT or for HIV care.

**SELECTION OF HIV-RESISTANCE MUTATIONS AFTER ANTIRETROVIRAL PROPHYLAXIS FOR PMTCT**

The risk of emergence of resistance mutations varies according to the type of prophylactic regimens used. The acquisition of resistance mutations to AZT following exposure to AZT monotherapy during pregnancy is relatively rare. Selection of 3TC-resistance mutations is more frequent and has been reported in up to 33% of women exposed to 3TC during pregnancy. However, the ARV drug that is of most concern with regards to resistance mutations is NVP; when the most frequent mutation (K103N) is present, it may compromise the efficacy of both NVP and efavirenz, the two most useful currently available non-nucleoside reverse transcriptase inhibitors (NNRTIs).

The selection of NVP-resistant virus following a single intrapartum dose of NVP has been reported in up to two-thirds of women with detectable viral loads at the time of delivery. Although these mutations tend to fade over time, they reappear and can have clinical consequences when ARV pressure is reapplied. In the PHPT-2 study in Thailand, women exposed to intrapartum NVP and who subsequently needed therapy for their own health were less likely to have virologic suppression after six months of postpartum treatment with an NVP-containing regimen. Similar results were observed in Botswana, following the Mashi trial, in women who started NVP-containing ART regimens less than six months after peripartum NVP exposure. However, this effect was not seen in those starting combination ART more than six months after peripartum exposure. Furthermore, the efficacy of sdNVP for PMTCT may be decreased in women who have been exposed to sdNVP during a previous pregnancy, as suggested by preliminary results from a study in South Africa in which the rates of transmission in the second pregnancies were higher than in the first.

To prevent the emergence of such resistance mutations, a four- or seven-day course of AZT plus 3TC has been proposed to cover the postpartum NVP tail. Reported results of this strategy have shown a significant reduction in the rate of NVP-resistance mutations. A similar effect was observed in the DITRAME 1.1 Plus study, which used a dual combination of AZT plus 3TC started at 32 weeks gestation that continued for three days postpartum.

Studies have also documented a high rate of NVP-resistance mutations in HIV-infected infants exposed to sdNVP in the first days of life. Although NVP saves the lives of many children by protecting them from infection, NNRTI-resistance mutations in those infants who are infected despite prophylaxis may have a major impact on the efficacy of subsequent therapies. In the Mashi trial in Botswana, HIV-infected infants exposed to sdNVP had considerably higher virological and immunological failure rates after six months of NNRTI-based treatments, as compared with unexposed infants (77% vs. 9%).

**USE OF ANTIRETROVIRALS DURING PREGNANCY**

The ultimate goals of PMTCT are to minimize the risk of HIV transmission to the child, and to preserve the mother’s health in relation to HIV, without exposing mother or child to short- or long-term risks related to ARVs. In all clinical trials and subsequent cohort studies, the safety of ARVs
Mitochondrial Dysfunction Associated with Exposure to Nucleoside Reverse Transcriptase Inhibitors

It has been shown that perinatal exposure to AZT was associated with transient anemia and neutropenia due to its well-known bone marrow toxicity. The association between AZT or AZT plus 3TC and severe mitochondrial dysfunction is still debated. A study in France reported that within a cohort of 1,754 uninfected infants born to HIV-1-infected women, eight infants with in utero or neonatal exposure to either AZT plus 3TC or AZT alone developed mitochondrial dysfunction after the first few months of life, including two infants exposed to AZT plus 3TC who died with severe neurological disease. An increased risk of febrile seizures during the first 18 months of life in uninfected infants with ARV exposure was also reported. In addition, the follow-up of 1,020 HIV-negative children born between 1991 and 2002 within the PACTG 219/219C study found possible cases that had signs consistent with mitochondrial dysfunction, particularly when exposure to 3TC or to AZT plus 3TC began in the third trimester (OR 6.3 and OR 5.9, respectively, vs. unexposed). However, the review of all deaths among more than 16,000 HIV-negative children with and without ARV exposure who were followed in five large prospective U.S. perinatal cohorts reported neither deaths nor clinical findings attributable to mitochondrial dysfunction.

In terms of pregnancy outcomes, the risks associated with in utero AZT exposure have been thoroughly studied. In all placebo-controlled studies in which AZT was used, congenital anomalies, prematurity, and anthropometric and developmental parameters in the placebo and in the AZT groups were similar. In the PHPT-1 study, a slightly lower birth weight was observed in HIV-negative children with longer exposure to AZT, but the difference did not persist after six weeks. No tumors of any nature were observed among 727 children perinatally exposed to AZT after a mean follow-up of 38 months in the PACTG 219 study.

Non-nucleoside Reverse Transcriptase Inhibitors during Pregnancy

Efavirenz is known to induce congenital central nervous system abnormalities and therefore must be avoided during the first trimester of pregnancy. Although sdNVP appears to be very safe in both mothers and infants, an increased risk of severe hepatic and cutaneous toxicities, some of them fatal, have been described in women initiating NVP-based ART regimens during pregnancy, especially when their CD4 count was above 250 cells/mm³. Therefore, initiation of NVP-containing ART regimens during pregnancy must be avoided in women who are not immunocompromised.

Protease Inhibitors during Pregnancy

Known toxicities associated with the use of protease inhibitors (PIs) during pregnancy are hyperglycemia, diabetes, and ketoacidosis. In addition, there are known life-threatening drug interactions between either PIs or NNRTIs—which can both interfere with cytochrome P450 metabolism—and some drugs (e.g., methylergonovine) that are commonly used for managing postpartum hemorrhage or uterine atony.

Combination Antiretroviral Therapy during Pregnancy

When ART is provided during pregnancy, the toxicities described above related to each ARV component should be considered. Data regarding women receiving combination ART during pregnancy are conflicting in terms of adverse pregnancy outcomes, such as preterm delivery, low birth weight, low Apgar scores, or stillbirth. Initially, a Swiss retrospective study of
limited sample size suggested an association between exposure to ARV combination therapy and pre-term delivery. In the larger European Collaborative Study, however, after adjusting for CD4 count and intravenous drug use, there was a 2.6-fold increase in the odds of preterm delivery for infants exposed to combination ARV with or without PIs, as compared with ARV-unexposed infants. Moreover, women already on ARV before pregnancy were twice as likely to deliver prematurely compared with women who started ARV during the third trimester of pregnancy. However, this association was not found in PACTG 367 or in a meta-analysis of seven clinical trials. Furthermore, a trend toward a decreasing incidence of low birth weight and preterm birth from 1989 to 2004, which was an era of increased maternal ARV therapies, was found in 11,321 infants tested in the longitudinal Pediatric Spectrum of HIV Disease study. However, in a recent report from Côte d’Ivoire, among children born to mothers eligible to receive combination ART during pregnancy, the rate of low birth weight was nearly two times higher in children exposed to NVP-based HAART (22.3%) than in children exposed to AZT (or AZT plus 3TC) plus sdNVP (12.4%) (P=.02).

**Discontinuation of Antiretroviral Therapy after Delivery in Women Who Are Not Severely Immunocompromised**

When a virologically suppressive therapy, such as ART, is given to non-severely immunocompromised pregnant women to reduce perinatal transmission, the therapy is discontinued after delivery since the mother does not yet require therapy for her own health. Therapy is then reinitiated as needed at a later date according to standard criteria for non-pregnant women. The consequences of such treatment discontinuation are still unknown. The results of two large trials of structured treatment interruptions—the Strategies for Management of Antiretroviral Therapy (SMART) and Trivacan / ANRS 1269—demonstrated an increased risk of adverse events and deaths in patients who were randomized to interrupt their treatment, raising concerns regarding the safety of such strategies. The relevance of these observations to the situation in which postpartum women, who do not have indications for therapy, would discontinue a virologically suppressive regimen received for approximately three months during pregnancy is not clear. These safety concerns mandate careful long-term clinical and biological evaluation of women after discontinuation of potent ARV combinations for PMTCT. Moreover, upon discontinuation of ARVs at the end of pregnancy, drugs that have significantly different plasma half-lives may result in functional monotherapy for a period of time, with the risk of selection of resistance mutations.

**Pharmacological Modifications Induced by Pregnancy and the Selection of HIV Mutations Associated with Antiretroviral Resistance**

Selection of HIV-resistance mutations to AZT, 3TC, or NVP following the use of nonsuppressive prophylaxis regimen for PMTCT has been discussed earlier in this chapter. When adherence and drug exposure are adequate, there is no evidence that the use of potent ARV combinations during pregnancy is associated with an increased risk of selection of resistance mutations. However, although the pharmacokinetics of nucleoside reverse transcriptase inhibitors (NRTIs)—with the exception of tenofovir (TDF)—and NNRTIs have not been found to be significantly altered during pregnancy, lower drug exposures for unboosted PIs (nelfinavir, indinavir, and saquinavir) and boosted lopinavir (LPV/r) during the third trimester of pregnancy have been reported. Studies are ongoing to systematically evaluate the pharmacokinetics of ARVs within various combinations during pregnancy, as decreased drug exposure may affect efficacy and the risk of selection of resistance mutations.
prevention of mother-to-child transmission of HIV

facilities to provide ART for all HIV-positive pregnant women, regardless of their immune or clinical status in high-prevalence, resource-limited settings, pose a much greater public health challenge than in low-prevalence, and resource-rich countries.

High-Income Countries

In high-income countries, where clinical and biological follow-up of women and infants are available and feasible, recommendations for PMTCT vary. However, all recommendations essentially focus on early diagnosis of HIV infection in pregnant women, with virological and immunological evaluation and initiation of ART during pregnancy in all HIV-positive women, regardless of their immune status. When viral load is not totally suppressed at the end of pregnancy, programmed C-section (C-section before onset of labor) is recommended.

The various uncertainties regarding the risks and benefits of potent ARV combinations for women who do not need treatment for their own health are reflected in the 2008 U.S. guidelines for the use of antiretroviral drugs in pregnant HIV-infected women: “The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussing with her health-care provider the known and unknown benefits and risks to her and her fetus.”

Low- and Middle-Income Countries

In the most recent (2006) WHO guidelines for PMTCT in resource-limited settings, ART is recommended for pregnant women following the same criteria used for nonpregnant adults in all settings: WHO clinical stage IV irrespective of CD4 count; WHO clinical stage III, with CD4 <350 cells/mm³ or all stage III if CD4 is not available; or WHO clinical stage I or II disease with CD4 <200 cells/mm³. While acknowledging the uncertainties associated with the special circumstances of pregnancy, the guidelines stress that optimal ART should be

Risks in Coinfected Patients

The relatively high prevalence of coinfections with hepatitis B virus (HBV), tuberculosis (TB), and other infectious diseases among HIV-positive pregnant women in resource-limited settings may complicate ARV management. In patients with TB, a disease still difficult to diagnose in many resource-limited settings, certain ARV combinations may trigger a potentially life-threatening immune reconstitution inflammatory syndrome (IRIS). Emtricitabine (FTC), 3TC, and TDF are drugs that also suppress HBV replication; and in HIV/HBV-coinfected adults, discontinuation of 3TC after several months has been associated with clinical hepatitis, which, in rare cases, can be fatal. These adverse events are also a threat for the fetus.

All these reports point to the necessity of balancing the risks and the benefits of ARVs in pregnant women. Nevertheless, when balancing the severe risk of death in the case of pediatric HIV infection with the high efficacy of ARV prophylaxis, it is clear that ARVs should be systematically offered to all HIV-positive pregnant women, while carefully assessing the safety of the mother and child with continuous vigilance and long-term follow-up. Pregnancies in HIV-positive women exposed to ARVs should be reported prospectively to the Antiretroviral Pregnancy Registry so that any increase of congenital abnormalities can be detected.

Current Guidelines for Antiretroviral Therapy in Pregnancy

Although the benefits of combination ART during pregnancy are evident for immunocompromised pregnant women who require treatment for their own health, the risks and benefits of ART for PMTCT in non-immunocompromised women have not been fully evaluated. Furthermore, the costs, logistics, and capacity of health-care facilities to provide ART for all HIV-positive pregnant women, regardless of their immune or clinical status in high-prevalence, resource-limited settings, pose a much greater public health challenge than in low-prevalence, and resource-rich countries.
provided to both improve the mother’s health and prevent HIV transmission to her child.

For women who are not immunocompromised, WHO guidelines recommend AZT monotherapy starting at 28 weeks of pregnancy or as soon as possible thereafter plus sdNVP in both the mother and the child. A one-week maternal postpartum AZT plus 3TC treatment can be considered to reduce the selection of NVP-resistance mutations. This regimen for women who are not immunocompromised will yield very low transmission rates, as low as those obtained using more complex ARV combinations and for which the potential risks are still debated.\(^{40}\) For women with CD4 counts in the 200-350 cells/mm\(^3\) range, who require therapy shortly after delivery, some experts suggest ART during pregnancy and continued postpartum to avoid the risk of compromising future NNRTI-based ART when exposed to sdNVP.\(^{28}\)

**CHALLENGES TRANSLATING PMTCT CLINICAL RESEARCH INTO PRACTICE**

Although there has been extraordinary progress in expanding access to ARVs in developing countries, the scale-up of perinatal HIV prevention has comparatively stalled. This raises the question of why it appears to be easier to provide ART to patients with advanced HIV disease than to provide short-term prophylaxis to pregnant women who are mostly asymptomatic. The answer is twofold. First, a successful, countrywide program that reaches all women is not as simple as it may at first appear and represents a profound change in the antenatal care routine. Second, the successful expansion of PMTCT programs is reliant upon political will at the highest level.

**Political Will**

If there is any lesson to be learned from Thailand, the only developing country that has had a truly successful PMTCT program, it is that political will is the essential ingredient for success. In the early 1990s, the Thai government rapidly responded to the HIV epidemic by implementing a multisector program under the chairmanship of the prime minister and involving all ministries as well as civil society. This program, heavily supported financially by the government, had identified four key components: information for the public on prevention, protection of human rights and promotion of social support for HIV-positive patients, research, and care. Through the large involvement of nongovernmental organizations, religious organizations, and businesses, HIV-positive people were able to actively participate in the program’s implementation.

In the early 1990s, as soon as pediatric HIV was recognized as a major public health and humanitarian crisis in the country, the Ministry of Public Health organized countrywide trainings on HIV counseling to nurses within the antenatal care settings. In addition, HIV-positive women screened during pregnancy were advised not to breastfeed and formula milk was provided for free to the poorest HIV-positive women. While ongoing clinical research programs worked to determine the optimal use of AZT for PMTCT, a large pilot PMTCT program was implemented in the six northernmost provinces of Thailand. A sharp decrease in the number of pediatric AIDS cases in the northern hospitals rapidly followed.\(^{97}\) Two years later, when the results of the clinical trials were published, national PMTCT guidelines were published, and the large-scale operation was scaled up nationally. Among all pregnant women who had antenatal care (97%), 93% were tested for HIV. Of all the HIV-positive women, 70% were treated with AZT during pregnancy, 89% of the infants received AZT, and 83% of the children were formula fed.\(^{98}\)
of government and the public health authorities. In the absence of a clearly articulated policy, the public will continue to be uninformed, the health-care system will be unprepared, and the opportunity for HIV testing during pregnancy and provision of ARVs will continue to be missed. When such an impulse is given from such high levels, it can have a domino effect that not only helps put the programs in place but also reduces the stigma and denial that otherwise hamper progress at all levels, while also improving mother and child health services as a whole.

Obviously, all countries confronted with the HIV epidemic do not benefit from Thailand’s level of economic development and its sophisticated public health system. On the other hand, however, there are enormous external funding opportunities at present. Rather than considering PMTCT as an additional burden, it can be seen as representing a unique opportunity for improving the overall mother-child health system, even beyond the HIV field.

Lack of Access to Health Facilities
In remote areas, women have limited or no access to antenatal care, and deliveries may take place at home, in the presence of a traditional birth attendant. Even in places where facilities exist, such as in large cities, a significant proportion of women still do not attend them because, in an offsetting of limited individual resources, they are unable or unwilling to pay for mother and child services. Free or affordable antenatal care, and/or provision of PMTCT at the community level, may improve PMTCT coverage. It is important to recognize that the complexity of PMTCT resides much more in the proper coordination of each element of the intervention than in the technical complexity of any one of these elements. HIV information and counseling and the provision of ARV prophylaxis require neither institutionalized antenatal care nor giving birth in a maternity clinic. Even HIV testing can be performed outside a laboratory, as long as personnel are properly trained and supervised. In addition, the initiation of AZT prophylaxis at the beginning of the third trimester of pregnancy can be achieved with a remarkable degree of accuracy by properly trained traditional birth attendants. However, all of these elements, particularly when combined, require profound changes in the antenatal care routine in most resource-limited settings.

HIV Testing Uptake during Pregnancy
Poor acceptance of HIV testing is an important barrier to PMTCT. Acceptance rates as low as 20% have been observed in some settings. In Africa, where fertility is high, maternity is highly valued by the family and society. A pregnant woman is accountable to a network that goes far beyond the nuclear family. The clan's economic and political alliances, as well as lineage continuity, are at stake. Pregnant women may therefore be reluctant to be tested during pregnancy, because an HIV-positive test result would jeopardize a highly valued status that is conditioned by the birth of a healthy child. At a more personal level, and like everywhere else, an HIV-positive test result would mean the possible infection and death of the child. It also projects the women's own disease and death and the prospect of leaving other children behind as orphans. Finally, women may fear that their partner(s) may also be HIV-infected and that they may be accused of having passed the infection to them.

Routine HIV testing in the antenatal care setting with opt-out strategies has been proposed to improve the acceptance of HIV testing. Pregnant women may be more inclined to be tested if they are convinced that it has a benefit for them and their baby. Therefore, successful HIV testing requires public education, respectful and confidential medical services, accurate testing, prompt availability of results, skilled post-test counseling, and effective subsequent prevention and care.

of government and the public health authorities. In the absence of a clearly articulated policy, the public will continue to be uninformed, the health-care system will be unprepared, and the opportunity for HIV testing during pregnancy and provision of ARVs will continue to be missed. When such an impulse is given from such high levels, it can have a domino effect that not only helps put the programs in place but also reduces the stigma and denial that otherwise hamper progress at all levels, while also improving mother and child health services as a whole.

Lack of Access to Health Facilities
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Antiretroviral Adherence
Lack of adherence may lead to PMTCT failure. Women may not adhere to PMTCT if they are not fully informed of the risk of transmission and the consequences of HIV infection for their child. Furthermore, because the majority of women who are receiving PMTCT are still asymptomatic, they may be in denial about their own HIV infection or be concerned that their taking of ARVs may disclose their HIV status. Finally, when suboptimal interventions, such as sdNVP only, are provided, the health-care workers may not be sufficiently convinced themselves of the efficacy of the intervention and may therefore not be successful in convincing women to accept treatment. As for HIV testing, pregnant women are much more likely to adhere to PMTCT if they believe it can benefit their child. Thus, to improve adherence to PMTCT, it is essential that health-care workers receive appropriate training to counsel women about the benefits of PMTCT and that all efforts are made to implement the most effective PMTCT interventions.

Confidentiality Issues
Confidentiality is not a straightforward concept in societies where life events, such as death, marriage, pregnancy, and disease, traditionally mobilize family solidarity. Some women may be reluctant to take ARVs during pregnancy because they fear that the drug intake will identify them as HIV positive, and they do not want to share their serostatus with their spouse or family.

In a closed society and in a context where AIDS is heavily stigmatized, knowledge of one’s HIV status is a source of considerable power. The importance of confidentiality within the health-care setting is not always well understood. This concern for breach of confidentiality explains why some HIV-positive women do not come back to the health facility after learning their HIV status or do not disclose their HIV status to health workers who could provide them with ARVs at the time of delivery. Training about the importance of confidentiality for all personnel—not just the health-care staff—at the antenatal, as well as at the maternity and infant care levels, is essential.

Integration of Care with PMTCT
The extension of PMTCT to include long-term provision of ART to immunocompromised mothers and their HIV-positive children is referred to as MTCT-Plus. Ideally, an HIV-positive result should be immediately followed by an assessment of the disease stage. When CD4 evaluation is available, immunocompromised pregnant women could immediately initiate HAART within the HIV care system under the integrated supervision of both medical and antenatal services. Women who do not yet require ARVs for their own health can receive AZT from 28 weeks of pregnancy and sdNVP at delivery at the antenatal/maternity care level. In the postpartum period, appropriate referral for follow-up within the HIV care system needs to be organized for timely initiation of ART when needed. In the absence of CD4 evaluation, prevention strategies could be based on the clinical or total lymphocytes assessment.

However, the linkage between treatment programs and maternal and child care—of which PMTCT is generally a part—is not easily achievable. It requires improved communication among health-care workers at the antenatal care facilities, the well-baby clinics, and the obstetrics, pediatrics, and internal medicine departments. Such links require changes in the established practices of many parts of the health-care system. This difficulty is well illustrated by the recent report of the multi-country PMTCT effort supported by the Elizabeth Glaser Pediatric AIDS Foundation, which showed that the percentage of women accessing ART for their own health after they had participated in a PMTCT program remained low.106
CONCLUSION

It has been a little more than 10 years since a treatment to reduce mother-to-child transmission of HIV was discovered. A huge research effort was rapidly put in place to define treatment strategies that could be accessible to women living in the countries most affected by HIV. However, the implementation of these very successful research results has failed to live up to their potential.

In contrast, following a strong message from the United Nations general assembly in 2001, an extraordinary scaling up of the use of potent ARV combinations to treat HIV-positive patients in the most affected countries was made possible through the Global Fund, the President’s Emergency Plan for AIDS Relief (PEPFAR), or private foundations such as the Bill & Melinda Gates Foundation. In 2005, according to UNAIDS, more than 50% of the patients who needed treatment were receiving ARVs in 21 heavily affected countries. It is shameful that PMTCT, one of the most successful and cost-effective interventions, has lagged so far behind. Ironically, greater access to ART for adults and children may represent the tipping point that leads to a wider implementation of PMTCT.
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For more than a decade, antiretroviral drugs (ARVs) have been shown to be highly effective at reducing perinatal transmission of HIV and reducing AIDS-related morbidity and mortality. More recently, financing initiatives such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria (the Global Fund) and the President’s Emergency Plan for AIDS Relief (PEPFAR) have been established to expand access to HIV prevention, care, and treatment in countries most severely affected by the HIV pandemic. But with these increased resources comes increased responsibility. National health systems must do their part to ensure that all possible strategies are employed to maximize access to HIV prevention, care, and treatment services, especially among women and children, who are often the most vulnerable to HIV infection.

In the early 1990s, the International Conference on Population and Development called for reducing maternal mortality by half by the year 2000. This goal was never reached, partly due to the severity of the HIV epidemics in several countries. Postpartum morbidity and mortality among HIV-positive women has been found to be higher than in the general population, as has been reported in Kampala, Uganda, and Harare, Zimbabwe, reflecting similar findings in the United States. In a variety of settings, 15% to 25% of pregnant women diagnosed with HIV infection during pregnancy are already severely immunocompromised (i.e., CD4 count below 250 cells/mm$^3$) and are thus at a high risk of death. Immunocompromised pregnant women should receive immediate cotrimoxazole and other available prophylaxes to prevent opportunistic infections. In addition, wherever possible, immediate initiation of a potent combination antiretroviral regimen can prevent mother-to-child transmission of HIV and allow for immune restoration, thus preventing maternal mortality in the postpartum period.

Compared with the general population of HIV-positive individuals, women accessing prevention of mother-to-child transmission of HIV (PMTCT) services represent a particularly important
opportunities to reach HIV-positive women and their families with access to lifesaving HIV care and treatment services. A woman who is newly diagnosed with HIV infection during her pregnancy is an ideal candidate for treatment assessment and referral to ensure her initiation on antiretroviral therapy (ART) as soon as it is needed—prior to disease progression. Her partner can then be encouraged to access voluntary HIV counseling and testing (VCT) as needed and be referred for treatment as appropriate. In addition, children born to HIV-positive mothers in the context of PMTCT programs benefit from access to medical follow-up and diagnosis, regardless of their HIV status. Children who are HIV-negative require varying degrees of care for other common childhood illnesses. Children who are HIV-positive will require longer-term care and follow-up.

This chapter will focus on some of the key challenges in improving access to PMTCT, as well as strategies for improving linkages between PMTCT and care and treatment services.

LINKING PMTCT TO HIV CARE AND TREATMENT SERVICES

A key focus of recent HIV/AIDS scale-up efforts in developing countries has been the rollout of PMTCT interventions. These programs are considered most effective when integrated into maternal and child health (MCH) centers, as MCH services are firmly established in most resource-limited settings. At the same time, the scale-up of access to ART for adults—and, more recently, children—has been predominately concentrated in urban hospital settings where facilities and infrastructure for laboratory monitoring of ARV regimens are readily available. Although there has been long-standing support for integrating PMTCT services with ARV treatment for the mother, partner, and child (e.g., PMTCT-Plus), there remain significant challenges in implementing these linkages.

HIV-positive pregnant women need to know their HIV status as early as possible in the course of their pregnancy. This is not only so they may benefit from PMTCT services, but also so they may receive ART for the improvement of their own health as soon as it is needed (whether during or after pregnancy). Their access to care and treatment services beyond PMTCT also increases the chance that their partners will access needed services, such as VCT and ART. In addition, reaching women during their pregnancy aids in the provision of HIV prophylaxis for HIV-exposed infants, follow-up and diagnosis of HIV infection in older children, and provision of pediatric ART.

Although a number of countries have made significant advances in provision of PMTCT, few have successfully integrated PMTCT with broader efforts focused on the scale-up of ART. This gap is of particular concern due to the association between advanced maternal HIV infection and mortality rates among HIV-positive and HIV-negative young children. This strong association has led many to advocate for improved linkages between HIV/AIDS care and MCH services, which in turn may also improve child survival.

Factors Influencing the Uptake of PMTCT Services

The potential of PMTCT to serve as the entry point for family-based HIV care can only be realized if there is wide utilization of antenatal care (ANC) services, availability of PMTCT services, and widespread uptake of VCT during pregnancy. In some settings, low uptake of some or all of these services remains a major limitation to scaling up care linkages. For instance, a 2007 report from the World Health Organization (WHO), Joint United Nations Program on HIV/AIDS (UNAIDS), and the United Nations Children's Fund (UNICEF) stated that coverage for HIV counseling and testing remains very
low in most countries affected by the epidemic: in more than 70 low- and middle-income countries surveyed that reported data for 2005, only 10% of pregnant women received an HIV test (less than 10% in Nigeria, India, Democratic Republic of the Congo; between 40% and 50% in Africa, Latin America, and the Caribbean; and 75% in Eastern Europe and Central Asia).  

While the utilization rate of health-care facilities during pregnancy may be relatively high in many countries, there are large variations between countries and within the same countries. For example, a study in a rural community in South Africa found that 44% of women delivered their babies at home, mostly without assistance from a traditional birth attendant. In a district of Rajasthan state, India, 71.4% of pregnant women in urban areas and 36.1% in rural areas received more than three ANC visits. In Fès, Morocco, 77% of women had some form of antenatal care. Without ANC, women cannot benefit from HIV diagnosis or any of the PMTCT and treatment interventions available to them or their families. Reported factors influencing a woman’s decision whether to deliver in a health-care facility included proximity to the facility, transportation costs, and education and marital status. Although women in the South African study were aware of the risk of mother-to-child HIV transmission, only 9% of the pregnant women surveyed had ever been tested for HIV.  

Accessibility of ANC and PMTCT services in sub-Saharan Africa varies greatly across and within countries (e.g., urban versus rural areas), depending on economic, geographic, cultural, and social characteristics. A 2003 evaluation of UN-supported pilot PMTCT projects in 11 countries (Botswana, Burundi, Côte d’Ivoire, Honduras, India, Kenya, Rwanda, Tanzania, Uganda, Zambia, and Zimbabwe) found that among women who came to health centers for antenatal care, uptake of HIV counseling and testing ranged from 25% to more than 90%. However, only 64% to 83% of women who accepted an HIV test returned to collect their results. Factors associated with acceptance of HIV testing among pregnant women attending antenatal clinics include education level, knowledge of MTCT and HIV testing, and partner participation or perception that the clinic offers privacy and that social support from relatives and peers is available.  

In addition to factors specifically affecting uptake of ANC services, there have also been reports suggesting a need for improvements in the quality, frequency, and duration of HIV counseling. Although some studies have found that discrimination in the community toward HIV-positive women may not be a major limitation, it remains clear that stigma and discrimination, lack of male partner support, and negative attitudes of health workers toward pregnant women are still significant barriers to women’s participation in PMTCT programs, as observed in a program in Gaborone, Botswana, despite women being offered free access to ARVs and formula feeding.  

In summary, low acceptance of VCT among pregnant women remains a major rate-limiting step in the uptake of PMTCT. This, in turn, limits opportunities for referral to other HIV care and treatment in many settings, as highlighted in a recent report by the Global Fund, which states: PMTCT programs continue to face major implementation challenges, as evidenced by both poor performance and the very modest absolute targets set by grants. These problems are linked to important gender issues in HIV. Women often do not agree to be tested during pregnancy, they tend to be “lost” in the clinical and referral system and they lose access to treatment for themselves and to prevent transmission to their children.
INTERVENTIONS TO EXPAND ACCESS TO PMTCT AND OTHER HIV-RELATED SERVICES

The following is a brief summary of three interventions that, if appropriately designed, can help increase the uptake of PMTCT and, in turn, other HIV prevention, care, and treatment services.

HIV Counseling and Testing as an Entry Point to PMTCT

Several approaches have been proposed and tested to address the variety of barriers to HIV testing uptake mentioned earlier in this chapter. Knowing one’s status is the obligatory first step to receiving HIV care services. Strategies such as universal single-dose nevirapine prophylaxis for all pregnant women in the absence of HIV counseling or testing (once considered by some to enhance the delivery of effective PMTCT interventions in the short term) cannot serve as an entry point for further HIV care, as women who do not know their HIV status cannot access long-term treatment. However, proven methods do exist to increase uptake of PMTCT services, including clinic-based health education interventions, group pretest counseling, and education via alternative PMTCT information sources, such as radio and television. The opt-out testing strategy in the context of antenatal care, in which women are tested for HIV after being notified that (1) the test will be performed and (2) the patient may elect to decline or defer testing, has been promoted for several years by the Elizabeth Glaser Pediatric AIDS Foundation and others and is associated with significant increases in testing uptake in various resource-limited settings.

Rapid HIV Testing

The availability of rapid HIV tests has greatly facilitated access to HIV testing. These tests require minimal equipment, as compared with Enzyme-Linked ImmunoSorbent Assay (ELISA) and other antibody tests, and can be used on whole blood. In addition, most of these tests can be stored at room temperature. Moreover, because trained health-care workers can perform a rapid test in 10 to 30 minutes, results can be given on the same day, greatly increasing the chances that women will receive their results. Rapid HIV testing can be implemented together with the opt-out testing strategy.

Partner Participation

Although the greater involvement of male partners has long been advocated, there are limited data demonstrating the impact of this involvement on PMTCT uptake. One example of where this has been effective is Cambodia, where a study conducted in the context of the country’s national PMTCT program showed a strong link between HIV testing acceptance rates among women and attendance at a pretest counseling session with a male partner. However, approaches that actively involve male partners have yet to become common practice in many developing countries. For example, in a PMTCT program conducted in Abidjan, Côte d’Ivoire, the proportion of male partners tested for HIV was only 23.1% among partners of HIV-positive women and 14.8% among partners of HIV-negative women; in a cohort of 799 HIV-positive pregnant women in Bangkok, Thailand, 22.6% still had not disclosed their HIV status to their partners by four months after the initial HIV test.

Provision of ART to Pregnant Women

Antiretroviral therapy is often provided to pregnant women through referral systems since it is not always available where ANC and MCH services are being offered. Ideally, an HIV care team should be available wherever pregnant women are regularly being seen. This team should include not only health-care professionals but also those who can
offer various forms of support, such as representatives of patient and community groups. This helps ensure that feedback is provided to health-care workers to inform the continuous improvement of care. In this context, long-term follow-up of women in the postpartum period can be organized early in pregnancy. Even in health facilities that do have the capacity to deliver ART regimens, simple interventions, such as the introduction of the patient to the care team in charge of future HIV care, can prevent women from being lost after pregnancy within an anonymous referral system.

The question of whether ART can be safely and efficiently provided in any health facility is complex. ART services tend to be located at referral facilities for various reasons (e.g., more extensive training of health-care workers, storage of ARVs, numbers of HIV-positive patients), whereas PMTCT services are more commonly located at lower-level health facilities, which are often unable to support more complex ART regimens. Therefore, patients either have to be referred to higher-level facilities for ART or ART services have to be decentralized. Often, systematic referral to urban facilities is not a viable solution due to distance, associated travel costs, time constraints for mothers in charge of young children, logistics issues (e.g., sporadic public transportation, weather, poorly maintained roads), as well as social factors, all of which increase the risk of loss to follow-up and discontinuation of ART.

The full decentralization of ART services requires time, resources, and considerable effort, particularly for training the large number of health-care providers at lower-level facilities. Yet decentralization of the health-care system is what is most needed in many settings and may be the only viable strategy to address widespread, resource-intensive chronic health conditions such as HIV infection. In the current context of increased international support for HIV/AIDS programs, which is often conditional upon the demonstration of a clear short- or mid-term impact, some recipients of international funding may consider decentralizing ART services to be a less effective strategy than limiting these services to urban areas. Innovative approaches must be developed to blend these two models—for instance, periodic (e.g., initial or biannual) patient assessments could be performed in higher-level health facilities where highly trained health-care providers and laboratory exams, such as CD4 counts and viral loads, are readily available. These experts could then provide health-care providers in remote areas with specific advice and guidance in the provision of ART, using available communications technology (e.g., telephone, fax, Internet, e-mail).

**CONCLUSION**

The linkage between PMTCT and care is crucial to the long-term success of PMTCT, as children need a healthy family to ensure that they grow up minimally affected by HIV. PMTCT offers a great opportunity to link all members of the family to needed care and support services. The health-care systems should be ready to deliver long-term active follow-up and care for those patients not yet on treatment, as well as those already receiving treatment. Indeed, while about one in four HIV-positive pregnant women does require immediate antiretroviral treatment for her own health,5–7 the others need appropriate active follow-up for timely initiation of ART in the future.

At the population level, stigmatization and discrimination remain as significant obstacles to increasing access to PMTCT and other care and treatment services. Because universal access to ART has been shown to be the most powerful intervention to reduce stigma,8 interventions linking PMTCT with HIV care and treatment may prove to be a powerful tool for reducing HIV/AIDS-related stigma and discrimination.
REFERENCE LIST


PEDIATRIC AND ADOLESCENT HIV CARE
At the end of 2007, an estimated 2.1 million children were living with HIV, with the burden of this disease being largely borne by countries in sub-Saharan Africa. Approximately 700,000 children become newly infected with HIV each year, predominantly as a result of mother-to-child transmission, making HIV a significant contributor to pediatric morbidity and mortality globally. Increasing access to antiretroviral therapy (ART) for infants and children in the most affected countries will require a concerted effort to (1) expand appropriate early testing strategies to make a definitive diagnosis of HIV, (2) increase the numbers of appropriately trained clinical and laboratory health-care practitioners, and (3) hasten and improve the development of appropriate, acceptable, and affordable antiretroviral (ARV) formulations for pediatric disease management. This chapter summarizes the currently available testing strategies for infant diagnosis of HIV, along with key considerations for their introduction and use in resource-limited settings.

The Case for Early Diagnosis
Early diagnosis of HIV infection in infants is a necessity. Approximately 35% to 40% of infants living with HIV die within their first year of life, and more than 50% die before their second birthday. A 2007 study from Zimbabwe demonstrated high mortality in perinatally infected infants between 2 and 6 months of age; interestingly, it was observed that mortality was also higher in HIV-uninfected infants born to HIV-positive mothers than those born to HIV-negative mothers. A study conducted in South Africa showed that over a 24-month period, 60% of infants born to HIV-positive mothers were lost to follow-up by 6 weeks of age, increasing to 85% by 12 months of age. These data support earlier work by Lambert and colleagues in the United States, who demonstrated significant differences between lymphocyte subsets in HIV-exposed, -infected, and -uninfected infants as early as 6 weeks of age.

A recent randomized controlled clinical trial in South Africa has demonstrated that there was a significant increase in survival among infants who received immediate ARV therapy versus those who received ARVs following significant immunological deterioration. This has guided the revision of treatment guidelines for infants, thus confirming the need for early diagnosis in HIV-exposed infants.
Many infants are lost to follow-up while waiting for an Enzyme-Linked ImmunoSorbent Assay (ELISA), which can only be given starting at 15 to 18 months of age. Yet solutions do exist. Operations research activities in South Africa have previously demonstrated the cost-effectiveness of using a single nucleic acid test at 6 weeks of age to reduce the costs of infant follow-up, with efforts being focused on getting HIV-infected children into appropriate care programs as early as possible.11,12 Other benefits of early testing include reductions in antibiotic prophylaxis for HIV-uninfected infants, a reduction in maternal anxiety, and the ability to monitor the effectiveness of prevention of mother-to-child transmission programs.13

TESTING STRATEGIES

Early definitive diagnosis of HIV infection in infants is critical to ensuring that HIV-infected infants receive appropriate and timely care and treatment. For this reason, the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF), and the Centers for Disease Control and Prevention (CDC) have recommended that countries provide access to early virological testing for HIV-exposed infants.10,14,15

A number of different testing strategies for early infant diagnosis have been investigated, including surrogate markers, such as hypergammaglobulinemia, IgA HIV antibodies (since this antibody subtype is not transferred across the placenta but is produced by the infant), qualitative p24 antigen assays, determination of reverse transcriptase activity, and HIV viral culture (previously the gold standard assay). Assays currently favored for early infant definitive diagnosis include nucleic acid testing using polymerase chain reaction (PCR) assays (both qualitatively [DNA and RNA] and quantitatively [RNA]), and p24 antigen quantitation. More recent experimental approaches have included investigation of CD4/CD8 ratios for distinguishing HIV-infected from HIV-uninfected infants at an early age following exposure to HIV.16,17 Although as sensitive as DNA PCR, the use of viral culture in the setting of routine diagnosis has largely been abandoned for reasons of complexity, cost, and a delay in result reporting of at least two to four weeks.18

Antibody-Based Assays

Antibody-based assays (e.g., ELISA and rapid tests) are simple, cheap, and highly accurate tools for diagnosing HIV infection in adults and in children older than 18 months of age. However, in infants and children under 18 months of age, these tests cannot differentiate between persistent maternal HIV antibodies transferred across the placenta into the baby’s circulation (i.e., HIV exposure) and HIV antibodies produced by the child (i.e., HIV infection). All babies born to HIV-positive women will have a positive HIV antibody detection test result at birth. This result may remain positive until up to 18 months of age, though more commonly it becomes negative (seroreverts) in an HIV-uninfected infant much earlier.

In children younger than 18 months, HIV antibody detection assays can be useful, provided the results are correctly interpreted. If the child tests positive, HIV exposure is confirmed. Exposed children require specific care (e.g., prophylactic cotrimoxazole, infant feeding counseling) and further testing to establish their HIV infection status. If the child tests negative, HIV infection can be excluded, provided the child has not been breastfed in the past six weeks and has no clinical stigmata of HIV infection. If the child is being breastfed, testing should be repeated six weeks after breastfeeding has ceased to exclude postnatal transmission.13,15 Repeat HIV testing is also indicated if breastfed children develop clinical symptoms suggestive of HIV infection. Innovative work in Rwanda and Uganda has suggested diagnostic algorithms using frontline screening with rapid HIV tests, thus reducing the number of further virological assays that are needed.15,19
Rapid Testing
Preliminary work with rapid HIV tests suggests that seroreversion can be documented as early as 4 months of age. A Ugandan study reported that rapid tests could rule out infection in more than 30% of infants at 3 to 6 months and in 66% of infants at 6 to 9 months of age. A recent study from South Africa demonstrated the low sensitivity of the rapid Capillus HIV-1/HIV-2 test (Trinity Biotech) in detecting HIV-infected children on treatment. Sherman and colleagues in South Africa proposed the use of less-sensitive oral-fluid screening assays to more efficiently exclude HIV infection at 12 months of age; however, screening with these assays for HIV exposure in 6-week-old infants has yielded disappointing results. These results indicate that further studies are needed to determine the age at which rapid HIV testing of exposed infants would be most cost effective in relation to sensitivity, specificity, and positive and negative predictive values. These parameters will vary according to the type of rapid HIV test used.

Considerations that make a routine rapid-testing screening approach attractive include the following: (1) rapid tests are simpler, cheaper, and more widely available; (2) many uninfected HIV-exposed children lose maternal antibodies before 9 months of age; and (3) breastfed infants can be retested by rapid tests six weeks after weaning. It is now generally accepted that if an infant between 9 and 18 months of age has never been breastfed or has stopped breastfeeding for at least six weeks and has had a negative HIV rapid test result, then the child should be considered uninfected, with no further molecular testing performed unless symptoms develop.

Viral Detection Assays
Viral detection assays directly detect the virus by demonstrating the presence of viral nucleic acids (DNA, RNA, or both) or viral antigens (e.g., p24 antigen). Although positive HIV viral detection assays accurately detect HIV infection at any age, they are not routinely used for diagnosis of HIV infection over 18 months of age. These assays are essential for definitively determining the HIV infection status of infants early in life, so that infected infants can receive appropriate care services. Yet despite their proven effectiveness, these assays, until recently, have been widely regarded as being too expensive for use in resource-limited settings, where the vast majority of pediatric HIV infections occur.

p24 Antigen Quantitation Assay
The use of the Perkin Elmer heat-denatured p24 antigen quantitation assay, designed by Schüpbach and colleagues, has been extensively evaluated as a tool for infant diagnosis and monitoring in several countries across different subtypes. The assay’s sensitivity in different subtypes has been determined to be in the range of 97.7% to 100%, with specificities similarly being between 97% and 100% (see Table 1). Access to this assay has at times been limited, with manual preparation of a separate buffer required to ensure adequate sensitivity. The assay has been evaluated on other sample collection media, such as dried plasma and blood spots. Recently, Patton and colleagues confirmed the feasibility of using this assay on dried blood spots, thus dramatically expanding its potential value in infant diagnosis.

The excellent performance of this assay in dried blood spots in HIV subtype C was also confirmed by Knuchel and colleagues in 2007. The general conclusion from published data is that the HIV-1 p24 antigen in blood is sensitive enough for early diagnosis of HIV infection in infants and young children across different subtypes, but only if the ultrasensitive HIV p24 antigen assay described earlier is used. In addition, it should be noted that this assay cannot be widely
CDC-developed assay, with primers designed for the long terminal repeat (LTR) region of the HIV genome.\textsuperscript{44-46} This assay is referred to as the total nucleic acid (TNA) real-time, reverse-transcriptase PCR assay and has also been optimized for use on dried blood spots.\textsuperscript{45} The assay is semiquantitative, with such advantages as reduced cost, increased throughput per run, and improved automation over commercial assays. An additional feature is the inclusion of an internal target ribonuclease P (RNase P), which ensures that successful amplification has taken place. A study from Uganda evaluating this assay’s performance reported a sensitivity of 96\% and a specificity of 94\% as compared with the Roche Amplicor assay on dried blood spots and cell pellets.\textsuperscript{44} In a further study evaluating the same assay in Uganda, Kenya, and Cameroon on dried blood spots, concordance of the results with plasma samples in Uganda was 99.2\%, and concordance of the real-time assay with the Roche assay in the dried blood spot samples from Cameroon and Kenya was 99.7\%.\textsuperscript{46}

In-house DNA assays targeting a variety of regions of the HIV genome are also available in many laboratories across the developing world. Recent success has been demonstrated using the CDC-developed assay, with primers designed for the long terminal repeat (LTR) region of the HIV genome.\textsuperscript{44-46} This assay is referred to as the total nucleic acid (TNA) real-time, reverse-transcriptase PCR assay and has also been optimized for use on dried blood spots.\textsuperscript{45} The assay is semiquantitative, with such advantages as reduced cost, increased throughput per run, and improved automation over commercial assays. An additional feature is the inclusion of an internal target ribonuclease P (RNase P), which ensures that successful amplification has taken place. A study from Uganda evaluating this assay’s performance reported a sensitivity of 96\% and a specificity of 94\% as compared with the Roche Amplicor assay on dried blood spots and cell pellets.\textsuperscript{44} In a further study evaluating the same assay in Uganda, Kenya, and Cameroon on dried blood spots, concordance of the results with plasma samples in Uganda was 99.2\%, and concordance of the real-time assay with the Roche assay in the dried blood spot samples from Cameroon and Kenya was 99.7\%.\textsuperscript{46}

The performance of the commercially available Roche HIV DNA PCR version 1.5 assay has been evaluated in several laboratories across a

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalent Subtype</th>
<th>Sensitivity and Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanzania\textsuperscript{32}</td>
<td>A, D</td>
<td>99% sensitivity, 100% specificity</td>
</tr>
<tr>
<td>Uganda (Mulago)\textsuperscript{33}</td>
<td>A, D</td>
<td>94% sensitivity, 98% specificity overall (compared with Roche DNA PCR)</td>
</tr>
<tr>
<td>Switzerland and United States\textsuperscript{29,31}</td>
<td>B</td>
<td>97%–98% sensitivity, 98%–99% specificity</td>
</tr>
<tr>
<td>South Africa\textsuperscript{38}</td>
<td>C</td>
<td>97.7% sensitivity, 100% specificity at 6 weeks</td>
</tr>
<tr>
<td>Zimbabwe\textsuperscript{35}</td>
<td>C</td>
<td>96.7% sensitivity, 96.1% specificity</td>
</tr>
<tr>
<td>Thailand and Cambodia\textsuperscript{16,30}</td>
<td>E</td>
<td>97%–98% sensitivity, 97%–99% specificity</td>
</tr>
<tr>
<td>Vietnam\textsuperscript{27}</td>
<td>E, recombinant AE</td>
<td>100% sensitivity, 100% specificity</td>
</tr>
</tbody>
</table>
procedures using such technologies as the Roche MagNA Pure analyzer. Extraction of liquid blood samples has been very successful, with large studies demonstrating sensitivities and specificities equivalent to manual extraction methods. A slightly reduced sensitivity has been noted for dried blood spots using the Roche MagNA Pure analyzer; further optimization is required. The need to automate extraction procedures is particularly acute in South Africa, where antenatal prevalence figures in certain provinces have reached or exceeded 30%, translating into approximately 300,000 HIV-exposed infants in need of testing each year. The issue of automation is also currently being addressed in a trial in South Africa, in collaboration with Roche, using a newly designed assay for the Roche Cobas TaqMan instrument and the Roche Cobas Ampliprep analyzer for automated TNA extraction. Compared to the Roche DNA version 1.5 assay, this combination showed good clinical specificities and sensitivities of 100% and 99.7% for whole blood and dried blood spots, respectively. In addition, the assay showed improved automation and sample throughput and can be recommended for implementation in high-volume laboratories.

### Quantitative HIV RNA Assays
Interest has also been expressed in using quantitative HIV RNA assays for infant diagnosis, because many studies have confirmed that RNA

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**Table 2. Summary of Performance of Roche Amplicor HIV DNA PCR Assay Version 1.5 in Different Subtypes**

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalent Subtype</th>
<th>Sensitivity and Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimbabwe&lt;sup&gt;43&lt;/sup&gt;</td>
<td>C</td>
<td>100% sensitivity, 100% specificity</td>
</tr>
<tr>
<td>Tanzania&lt;sup&gt;42&lt;/sup&gt;</td>
<td>A, C, D</td>
<td>99.1% sensitivity, 97% specificity</td>
</tr>
<tr>
<td>Rwanda&lt;sup&gt;42&lt;/sup&gt;</td>
<td>A</td>
<td>100% sensitivity, 98% specificity</td>
</tr>
<tr>
<td>Uganda&lt;sup&gt;44&lt;/sup&gt;</td>
<td>A, D</td>
<td>96% sensitivity, 94% specificity</td>
</tr>
<tr>
<td>South Africa&lt;sup&gt;11,49&lt;/sup&gt;</td>
<td>C</td>
<td>99.3% sensitivity, 99.5% specificity</td>
</tr>
</tbody>
</table>

... variety of different subtypes, with sensitivities and specificities ranging from 96% to 100% and from 94% to 100%, respectively (see Table 2). A CDC-sponsored meeting held in Uganda in 2005 presented the collective experience with the assay from several different African countries. This meeting had representation from 17 countries and included 60 participants with both clinical and laboratory experience in the field of infant diagnosis. Participants at the meeting from Uganda, Zambia, Mozambique, Kenya, Namibia, Rwanda, Côte d’Ivoire, Botswana, and South Africa shared data demonstrating the overall positive performance of the DNA PCR version 1.5 assay across different settings and HIV subtypes. Most sites had implemented the use of dried blood spots as the collection device prior to performing the assay.

Problems with the assay identified by users at the meeting included the manual nature of current extraction processes, the low throughput of the assay, the skill required, and the specific workflow requirements characteristic of any PCR-based technology. The consensus reached was that the use of dried blood spot specimens from infants was an acceptable means of ensuring greater accessibility to serological and virological testing for HIV infection. To address some of the implementation concerns previously described, a variety of centers have explored ways to automate the extraction...
is as sensitive as DNA PCR for early diagnosis. Further rationale for this approach would be not only to ensure diagnosis but also to provide a baseline viral load for treatment implementation in the infected infant. Use of this assay is a departure from conventional clinical laboratory practice, which advises against using quantitative assays for diagnosis. Studies conducted by the CDC in 1997 in a perinatal cohort from New York suggested that HIV RNA was detected earlier in plasma than was HIV DNA. Numerous commercial assays used for HIV viral load monitoring could be considered in this regard, including (1) the Roche Amplicor HIV-1 Monitor and Cobas TaqMan assay, (2) the Abbott Real-Time HIV-1, (3) the Bayer Versant HIV-1 RNA 3.0 (bDNA), and (4) the bioMerieux NucliSENS HIV-1 QT and NucliSENS EasyQ HIV-1.

The difficulties presented for the use of HIV RNA assays include the lack of published protocols evaluating and standardizing the extraction of RNA from dried blood spots, which is an important technique for resource-limited settings. Additionally, uncertainties remain as to whether maternal or infant ARV prophylaxis affects the sensitivity of RNA-based assays. The field is progressing rapidly, however, with protocols emerging rapidly for extraction of RNA from dried blood spots followed by use of the commercial assays described above. Examples of these include the Nuclisens EasyMag/EasyQ combination and the Roche assay. In addition, RNA qualitative assays, such as the Gen-Probe Aptima assay used in blood bank screening, are now being investigated for their role in infant diagnosis.

**Overcoming Implementation Challenges**

Challenges that have arisen in implementing early infant diagnostic testing algorithms have included limited phlebotomy skills, which are required to collect samples from infants, and difficulties transporting blood samples to central facilities for testing. Sample collection of dried blood spots has routinely been used for infant screening for decades. As discussed earlier, many studies have now demonstrated good performance of conducting p24 antigen quantitation and nucleic acid testing from material extracted from dried blood spots. Although there have been concerns about the differences that might arise in results when using venous blood compared with capillary blood for dried blood spot collection, no differences in HIV DNA PCR results were noted when these different methods of blood collection were compared.

Some consider the manual nature of cutting out spots using scissors to be a rate-limiting step in the sample processing chain for dried blood spot testing. Other approaches for obtaining dried blood spots include the use of manual or automated card punches. Concerns have been raised about potential cross-contamination of samples during manual or automated card punches. Driver and colleagues, however, demonstrated that the risk of contamination using either a manual or an automated punch is low and that both these approaches could be used in settings that require scaling up of implementation practices.

Although important in high-volume settings, the use of automated punches is complicated by the following issues: (1) the high cost of the analyzers; (2) space requirements (these instruments have large footprints); and (3) the cost of custom-made, framed cards.

The feasibility of using dried blood spots for large-scale, anonymous surveillance of HIV infection in infants at immunization clinics has been demonstrated. In this case, surveillance was being performed to measure the success of prevention of mother-to-child transmission programs.

Much debate has ensued regarding the need to repeat PCR-based diagnostic assays. Many South
African sites follow an algorithm of repeating all positive results. Other sites have widened the optical density (OD) cutoffs for the Roche DNA version 1.5 assay, thus expanding the number of samples that would be considered indeterminate or equivocal and that would result in repeats. In a recent survey of the program over a six-month period in a single laboratory in Johannesburg, up to 6% of 11,000 tests had to be repeated for a host of reasons, including control failures, discrepant results (due to sample labeling and mishandling errors at both clinic and laboratory), and defined equivocal results. These approaches would need to be evaluated independently at each site, with consideration given to the staff's skill level and the volume of samples. As the volume of samples in a particular laboratory increases, so does the risk of potential sample contamination.

Ensuring Quality

It is important for PCR technology, like any other laboratory test, to be implemented according to good laboratory practice guidelines, including appropriate workflow with designated areas and equipment as per standard PCR protocols. Appropriate documentation of staff training and ongoing performance assessment is critical for monitoring quality. Tests must have defined internal quality-control practices. This quality-control process should include appropriate negative and positive controls in each run. In addition, the inclusion of an internal control within each sample, where possible, is important for excluding false-negative results based on inhibition. Accepted method-validation protocols must be followed to assess the assay's performance in the local setting.

Factors to be considered before assay selection include the volume of tests to be conducted, clinical algorithm and required result turnaround time, geographic location, skills of clinical and laboratory staff, and availability of a courier network and supplier support in the region. Enrollment in appropriate external quality assessment (EQA) programs is an important part of the implementation process to ensure that performance is monitored on an ongoing basis. The CDC has recently introduced a pilot external proficiency program for dried blood spot DNA-based assays.

ALGORITHMS FOR INFANT TESTING

Specific algorithms must be developed to ensure that assays are conducted at appropriate times and are interpreted correctly. In 2008, the U.S. National Institutes of Health (NIH) working group for guidelines on the management of pediatric HIV infection recommended the following criteria for pediatric diagnosis of HIV: (1) two positive HIV virologic tests on separate blood samples, regardless of the infant's age, or (2) a positive HIV antibody test with confirmatory Western blot for those 18 months of age or older.

To rule out HIV infection, NIH recommends: (1) two or more negative HIV tests, one conducted at least at 4 weeks of age and the second at more than 4 months of age, or (2) loss of HIV antibody in a child with previous HIV-negative virological assays. Thus, for infants less than 18 months of age, virological assays—either HIV RNA or DNA PCR—are recommended. Testing should be conducted at three times: (1) 14 to 21 days, (2) 1 to 2 months, and (3) 4 to 6 months. In addition, seroreversion should be documented at 12 to 18 months in HIV-uninfected infants. For infants older than 18 months, HIV ELISA antibody assays are recommended.

However, the algorithm recommended by NIH is neither feasible nor affordable in most resource-limited settings; therefore, these recommendations have been substantially modified by WHO to improve access to testing. WHO recommends...
a single viral detection assay at 6 weeks of age for early diagnosis of HIV infection in all HIV-exposed infants. Although a second viral detection assay on a separate sample is recommended to confirm a positive viral detection assay, it is recognized that this is unlikely to be possible in many settings. A similar caveat holds true for using an antibody detection assay at 18 months of age to confirm a child’s HIV infection status.10,15

Many centers have demonstrated that if a single testing time point must be selected and if additional testing is difficult due to cost and follow-up, 6 weeks of age represents a good opportunity with good test performance.11,66 The caveat placed on this guideline is that earlier testing may be required should the infant display clinical features suggestive of HIV infection and that uninfected, breastfed infants must receive additional testing to exclude postnatal transmission.

**CONCLUSION**

Once further data on the performance of specific rapid HIV tests are available, current diagnostic algorithms for resource-limited settings can be further refined to reduce the need for virological testing. Consensus between working groups from the WHO and CDC have finalized diagnostic algorithms for both sick and well HIV-exposed infants.14,15 The time points identified also represent the times at which many centers would conduct postnatal visits and schedule infant immunizations. The coordination of different programs of immunization, maternal postnatal care, and diagnostic services is thus essential to ensure access for infants. Close collaboration with pediatric care services is also required to ensure appropriate referral and care for infected infants. In addition, close links should be maintained between the clinic and the laboratory to ensure ongoing monitoring of assay performance.
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The capacity to make a definitive diagnosis of HIV infection in infants and children in resource-limited settings remains limited despite the wider availability of comprehensive HIV care services, including anti-retroviral therapy (ART). This is due to the cost and complexity of the HIV tests used to diagnose younger patients, as well as a variety of psychosocial factors including stigma, discrimination, and the perceived hopelessness associated with diagnosing young patients with HIV infection. In addition, a higher level of clinical skill is required to diagnose HIV infection in children as compared with adults due to variables such as age, clinical and breastfeeding status of the child, and the need to interpret a wider variety of HIV tests.

This chapter will discuss the experience of rolling out a protocol for the detection of HIV infection in infants and children in Johannesburg, South Africa, as part of a national strategy. The associated successes and challenges, as well as lessons learned relevant to other settings, will be highlighted.

Early experiences: clinical follow-up of HIV-exposed infants

In the absence of viral detection assays, many ministries of health in resource-limited settings adopted a diagnostic protocol that involved the testing of all pregnant women in order to identify HIV-exposed infants at birth. These infants were then to be clinically followed up on cotrimoxazole prophylaxis until 15 to 18 months, when an HIV Enzyme-Linked ImmunoSorbent Assay (ELISA) test could be performed. Yet when this protocol was adopted in Johannesburg, South Africa, in the early 1990s, very few children ended up being tested for HIV. For example, 85% of infants identified as HIV exposed had been lost to follow-up by 12 months of age for a variety of reasons. Even when HIV-exposed children were successfully identified and followed up, 38% of HIV-infected infants died before 12 months of age and before a definitive diagnosis could be made. Furthermore, the majority of HIV-positive pregnant women were never identified antenatally, leaving their HIV-exposed infants with no avenue to access HIV diagnostic services.
The failure of this protocol was highlighted once again when prevention of mother-to-child transmission (PMTCT) programs were initiated in South Africa. The mother-to-child HIV transmission rate, established by determining the HIV infection status of vertically exposed infants, is essential for measuring the effectiveness of PMTCT programs. Without the ability to diagnose HIV infection in infants, it was not possible to perform an accurate assessment of the 18 PMTCT pilot programs initiated in South Africa in 2000. The need for improved diagnostic protocols for resource-limited settings became even more pressing when antiretroviral drugs (ARVs) started to be made more widely available. Without access to the proper HIV diagnostic tools for children, the ability to identify HIV-infected children and, subsequently, to increase the proportion of children receiving ART remained disappointingly low.

THE ROAD TO EARLY INFANT DIAGNOSIS

In 2000, the South African national antenatal clinic HIV prevalence rate was 24.5%, translating into approximately 250,000 infants being vertically exposed to HIV in a single year. HIV viral assays and ARVs were essentially unavailable, and the protocol requiring clinical follow-up of all HIV-exposed infants identified at birth resulted in large clinics filled with predominantly healthy children. Little clinical time remained for the care of children who were actually ill from HIV infection, making for inefficient use of scarce resources.

The Infant Diagnostic Study

Preliminary experiences using either a single Roche Amplicor HIV DNA-1 polymerase chain reaction (PCR) assay or a semiquantitative HIV ELISA test, in conjunction with a clinical assessment, suggested that an improved diagnostic protocol enabling earlier diagnosis of HIV infection in infants was attainable in resource-limited settings. These findings prompted a 2002 study of three hundred HIV-exposed infants born at Coronation Women and Children’s Hospital in Johannesburg, with the primary aim of determining an accurate, affordable diagnostic protocol for infants in South Africa. Secondary aims included assessing various age-appropriate HIV antibody and viral detection assays on blood and oral fluid to provide alternative options for diagnosing children and exploring the psychosocial consequences of an early HIV diagnosis.

The findings of the infant diagnostic study are as follows:

- Single-dose nevirapine for PMTCT administered in a routine clinical setting to predominantly exclusively formula-fed infants reduced the vertical transmission rate to less than 9% at three months of age.
- A single HIV DNA PCR test at six weeks of age detected all cases of HIV infection acquired in utero and intrapartum. The same applied to a single HIV RNA PCR test at six weeks of age, although one low false-positive result was obtained.
- The HIV DNA PCR assay could be adapted for use on dried blood spot (DBS) samples suitable for a high-throughput routine clinical laboratory without diminishing accuracy. This applied to DBS samples collected either from venous or capillary blood.
- The ultrasensitive p24 antigen assay was 96% sensitive and 100% specific at six weeks of age for subtype C virus and provided an excellent alternative to nucleic acid testing for early infant diagnosis in areas where PCR was not feasible. The assay was later modified for use on DBS samples without diminishing its performance.
- Using a single viral detection assay at six weeks of age would not only cost less than using the compromised diagnostic protocol adopted for children in resource-limited settings, but
would triple the identification of HIV-infected children.\textsuperscript{14}

- The Integrated Management of Childhood Illness clinical algorithm in the first year of life is not helpful in identifying HIV-infected infants for HIV testing.\textsuperscript{15}

- Where viral detection assays were unavailable, better use could be made of HIV antibody assays in excluding HIV infection in exposed children at 12 months of age or younger by employing the HIV ELISA assay results in a semiquantitative manner\textsuperscript{16} or using oral fluid HIV tests.\textsuperscript{17}

- Diagnosing HIV in infants involves complex psychosocial issues that require consideration in planning effective, supportive diagnostic services for children and their families.\textsuperscript{18}

**Roll-Out of Infant Testing**

The South African Department of Health (DoH) first made ARVs available for the treatment of HIV in the public sector in 2004. Their operational plan tasked the National Health Laboratory Service (NHLS) with the responsibility of providing laboratory services to support the national HIV/AIDS program.\textsuperscript{19} The plan recognized that a significant increase in laboratory capacity would be required but dealt predominantly with CD4 count and viral load testing and made no firm recommendations regarding the tests that should be used for early infant diagnosis. In that same year, based on evidence from the infant diagnostic study, the DoH guidelines recommended a single HIV DNA PCR test at six weeks of age for all HIV-exposed children if the test was locally available in the province.\textsuperscript{20}

**Overcoming Barriers**

In Johannesburg, the danger of false-positive HIV DNA PCR results was minimized by repeating all positive HIV DNA PCR assays on the same sample to check the result and by clinical guidelines that required all children to have a viral load assay, which serves as a confirmatory test, before commencing ART. Because the NHLS had very few laboratories performing HIV DNA PCR tests at the time, the DoH guidelines cautioned that PCR testing may not be available at all centers immediately. Considerable demand on the NHLS for HIV monitoring assays delayed the increase in building capacity for infant testing.

An additional obstacle to early infant diagnosis emerged: the lack of skills at the primary healthcare level for venesecting six-week-old infants. In the clinic, this was easily addressed if DBS samples were used instead of liquid blood samples. However, excising DBS samples in the laboratory was labor intensive, and the risk of cross-contamination between patient samples was unknown. The next setback was sourcing, procuring, and validating automated punches (BSD1000-GenePunch) to excise DBS samples in high-throughput environments. Only in mid-2007, when reasonably validated methods for automating parts of the testing process were available,\textsuperscript{21} were the number of NHLS laboratories capable of performing DBS HIV DNA PCR testing set to increase.

Increasing the capacity of centralized laboratories for HIV DNA PCR testing proved relatively simple in comparison to initiating infant diagnostic services for HIV in a multitude of peripheral primary health-care clinics. Significant challenges included obtaining “buy-in” from clinic management; a complex system of municipal and provincial clinics that did not view HIV testing of infants as their responsibility; convincing mothers and health workers of the benefits of infant diagnosis; training and supporting nursing staff who generally had heavy clinical loads and high turnover rates; developing and updating appropriate training materials; and logistical difficulties in obtaining consumables for DBS testing, since these were novel to laboratory and clinical staff. These challenges were exacerbated whenever national
policies changed. For example, different DBS cards had to be introduced to accommodate the automated punch, necessitating retraining of staff and updating of training materials and procedures for ordering consumables.

Once permission from regional authorities was obtained, training was conducted by a nurse-trainer in the form of half-day presentations covering the theory of testing, how to collect a blood sample, and clinical problem-solving exercises. The presentations were converted into handouts and finally into a training module for the provincial DoH to facilitate inclusion of early infant diagnosis into their HIV/AIDS curriculum. The same nurse-trainer followed each presentation with on-site practical training at individual clinics, at which time a starter pack of consumables for HIV DNA PCR testing (accompanied by instructions on how to order additional stock) and a laminated poster (which summarized the blood collection protocol and was intended for display in the clinic) was provided. Using laboratory records, the number of HIV DNA PCR tests originating from each trained clinic was monitored as a crude proxy of infant diagnostic service. Troubleshooting visits to clinics that failed to submit PCR tests after receiving training were conducted.

Timing the initiation of infant diagnostic services at clinical sites was problematic, since laboratories first had to be capacitated to perform viral detection assays. Each laboratory had to scale up to cope with unprecedented volumes of PCR tests that would be submitted at an unpredictable rate without the option of withdrawing the service once initiated. Few resources were available to “work smart” by improving laboratory methodologies to cope with the high throughput. In spite of these growing pains, by the end of 2006, HIV DNA PCR test volumes had increased dramatically in the eight laboratories capable of performing the assay (see Figure 1). However, almost three years into the national HIV/AIDS treatment program, this enormous increase in PCR tests amounted to testing only about one-third of all infants estimated to be HIV-exposed in South Africa annually.

**Ongoing Challenges**

Ongoing challenges faced in clinics and laboratories include training and retention of staff, sourcing physical space and additional staff for expansion of services, and monitoring the quality of the service provided in order to improve it.

Infants in many provinces still have no access to an HIV diagnosis, and much work remains to integrate HIV services into established child-care services so that HIV-exposed children are offered appropriate HIV testing. Provinces that do not have a laboratory capable of performing PCR testing should be shipping samples to neighboring provincial laboratories and not delaying PCR testing as intimated by the national guidelines. PCR statistics, readily accessible from the NHLS laboratory database, need to be made available on a regular basis to regional HIV/AIDS program managers to monitor infant diagnostic services.

There is still no ideal HIV viral detection assay for infant diagnosis, since the HIV DNA PCR test currently in use has yet to be automated. In high-throughput laboratories, this is not ideal considering that manual methods are more prone to human error and skilled technologists are in short supply. There is an urgent need for ongoing investigation to automate parts of the assay (e.g., an extraction method suitable for high volumes), to validate quantitative viral assays that are more widely available in South Africa for infant diagnosis on DBS, and to evaluate new assays. Laboratory capacity is much less of an impediment to testing children in Johannesburg; current barriers include the need to improve clinical services and address social factors that will allow caregivers to bring their children in for testing. The Psychosocial Aspects of Early Infant HIV Testing
The offer of HIV testing needs to be considered at every contact that a child has with health-care services, particularly in symptomatic children. In these settings, HIV antibody detection tests (preferably rapid HIV tests) can be used to determine HIV exposure. Depending on the age of the child, positive rapid tests would confirm HIV infection or allow a DNA PCR test to be submitted at the same visit. A rapid oral fluid test is less invasive and theoretically an ideal option for screening for HIV exposure at immunization clinics, but provisional results suggest the sensitivity is too low for this setting.23

Widely available rapid HIV tests remain underutilized in children, largely because there is very little data to support their use.24 This results in misleading guidelines stating that “rapid tests should not routinely be performed in children.”25

Rapid HIV tests available in South Africa are validated for adults only, and there are currently no...
recommendations for their use in children. In introducing HIV DNA PCR testing, guidelines were oversimplified, recommending a cut-off age of 15 months, below which PCR tests should be done. The use of rapid tests could reduce the need for PCR tests and return clinic visits to collect test results, resulting in considerable cost savings. For example, a clinically well 9-month-old child with a negative HIV rapid test can be diagnosed as HIV-uninfected without a PCR test during a single clinic visit, provided that no breastfeeding has occurred in the previous six weeks. The age at which rapid tests could be used to exclude infection in HIV-exposed children is yet to be determined, but may be earlier than 9 months. Further evaluation of rapid HIV tests is ongoing to inform recommendations for their use in infants.

LESSONS LEARNED

General lessons learned from the experience in Johannesburg include the following:

1. **Start now.** There is no perfect timing or perfect HIV test for initiating diagnostic services in children. Do the best you can with what is available, and work toward improvements guided by available information and local experience. Waiting for all parties to be ready is a recipe for major delays.

2. **Advocacy is vital.** Ensure that government, policymakers, and health workers are well informed regarding the importance of infant diagnosis so that sustainable clinical and laboratory services can be built from within the public sector.

3. **There is no “one size fits all” strategy.** Resource-limited settings comprise a range of diverse conditions in which clinical expertise and laboratory services vary. National health-care policymakers require access to information and expertise in this field to enable them to tailor a diagnostic policy to suit their circumstances. Foreign technical experts are unlikely to understand local conditions, and input from local health workers is essential. For example, there is little point specifying the consumables to be used for testing unless these can be made available locally and reliably. Infant diagnosis will be hindered if strategies from other settings are imposed. Develop the capacity for clinical and laboratory operations research to inform practice.

4. **Keep it simple, yet provide enough information.** Guidelines are often followed blindly and inflexibly (e.g., sick children with features of HIV infection less than six weeks of age will not be tested because the algorithm states that HIV DNA PCR should be done at six weeks of age). Various scenarios need to be considered and taught, necessitating ongoing training to minimize confusion among health workers.

5. **It is difficult to do worse.** The introduction of a new policy may be accompanied by the fear of failure. Diagnosis of infants and children, the cornerstone of addressing the pediatric HIV epidemic, is being executed so poorly that well-planned attempts to improve the service are unlikely to worsen the outcome.

6. **Persist, persist, and persevere.**
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CHILDREN CONSTITUTE AN ESTIMATED 7% of all HIV infections, yet they account for 16% of all AIDS-related deaths.¹ This extreme difference is partly due to the high risk of mortality in perinatally infected infants during the first year of life. Without antiretroviral therapy (ART), up to 40% of infants living with HIV may die before their first birthday.²³ The World Health Organization (WHO) guidelines recommend that ART be initiated as early as possible in perinatally infected infants, including those in resource-limited settings.⁴ Most HIV-exposed infants in resource-limited settings, however, can only be diagnosed by serology at 15 to 18 months of age, when maternal antibodies have disappeared from the child's blood. While serology testing is relatively cheap (US$1–$2) and widely available, it cannot identify HIV-infected infants during the first months of life, the period during which they would benefit most from initiation of ART.⁵

WHO guidelines recommend HIV diagnosis of exposed infants as part of routine care from as early as six weeks of age.⁴ This recommendation is common practice in developed countries, where the Roche Amplicor HIV-1 DNA Test may be considered to be the “gold standard” for diagnosis of HIV-exposed infants. The Roche test has been successfully used for early diagnosis of infants in Asia and Africa, but its availability has been limited to clinical research settings due to prohibitive costs (up to US$50 per test) and the need for molecular biology laboratory infrastructure and trained personnel to perform the testing. In search of more affordable and feasible diagnostic tools, researchers have developed alternative virologic tests using a real-time polymerase chain reaction (PCR) technique or an ultrasensitive p24 antigen assay, with dried blood spots (DBS) for sample collection.⁶

In this chapter we will describe the processes of technology transfer and piloting of a low-cost in-house HIV DNA PCR technique using DBS for early HIV diagnosis of infants born to HIV-positive women in Thailand. The in-house technique was developed in France and transferred to Thailand, where it was validated in a clinical trial on prevention of mother-to-child transmission (PMTCT) and then piloted as part of routine care in a network of
public hospitals throughout the country. The first part of the chapter describes the key steps in capacity building and technology transfer of the in-house HIV DNA PCR technique, building upon existing HIV research infrastructure. The second part of the chapter focuses on the lessons learned from the implementation of early HIV diagnosis as part of standard care and the importance of health-care worker training, community partnerships, monitoring and evaluation, and quality control.

**PMTCT, HIV Diagnosis, and Care for Children in Thailand**

Thailand was one of the first Asian countries to be affected by the HIV pandemic and, to date, more than 1 million of its 64 million population have been infected with HIV. In 2007, the prevalence of HIV-1 infection among pregnant women presenting at antenatal clinics was 0.8% nationwide, but with regional disparities. Thailand has a strong public health infrastructure, and the Ministry of Public Health has been actively involved in the implementation of large-scale clinical trials on PMTCT of HIV and the rapid translation of research results into policy and practice.

The Ministry of Public Health currently recommends that pregnant women who do not require combination ART for their own health (ART is available under the national universal health coverage system for women with CD4 counts below 250 cells/mm³) receive zidovudine (ZDV) prophylaxis from 28 weeks’ gestation or as soon as possible thereafter, through labor, plus single-dose nevirapine (sd-NVP) during labor. For neonates, sd-NVP after birth plus ZDV for 1 week (or 6 weeks if the mother received less than 4 weeks of ZDV during pregnancy) is recommended. Moreover, all HIV-positive mothers are advised not to breastfeed, and free formula is provided to those who need it for a period of one year.

Uptake of PMTCT services in Thailand is high. A recent evaluation study reported that 97% of pregnant women received antenatal care, of which 93% received an HIV test; 70% of HIV-positive women received antiretroviral (ARV) prophylaxis prior to delivery. The study reported a vertical HIV transmission rate of 6.8% among all cases with determined HIV diagnosis of infants; a lower vertical transmission rate of 3.9% was found for mother-infant pairs that received the full ARV prophylaxis regimen in accordance with national guidelines. Formula is provided for free under the national PMTCT program, and formula feeding was reported to be practiced by 96% of HIV-positive mothers.

As in most resource-limited settings, infants born to HIV-positive mothers in Thailand are routinely tested by standard serology at 12 to 18 months. While the antibody tests are valuable in identifying HIV-exposed children in need of prophylaxis for opportunistic infections, they fail to identify HIV-infected infants who would benefit most from timely initiation of ART. Furthermore, waiting until the child reaches 18 months of age to confirm HIV status with serology represents a long and stressful waiting period for families and a significant follow-up time for pediatric teams. Early diagnosis and treatment of HIV-positive children can reduce early mortality, while early confirmation of HIV-negative status can reduce the workload and improve the morale of health-care workers and in turn increase their willingness to advocate for greater PMTCT uptake.

In 2006, the Thai national guidelines were revised to recommend early definitive HIV diagnosis from eight weeks of age by virologic testing. It is also recommended that all infants born to HIV-positive mothers receive Pneumocystis carinii pneumonia (PCP) prophylaxis until confirmation of HIV status, and that infants confirmed as HIV-positive be initiated on ART within the first year of life. Yet while the need and potential benefit of early HIV diagnosis was clearly stated and early testing was officially recommended, a gap remained in terms of the
availability of feasible and affordable technology to enable early HIV diagnosis as part of routine care for all HIV-exposed infants.

TECHNOLOGY TRANSFER AND CAPACITY BUILDING

Thailand has participated in numerous clinical studies on PMTCT that have contributed to building the capacity of HIV research facilities and health-care professionals across the country. One example of this is the international collaboration between the Ministry of Public Health, the research consortium Programs for HIV Prevention and Treatment (PHPT), and the Faculty of Associated Medical Sciences (AMS) at Chiang Mai University, which implemented two major PMTCT clinical trials: PHPT-1, on the efficacy of short- versus long-course ZDV prophylaxis; and PHPT-2, on the efficacy of the addition of sd-NVP to ZDV for PMTCT. Through these collaborative studies, a dedicated HIV molecular biology laboratory was established at AMS to perform specialized HIV tests, including early HIV diagnosis of exposed infants, in accordance with international quality standards.

A key objective of the research collaboration with Chiang Mai University was capacity building through technology transfer and education, involving key members of the academic staff and postgraduate students. Early HIV diagnosis of infants using in-house DNA PCR testing on blood samples collected on filter paper as DBS is one example of a successful technology transfer between developed and developing countries. The three key steps in the technology transfer process are outlined here.

**Step 1: Early diagnosis using Roche Monitor HIV-1 with DBS**

As part of the PHPT-2 clinical trial on PMTCT, the PHPT/AMS dedicated HIV research laboratory was established. Equipment and training on early diagnosis of HIV using the Roche Amplicor HIV-1 DNA version 1.5 Test were prepared. From 2000 to 2002, more than 1,400 infants in the study were tested using blood samples collected on filter paper or DBS. The research team used DBS rather than fresh samples in order to bypass the time-limit constraint of fresh samples and to ensure easy transportation, as the study involved more than 40 public hospitals throughout the country, including sites in rural and remote areas. In this study, 97% of live-born infants had confirmation of HIV status by six months of age, demonstrating the feasibility of early diagnosis using DBS in Thailand, albeit in the setting of a very closely monitored clinical trial. However, due to the prohibitive costs (over US$50 per test) of the testing technology being employed, the diagnosis tool was not considered affordable for nonresearch settings.

**Step 2: Technology transfer of in-house, real-time DNA PCR technique and validation**

The virology laboratory in Necker-Enfants Malades Hospital in France developed an in-house real-time DNA PCR technique, at a cost of US$15 per test, which became routinely used for early HIV diagnosis of exposed infants in France. To promote this development, the French National AIDS Research Agency (ANRS) supported technology transfer of the technique to interested partners in developing countries.

In 2003, with funding from the Franco-Thai collaboration, Sidaction, the PHPT/AMS laboratory participated in the technology transfer program, which involved a number of the Thai laboratory staff being sent to France for intensive training on the in-house technique and quality controls. To validate the in-house technique against the Roche DNA test and ensure its compatibility with DBS, more than 1,300 DBS samples were tested by both methods at the Chiang Mai laboratory. The tests were conducted by trained laboratory technicians who were blinded,
and the results were 100% concordant.\textsuperscript{16} For quality control, the Chiang Mai laboratory participates in the Virologic Quality Assurance (VQA) program of the U.S. National Institutes of Health. The in-house real-time DNA PCR technique was shown to be equivalent to the Roche DNA test—for less than a third of the price (US$15 per test), making this a much more affordable option for Thailand. The next step was to assess the technique’s feasibility and acceptability under nonresearch conditions, as part of standard patient care.

**Step 3. Piloting early HIV diagnosis as part of standard care**

With support from Sidaction and the Global Fund to Fight AIDS, Tuberculosis and Malaria, a pilot program for free early HIV diagnosis for infants born to HIV-positive mothers was launched in 35 public hospitals in Thailand that had previously participated in the PHPT PMTCT clinical trials. As this was a shift from clinical research to standard care service, the procedures were revised and data collection was limited to ensure that the technique was feasible and acceptable to participating sites, while maintaining an emphasis on timely diagnosis, quality control, and confidentiality, as outlined below.

**Program testing schedule**

The following testing schedule was established for participating hospitals:

- Formula-fed infants born to HIV-positive mothers were tested at 8 weeks of age or as soon as possible if presenting signs of HIV infection.

- If the infant tested positive, a confirmation test was immediately requested.

- If the infant tested negative, the second confirmation test was scheduled at 16 weeks of age (i.e., two months after the first test).

This schedule was justified by the high rate of compliance with formula feeding in HIV-positive mothers in Thailand and coincides with the routine hospital visit schedule of infants at 8 weeks of age. This may be adapted for breastfeeding populations, with the first diagnosis at 6 weeks after weaning, as practiced in pilot programs in Rwanda, South Africa, and Botswana.\textsuperscript{6}

**Blood draw and labeling**

Blood samples were drawn by the nurse or laboratory technician into EDTA tubes or by heel prick, with five drops of blood spotted on the filter paper. The nurse or lab technician filed within the hospital records the lab request form, which contained an identification code, and placed the accompanying sticker on the DBS. The hospital file was updated to include records of the date of blood draw and the name of the child. To maintain patient confidentiality, the DBS sent to the lab was identified by only the coded sticker, the name of the hospital, and the date of blood draw. An accompanying information sheet was completed by the physician or nurse with details of the PMTCT prophylaxis received by the mother and infant, current treatment, age, and symptoms based on WHO clinical staging.

**Sample storage and transportation**

The blood spots were dried at room temperature and placed in a plastic bag with a desiccant to be stored at -20°C or in the refrigerator until shipment to the central laboratory in a prestamped envelope by regular mail. The sample was tested using the in-house DNA PCR technique. If positive, the result was immediately communicated to the hospital PMTCT team by telephone (and also sent by mail), with a request for confirmation testing as soon as possible. Negative results were sent to the hospital by mail, with a request for confirmation testing after two months. All participating hospitals were sent supplies of filter papers, forms, and coded stickers in advance to ensure consistent availability.
and, therefore, at high risk of transmitting HIV to their infants.

In addition, the pilot program highlighted the challenges in following up with all children for a confirmation test and care as needed. Of greatest concern is the high rate of loss to follow-up (68%) among the 41 infants who tested HIV positive.

Assessment of the program outcome at 12 months indicated a lower than expected testing uptake, relatively late testing, a low confirmation test rate, and a high rate of loss to follow-up. The program managers, therefore, tried to assess, at the level of the hospital staff and parents/caregivers, some of the reasons and possible barriers to accessing the service, in order to adapt the program objectives and activities for the following year. The feedback gathered from this assessment highlighted the following key barriers to accessing early infant diagnosis in standard care:

1. Social barriers (stigma and discrimination):
   • “Many mothers will not come back for confirmation testing. They will have the
baby tested somewhere else.” (health-care worker)

2. Informational barriers (lack of understanding):
- “The baby is too young to be tested and should not have the blood drawn so early.” (parent/caregiver)
- “We are not ready to know the result.” (parent/caregiver)
- “The baby seems healthy and doesn’t need to be tested.” (parent/caregiver)
- “The test is useful for cases we suspect have AIDS.” (health-care worker)

3. Systemic barriers (legal, financial barriers to care):
- “What do we do with the positive cases with no access to ART under the national system (i.e., non-Thai nationals)? We will need the treatment for the mother and the child.” (health-care worker)

The feedback from the sites indicated some of the reasons why parents or caregivers may not access the free early diagnosis service for their infants. These reasons can be related to lack of trust or concerns about confidentiality and stigma, or to lack of understanding (by both health-care workers and parents/caregivers) of the potential benefits of early diagnosis and early initiation of treatment for HIV-positive infants. These findings highlighted the need for more training of nurses and counselors on pre- and posttest counseling of parents and caregivers on the value of using early diagnosis to identify the children who would most benefit from early initiation of treatment, and the need to reassure caregivers on the confidentiality of the service.

The systemic barrier exemplified by lack of access to care for HIV-positive mothers and infants who are not eligible for care under the national universal coverage system due to legal, sociopolitical, or economic reasons (i.e., non-Thai nationals, migrants not registered at a particular hospital, or minority populations) had not been addressed. When facing such cases, some health-care workers seemed reluctant to offer the early HIV diagnosis service, as they believed that no treatment would be available for the mother or child if needed.

**Phase 2: Community-based program**

In response to the findings of the first phase of the pilot program, additional funding was secured from the international nongovernmental organization (NGO) Oxfam GB, for a community-based component of the pilot program, to be launched in a subgroup of 13 hospitals within the existing network. In addition to the provision of free early HIV diagnosis for infants, the program objectives were extended to the following:
- Training health-care providers on the benefits of early HIV diagnosis for timely initiation of treatment, pre- and posttest counseling for parents/caregivers, and follow-up for infants
- Information and education for the community in the form of outreach to vulnerable populations with limited access to antenatal care, PMTCT, and HIV care programs
- Support for ART for all HIV-positive infants and their families without access to treatment under the national program
- Monitoring of sites on a bimonthly basis

All nurses and counselors, including those experienced in pre- and post-HIV-test counseling, received intensive training on the specific issues of counseling parents and caregivers on early HIV diagnosis of infants. On-site monitoring assessed the number of HIV-positive mothers delivering at the hospital to measure the potential uptake versus actual uptake and to assist in resolving any laboratory or logistics issues at the site.

The second objective of the outreach component aimed to provide information and education on PMTCT, early HIV diagnosis, and care of children.
at the community level to target the most vulnerable populations with limited access to PMTCT.

To help lead and implement the outreach and education activities at the local levels, Community Advisory Boards (CABs) were established at all participating sites. The CABs were composed of an average of 8 to 10 local volunteers who met monthly or bimonthly. Local community leaders; people living with HIV, especially mothers; staff of HIV-related NGOs; orphanage workers; and health-care workers were all invited to apply as CAB members. All members received basic training on HIV disease; HIV prevention, diagnosis, and care (with a particular focus on PMTCT and children); confidentiality; and stigma and discrimination. The CABs were then asked to assess the information needs at the local level and propose methods to promote awareness of PMTCT, early HIV diagnosis, and care of HIV-exposed infants.

All proposals were reviewed by an independent committee, and approved proposals were funded by the PHPT–Oxfam GB program. Local activities included information and education efforts targeting key populations such as migrant workers’ groups, housewives’ associations, and local networks of people living with HIV. In addition, a number of hospitals extended their trainings on PMTCT and early HIV diagnosis counseling to include primary health-care unit staff, in order to enable a referral system for HIV-positive pregnant women in more rural settings. Information on early HIV diagnosis was also incorporated into existing community-based HIV activities during the local World AIDS Day events and also in the training of local volunteers living with HIV. Some hospitals established more long-term and integrated interventions to promote the follow-up and support of families undergoing the early HIV diagnosis process. The hospital HIV care teams worked with the local networks of people living with HIV to establish “positive mothers’ support groups,” where women could meet during and after pregnancy, provide peer support, and organize home visits to support other families undergoing the PMTCT and early diagnosis process.

In addition, the revised program included the provision of ART to children and families with limited access to care under the national health system, for legal or socioeconomic reasons. To date, a total of four HIV-positive children with limited access to care (i.e., not eligible for treatment under the national program) are receiving support for ART within this program.

After the community-based program had been in operation for 18 months, a total of 588 infants had received early HIV diagnosis at 13 hospitals, at a median age of 2.2 months (IQR: 2.03–3.63). The vertical HIV transmission rate was markedly lower, at 5.2% (confirmed and unconfirmed), with a lower range of age at testing, indicating more routine use of early HIV diagnosis and a possible improvement in access to PMTCT. The greatest improvement was in the follow-up of the 30 HIV-positive cases: 24 children (80%) are on follow-up, including 4 who are receiving ART within this program and 16 who are receiving cotrimoxazole prophylaxis. There were no cases of death or withdrawal (see Table 2).

The overall rate of children (HIV positive and negative) who returned for a confirmation test, however, remained at 56%, the same rate as the first phase of the pilot program. There are many possible reasons for this situation. Some site staff again have reported that mothers have gone to other hospitals for confirmation testing, in particular when the initial test result is positive. Also, it appears that when the results are negative, caregivers are satisfied with the results and do not understand the need for confirmation testing. These issues again highlight the importance of counseling parents and caregivers and of the potential benefits of the mothers’ peer support network and home visits to assist in following up with infants undergoing the diagnosis process.
early diagnosis of infants is under way in Rwanda, Uganda, South Africa, and Botswana.6

While this essential service is increasingly feasible and affordable for resource-limited settings, bridging the technology gap alone will not ensure the success of the program. As demonstrated by this pilot program, laboratory support by itself does not automatically result in high early testing uptake, nor does it necessarily result in treatment initiation for those in need.

To maximize uptake, barriers in the health-care system, particularly at the parent/caregiver level, must be identified and addressed. Targeted training of HIV health-care teams is critical—especially antenatal care nurses and counselors, but also pediatricians—in the context of counseling mothers/caregivers on the importance of early HIV diagnosis and the benefits of timely initiation of treatment for HIV-positive infants. Active community participation and leadership can provide powerful mechanisms to raise awareness of PMTCT and the availability of early HIV diagnosis, extend the reach of care for children in the community, and help strengthen and support networks of affected families.

However, for such a public-health intervention to reach its full potential impact on the survival of children born to HIV-positive mothers, early diagnosis must become fully integrated into the PMTCT process. This full integration requires that early infant testing be discussed and planned well in advance of labor and delivery, while the mother is pregnant and receiving appropriate ARV prophylaxis for her own health. In Thailand, the strong commitment and support of the National Health Security Office in the scale-up and integration of this service as part of standard care may be the key ingredient for its future success.

### Table 2. Summary of Community-Based Outreach Program Results at 18 Months

| Total number of HIV-exposed infants tested | 588 |
| Number of infants with confirmed results (% of total infants tested) | 329 (56%) |
| Number of infants who tested HIV positive (% of total infants tested) | 30 (5.1%) (24 with confirmation test, 6 with no confirmation test) |
| Vertical HIV transmission rate | 5.1% |
| Follow-up status of HIV-positive infants (as of June 2007) | |
| On ART | 4 (13%) |
| Receiving follow-up | 20 (67%) |
| Lost to follow-up | 6 (20%) |
| Deceased | 0 |
| Withdrew | 0 |

**CONCLUSION**

With expanding access to PMTCT and ART in resource-limited settings, there is an urgent need for programs to incorporate services for early HIV infant diagnosis and care of HIV-exposed infants. Building capacity for early diagnosis involves investing in laboratory infrastructure and technology transfers of the most viable low-cost techniques, in order to ensure maximum access for those in need. As Thailand incorporates access to early HIV diagnosis under the universal health coverage system, the in-house real-time DNA PCR technique on DBS is scheduled to be transferred from Chiang Mai University laboratory to other regional laboratories by 2010. A similar scale-up of


REFERENCE LIST


Traditionally, access to antiretroviral therapy (ART) programs is linked to an HIV-positive test result. Especially in rural areas, there is still a high degree of fatalism in respect to treating HIV-infected children. Challenges in pediatric HIV testing remain one of the most important obstacles for access to ART for infants and children—these include the need for expensive and often unavailable tests for a definitive diagnosis of HIV infection in infants, the greater difficulty of performing phlebotomy on children, and the fear of needle-stick injuries.1,2

We will use the term HIV screening rather than HIV testing throughout this chapter. The American Heritage Dictionary provides two definitions of screening in the medical context: (1) “to test or examine for the presence of disease or infection” and (2) “a systematic examination or assessment to detect an unwanted substance or attribute.” We prefer the latter definition for a number of reasons. The determination of the serostatus of an infant or child is based not only on diagnostic tests but also the medical history of the child and his or her family, as well as information about infant-feeding practices. Even if infection cannot yet be determined, specific care is started based on the identification of HIV exposure. Some research findings have demonstrated differences in health indicators between exposed, HIV-uninfected children and nonexposed, HIV-uninfected children. While little is known about possible increased health risks of exposed, HIV-uninfected children, having a severely ill parent may already indicate the need for specific health-care interventions.3,4

Consistent with discussions about routine HIV testing in pregnant women, there is an increased awareness of the need to also pay closer attention to the systematic assessment of the serostatus of infants and children in high-HIV-prevalence areas.

INTERVENTION

Since several practical questions from the field concerning pediatric HIV screening have so far remained unanswered, we opted for a research project to investigate opportunities for simplification of pediatric HIV screening and, consequently, increased access to pediatric HIV/AIDS care.

An exploratory cross-sectional study was organized in Lubumbashi and Kinshasa in the Democratic Republic of the Congo (DRC) in 2003. A total of 941 children between the ages of...
one month and 12 years were enrolled.\textsuperscript{5} The specific goals of the study were as follows:

- **To validate the accuracy of the diagnostic ultrasensitive p24 Ag assay (Up24 Ag assay) in the case of non–subtype B infection.** The Up24 Ag assay is a type of p24 Ag assay with a much higher accuracy. It can be used for infant HIV testing and has less demanding technical requirements than DNA polymerase chain reaction (PCR). A comparable accuracy for Up24 Ag assay and DNA PCR has been observed in populations with subtype B HIV.\textsuperscript{6} Similar findings among non–subtype B populations would increase the options for infant HIV testing in countries that have mainly non–subtype B HIV.

- **To validate the accuracy of rapid tests in African children.** Previous research in Africa demonstrated that rapid tests can be used instead of Enzyme-Linked ImmunoSorbent Assay (ELISA) tests, but most of these studies did not include children in their study populations.\textsuperscript{7,8}

- **To investigate test performance of rapid tests on capillary samples stored in EDTA (ethylenediaminetetraacetic acid) tubes.** Use of capillary samples could simplify phlebotomy (eliminating the need for venous phlebotomy) and reduce the cost and required time for HIV testing (through allowing the use of only the number of tests required for diagnosis without the need for a second phlebotomy).

- **To investigate the test performance of the Up24 Ag assay on capillary plasma samples stored on filter paper.** Use of filter paper could facilitate phlebotomy, storage, and transporta-

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\textsuperscript{5}Determine HIV-1/2, Abbott Laboratories, Tokyo, Japan.

\textsuperscript{6}InstantScreen Rapid HIV-1/2, Gaifar GmbH, Potsdam, Germany.

\textsuperscript{7}Uni-Gold HIV, Trinity Biotech PLC, Bray, Ireland.

\textsuperscript{8}Vironostica HIV Uni-Form II plus O, bioMérieux BV, Boxtel, the Netherlands.

\textsuperscript{9}Enzygnost Anti-HIV 1/2 Plus, Dade Behring Marburg GmbH, Marburg, Germany.

\textsuperscript{10}INNO-LIA HIV, Innogenetics SA, Ghent, Belgium.

\textsuperscript{11}Viral load test, Cobas AmpliPrep/AmpliCor HIV-1 [V1.5], Branchburg, New Jersey.
spots stored on the same filter paper (Schleicher and Schuell, Ghent, Belgium).

A Determine test was also performed on samples from children younger than 18 months of age (for practical reasons this was done only on venous samples).

OUTCOME

This study in 153 Congolese children younger than 18 months (with an HIV prevalence of 8.5%) and 788 children older than 18 months (with an HIV prevalence of 3.9%) demonstrated the following:

- The serial rapid-test algorithm (using Determine, InstantScreen, and Uni-Gold) performed on the capillary samples stored in EDTA tubes from 788 children older than 18 months had a sensitivity of 100.0% (95% CI, 88.9%-100.0%) and a specificity of 100.0% (95% CI, 99.5%-100.0%). This is consistent with test performance on venous blood from adult Africans.\(^7,8\)

- The Up24 Ag assay performed on 150 frozen venous plasma samples had a sensitivity of 92.3% (95% CI, 66.7%-98.6%) and a specificity of 100.0% (95% CI, 97.3%-100.0%). The obtained specificity is consistent with previous research in mainly subtype-B pediatric populations.\(^6,11,12\) (Note: The low number of HIV-infected infants in this study complicated conclusions about the sensitivity of the assay.)

- The Up24 Ag assay performed on 87 samples of capillary plasma stored on filter paper had a sensitivity of 100.0% (95% CI, 56.5%-100.0%) and a specificity of 100.0% (95% CI, 95.5%-100.0%). This is consistent with the test performance of the Up24 Ag assay on venous samples.

- There were no false-negative Determine results observed either on the venous samples from 116 children younger than 18 months or on the capillary samples from 788 children older than 18 months, despite the low HIV prevalence and high heterogeneity of HIV-1 in the Congolese population. This demonstrates a high accuracy for the exclusion of HIV. (Note: The false-positive Determine results among children younger than or older than 18 months were 0.02% and 0.002%, respectively.)

- There were no needle-stick injuries reported during the study. Glucolets were perceived as a valuable and user-friendly means to simplify pediatric phlebotomy and to reduce procedural pain and occupational risks.\(^13\)

We will now discuss some technical issues relating to HIV screening in infants and children. This discussion is based on the practical implications of our research project in the DRC, observations during clinical work in South Africa and Botswana, and experience with project implementation in Zimbabwe.

POTENTIAL FOR INCREASING PEDIATRIC HIV SCREENING IN RESOURCE-LIMITED SETTINGS

Clinical Algorithms versus HIV Testing

Because of the operational difficulties in performing HIV testing in infants and children, efforts were made to identify a pediatric clinical case definition that could replace HIV testing (Tables 1a and 1b, following pages). The reported accuracy of rapid HIV tests in children in the DRC study (sensitivity and specificity of 100.0%) was greater than the reported accuracy of most pediatric clinical case definitions (sensitivity ≤ 80% and specificity ≤ 99%). Although clinical case definitions remain highly useful in settings and situations where it is not possible to perform laboratory tests, the use of HIV tests is preferred where the option exists.\(^14\) The difference in accuracy between clinical case definitions and definitive diagnostic tests is greater in children than in adults. Additionally, in infants HIV-related mortality may follow shortly after HIV symptoms draw medical attention (e.g.,
## Table 1a. Pediatric Studies Measuring Sensitivity and Specificity of WHO Clinical Case Definition in African Children

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country and timing of research</th>
<th>Study population</th>
<th>Age-group</th>
<th>n</th>
<th>HIV (%)</th>
<th>Gold standard</th>
<th>WHO definition</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Müller et al15</td>
<td>Uganda 1985–1989</td>
<td>Immune compromising conditions Chart review for outpatients</td>
<td>0–9 y</td>
<td>422</td>
<td>49</td>
<td>EIA</td>
<td></td>
<td>56</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Chart review for inpatients</td>
<td>89</td>
<td>51</td>
</tr>
<tr>
<td>Colebunders et al16</td>
<td>Democratic Republic of Congo 1986</td>
<td>Inpatients</td>
<td>1 m–12 y</td>
<td>163</td>
<td>13</td>
<td>EIA, WB</td>
<td></td>
<td>35</td>
<td>87</td>
</tr>
<tr>
<td>Msellati et al17</td>
<td>Rwanda 1990</td>
<td>Inpatients</td>
<td>15 m–18 y</td>
<td>465</td>
<td>15</td>
<td>EIA, WB</td>
<td></td>
<td>34</td>
<td>94</td>
</tr>
<tr>
<td>Bélec et al18,19</td>
<td>Ivory Coast 1991–1992</td>
<td>Inpatients in 1 of the 3 university hospitals</td>
<td>28 d–15 y</td>
<td>4443</td>
<td>8</td>
<td>EIA, WB</td>
<td></td>
<td>19</td>
<td>98</td>
</tr>
<tr>
<td>Jeena et al20</td>
<td>South Africa 1993–1994</td>
<td>Admissions to Intensive Care Unit for pneumonia</td>
<td>1–18 m</td>
<td>159</td>
<td>23</td>
<td>EIA, p-24 Ag</td>
<td></td>
<td>77</td>
<td>84</td>
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<tr>
<td>Yeung et al22</td>
<td>South Africa 1996–1997</td>
<td>Inpatients</td>
<td>0–5 y</td>
<td>281</td>
<td>26</td>
<td>EIA, Ig3, PCR, p24 Ag</td>
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<td>22</td>
<td>96</td>
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</tbody>
</table>

EIA=enzyme immuno assay; WB=Western blot; PCR=polymerase chain reaction; ICU=intensive care unit

*Source: DeBaets et al.*

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**Table 1b. Pediatric Studies Comparing Sensitivity and Specificity of WHO Clinical Case Definition (WHO) versus a Modified Definition (M)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country and timing of research</th>
<th>Study population</th>
<th>Age-group</th>
<th>n</th>
<th>HIV (%)</th>
<th>Gold standard</th>
<th>WHO/M definition</th>
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</thead>
<tbody>
<tr>
<td>Lepage et al</td>
<td>Rwanda 1986</td>
<td>Inpatients</td>
<td>1 m–14 y</td>
<td>221</td>
<td>15</td>
<td>EIA, WB</td>
<td>41 / 47</td>
</tr>
<tr>
<td>Otieno et al</td>
<td>Kenya 1992</td>
<td>Inpatients</td>
<td>0–12 y</td>
<td>156</td>
<td>23</td>
<td>EIA, CD4/CD8 ratio</td>
<td>60 / 80</td>
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<tr>
<td>Chintu et al</td>
<td>Zambia 1993</td>
<td>Inpatients</td>
<td>&gt; 6 m</td>
<td>134</td>
<td>22</td>
<td>Rapid tests, EIA, WB</td>
<td>69 / 79</td>
</tr>
<tr>
<td>van Gend et al</td>
<td>South Africa 2000</td>
<td>Inpatients</td>
<td>1 m–13 y</td>
<td>300</td>
<td>31</td>
<td>EIA, p24 Ag</td>
<td>14 / 63</td>
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<td></td>
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<td>200</td>
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<td></td>
<td>76 / 73</td>
</tr>
<tr>
<td>Horwood et al</td>
<td>South Africa 2001</td>
<td>Pediatric</td>
<td>2–59 m</td>
<td>690</td>
<td>29</td>
<td>EIA, VL</td>
<td>8 / 67</td>
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</tbody>
</table>

Excluding: studies with a sample size of less than 100.

EIA=enzyme immuno assay; VL=viral load; WB=Western blot; IMCI=Integrated Management of Childhood Illness

**Source:** De Baets et al.

*Pneumocystis jirovecii* pneumonia may be the first symptom but has a case fatality rate of up to 87%). The importance of early detection and commencement of HIV care is thus much greater in children than in adults. Yet children are different from adults in that their ability to access HIV care and the point at which they are seen by a medical professional are greatly determined by the initiative and the health beliefs of their caregivers.

**Identification versus Exclusion of HIV Infection**

Traditionally, HIV testing has focused on the identification of HIV infection (Figure 1). Consequently, many health-care workers have felt so overwhelmed by the cost and complexity of infant HIV testing that they have ceased attempting to test all children for HIV. However, for children older than 18 months of age, rapid tests can be used just as in adults, but they...
Figure 1. Model for operational analysis of routine pediatric care in relationship to HIV/AIDS care

Source: De Baets et al.33

Symptoms not related to HIV (e.g., fracture)

Symptoms of HIV infection

Health-care worker thinks of HIV

Health-care worker does not think of HIV

Clinical case definition is positive or risk factor is identified

Clinical case definition is negative or no risk factor is identified

HIV test not proposed

HIV test proposed

HIV test not possible

Caregiver present and agrees to HIV test

Caregiver returns for posttest counseling

Accurate laboratory tests are done and accurate conclusions are made

Result: HIV+

Result: HIV−

No post test counseling done

Treated as HIV-infected child

Timely start of HIV-specific care and treatment

HIV-specific treatment accepted and good compliance

Safety and efficacy of proposed guidelines

Improved quality of life, reduced morbidity and mortality

Treated as HIV-uninfected child

Disease-specific treatment

Disease-specific treatment accepted and good compliance

Standard care provided

Health education and counseling provided

Caregiver returns for posttest counseling
are still underutilized.¹ The results of the study in the DRC described earlier allow for the simplification of the use of rapid tests in children.

Shifting the focus to an exclusion of HIV infection in infants and children puts rural health-care workers in a much more powerful position. The positive psychological impact of an exclusion of HIV should not be underestimated. An HIV-negative result may also influence the management of illness and access to referral hospitals and intensive care units (often there is no access to referral hospitals in suspected cases of HIV infection). This approach prevents health-care workers from allocating further time and resources to infants who are HIV exposed but uninfected.

In the DRC study, there were no false-negative Determine results observed in 788 samples of children older than 18 months of age. Since the World Health Organization (WHO) and most ministries of health in high-HIV-prevalence countries recommend serial testing, an HIV-negative diagnosis in a child 18 months or older can be based on a single negative rapid test, costing less than one dollar.⁹,¹⁰ There were also no false-negative Determine results observed in the 116 samples of children younger than 18 months of age. According to the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, for an asymptomatic child between 6 and 18 months of age, an HIV-negative diagnosis can be based on two consecutive negative rapid tests taken within a minimum interval of one month (provided the child did not ingest any breast milk in the previous six months).⁴ Since most seroconversions occur within six weeks of weaning, WHO recommends that antibody testing can be used six weeks after cessation of breastfeeding in children older than...
nine months.\textsuperscript{14,35} In some settings, exclusion of HIV with rapid tests may be a feasible strategy.

**PASSIVE VERSUS ACTIVE SCREENING FOR PEDIATRIC HIV**

A much more active approach to HIV screening for infants is warranted given that opportunities exist for the simplification of pediatric HIV testing and that, even in the absence of a definitive HIV diagnosis, clinical decisions can be guided by rapid-test results. In the traditional model for routine pediatric HIV care, HIV screening is attempted only after a child develops symptoms for which medical attention is sought (i.e., passive screening). The many arrows that cross the centerline in Figure 1 illustrate the ease with which children may be misclassified, resulting in HIV-infected children being treated as HIV-uninfected children and vice versa. Consequently, the real pathology may be ignored or mismanaged, referral for more optimal care at specialized centers may be deferred, and children may be stigmatized and even abused because they are perceived to be HIV infected. While it is important to remain sensitive to the potentially negative consequences of HIV testing, it is also important to recognize the potential damage that deferring HIV testing can cause.

To achieve increased access and timely commencement of pediatric HIV/AIDS care and ART, another algorithm should be followed, as proposed in Figure 2. Four possible entry points to care are identified. When children are identified for pediatric HIV/AIDS care during a pediatric consultation or admission, health-care workers should recommend the screening of siblings as well. When parents are seen for voluntary counseling and testing (VCT) or a medical consultation for signs and symptoms of HIV, health-care workers should recommend that all of their children be screened for HIV. When mothers are enrolled in a program for the prevention of mother-to-child transmission of HIV (PMTCT), health-care workers should also recommend HIV screening for all siblings of the “PMTCT baby.” Because HIV affects entire families, not just individuals, all family members (and not merely the partner) should be investigated to allow for specific HIV care to be given to all those who need it. This is a similar approach to the contact tracing that is done after one member of a family is diagnosed with tuberculosis. Such an approach may be more efficient and less stigmatizing than focusing on the partner alone. Finally, contact with health facilities for the purpose of routine immunization could be better utilized by emphasizing the possible benefits of HIV testing during the provision of health education to clinic attendees. Ideally, a free HIV test should be available to all children at the age of 6 to 14 weeks. But in the absence of the necessary funds and policies to offer this service, one positive rapid test at the age of 6 weeks could identify, in a timely manner, HIV-exposed children who need specific care and commencement of *Pneumocystis carinii* pneumonia prophylaxis.

While improving linkages between PMTCT programs and pediatric HIV care programs remains crucial, HIV screening in infants may still be a necessary safety net for settings with little to no access to PMTCT programs, a low uptake of PMTCT, or a low uptake of antenatal care and/or a high rate of home deliveries. Some parents may prefer to have their child tested before consenting to HIV testing for themselves. Finally, it may be necessary to perform HIV testing on a small group of infants who display signs and symptoms suggestive of HIV despite the fact that the mother tested HIV-negative during pregnancy. Most PMTCT programs test mothers early in pregnancy. Increased risk for HIV during pregnancy and breastfeeding may cause some mothers to seroconvert and transmit the virus after routine PMTCT testing has been performed.\textsuperscript{36}
PARALLEL VERSUS SERIAL TESTING ALGORITHMS

The serial rapid-test algorithm used in the DRC study had a sensitivity and specificity of 100% in the group of children studied. Previous studies have demonstrated that serial rapid-testing algorithms have comparable accuracy to parallel testing algorithms but are less costly, are less demanding in terms of technical requirements, and allow same-day receipt of test results. Some resource-limited settings continue to practice parallel testing for fear of lowering the accuracy of HIV testing. While it is necessary to have sufficient quality assurance for HIV testing so that standards are maintained, prevention of staff burnout and cost savings are equally important factors in achieving universal access to HIV testing for infants in resource-limited settings.7

For the distribution of rapid tests from the central level, it is important to match estimations for the required number of rapid tests with the HIV prevalence in the target group, while allowing for some spill and up to 5% indeterminate tests. For example, in the case of an HIV prevalence of 25% in the target population, each packet of 100 Determine tests may require 30 InstantScreen tests, seven Uni-Gold tests, and two bottles of chase buffer. In the field, many problems are caused by erratic distribution and the procurement of inappropriate proportions of rapid tests or insufficient amounts of chase buffer. While a health-care center may perform only a few rapid tests, it cannot share its bottle of chase buffer with another health-care center. If transport problems are expected, it may be more beneficial and cost-effective to supply rural centers with greater quantities of rapid tests rather than having a monthly distribution from central stores, to avoid labor-intensive administrative procedures and discontinuity of services in isolated settings.

VENOUS VERSUS CAPILLARY PHLEBOTOMY

Although the research and experience in the use of DNA/RNA PCR are still more extensive (as described in other chapters) than for the Up24 Ag assay, the latter test may be preferred in some settings experiencing technical or financial constraints. Several research groups are further investigating the test performance of the Up24 Ag assay and gaining experience with the test procedure, yet we are not aware of any country that has already included this test in its national policies. Recent findings illustrate that the Up24 Ag assay can also be performed on dried whole-blood spots, facilitating its use in centers that do not have a centrifuge (to obtain plasma samples), and that Whatman no. 1 filter paper can be used. That paper (as opposed to the Schleicher and Schuell filter paper) is widely available in Africa.38 Countries that would like to use the Up24 Ag assay and can organize the necessary logistics for the transport of samples to a distant laboratory and the timely receipt of test results would thus be able to increase access to infant HIV testing.

Performing venous phlebotomy on infants and children can be much more difficult than on adults and is accompanied by higher risks of occupational injury (since viral loads in children can be much higher than in adults).39,40 Traditionally, primary health-care workers have performed finger pricks for malaria blood smears using needles or lancets. This is perceived to be a very painful phlebotomy. Using Glucolets is less painful and threatening for the child while reducing occupational risks and biohazard material, since the procedure happens very fast and the needle is hidden in the top of the pen. For each child, a new lancet needs to be inserted. After phlebotomy, the needle disappears again in the lancet and it is impossible to use the lancet for another child unless the pen is opened and adapted. According to the manufacturer (Bayer), a capacity
of 7,000 finger pricks per instrument could be easily achieved, making this instrument very cost-effective. In this way, less skilled primary health-care workers who are able to perform rapid tests can also perform finger pricks in children, rather than having to refer them to the district hospital for venous phlebotomy.

The training of health-care workers in capillary phlebotomy using a Glucolet does not need to be time consuming. It is advisable to ask health-care workers to practice on each other to convince them of the difference from traditional capillary phlebotomy techniques. Because many children have traveled a long way before reaching the health-care center, rehydration before attempting phlebotomy may be advisable. Soaking the hand in warm water and observing a downward position of the arm and hand during phlebotomy are other important steps to emphasize during training. Small dots on Determine test strips, caused by blood clots, can be observed in the case of less experienced phlebotomists, but that phenomenon does not interfere with the readability of the test results.

**CONCLUSION**

Although providing infant HIV testing in the majority of remote areas may not yet be feasible, many opportunities exist to improve access to pediatric HIV/AIDS care through the use of rapid tests to guide clinical decisions and through improved linkages between different HIV programs. Especially for children older than 18 months of age, there are still many missed opportunities for HIV testing using serial rapid-test algorithms on capillary samples stored in EDTA tubes. The clinical care of thousands of children in resource-limited settings can also be further improved through routinely inquiring about previous HIV testing in the family and trying to convince clinic attendees of the benefits of HIV testing during routine health education sessions.

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REFERENCE LIST


ZIMBABWE REMAINS ONE OF THE countries at the heart of the HIV pandemic. It is estimated that 40,000 children acquire HIV infection each year in Zimbabwe, with more than 90% of those infections occurring perinatally.\(^1\) Perinatally acquired HIV infection in Africa is associated with more rapid progression of disease in a larger proportion of children than in developed countries. The youngest children are at the greatest risk for rapid disease progression and death.\(^2\) Mortality in children living with HIV could be reduced through provision of early and appropriate care. Identification of HIV-exposed infants and children thus represents the first critical step toward identifying the majority of HIV-infected infants and children through laboratory or clinical diagnosis, with further targeted management as appropriate and available.

Yet in practice, ensuring ongoing care and support for HIV-exposed infants and their mothers following delivery has proven extremely challenging. Data from a well-resourced and dedicated mother-infant follow-up clinic in an urban area of Harare demonstrated that over the three-year period from 2003 to 2006, only 35% of babies born to mothers testing HIV-positive during the antenatal period were enrolled into review and started on cotrimoxazole prophylaxis at six weeks of age; less than half of the enrolled babies were known to be alive and tested for HIV at 18 months of age.\(^3\) A study in Malawi showed that 90% (n=2,965) of women accessing antenatal care accepted voluntary counseling and testing for HIV and approximately one-quarter of those accepting testing were HIV-positive; yet more than three-quarters of this cohort were lost to follow-up by the six-month postnatal visit.\(^4\)

There are a number of possible reasons for these shortcomings, but one critical reason may be that prevention of mother-to-child transmission of HIV (PMTCT) programs are overly “vertical” in their implementation. Services for HIV-positive mothers and their exposed infants need to be integrated across a spectrum of established family and child health programs, and, when appropriate, ongoing care should be provided. One important consequence of poor integration of services in resource-limited settings is that there is typically no way for health-care workers to consistently and effectively identify, over time, mothers living with HIV and their HIV-exposed infants in need of care and treatment services. In addition, health-care
workers may not be fully aware of or may not communicate about the available care and support services that are appropriate at various points during the lifespan of both mother and infant. Women may face many logistical and financial constraints in accessing follow-up medical care services at centralized hospital settings and often seek primary health care closer to home. In addition, women are often geographically mobile and not aware of or able to attend scheduled follow-up visits for themselves or their infants at a fixed location.

DESCRIPTION OF THE INTERVENTION

Overall Strategic Approach

Given the scale of the HIV problem and the limited resources available in Zimbabwe, HIV prevention, care, and treatment need to be integrated as much as possible into the existing health system if “access for all” is truly to be achieved. Mothers and children may be extremely mobile in Zimbabwe for a variety of social and cultural reasons, and the actual resources available for prevention, care, and support are limited. Unlike in many well-resourced settings, there may be limited opportunities for continued care at a single, dedicated, specialized clinic, and health systems are not always equipped to accommodate ongoing, longitudinal care of individuals.

For these reasons, Zimbabwe’s Ministry of Health and Child Welfare (MOHCW) identified two specific needs that would have to be met if follow-up of mothers living with HIV and their HIV-exposed infants was to be improved. The first identified need was the rapid geographic expansion of services for PMTCT. This was undertaken in an effort to ensure rapid population-level coverage of basic services, including, at a minimum, antenatal counseling and testing for women and their partners and single-dose nevirapine for mother and infant (for PMTCT), with provision of other care and treatment services as available. This push for greater coverage was made to enable women and infants to receive basic services regardless of which health facility they visited across the country. The second identified need was to ensure some form of simple communication within the existing health system to facilitate access to and provision of HIV-related health services by women living with HIV and their HIV-exposed infants attending health facilities.

Including HIV Information on Handheld Child and Mother Health Cards

The child health card has a long and accepted history in the Zimbabwean national health system and among community members. The card has served as a tool for simple communication on the health of all children under five years of age. Because of its established usage, the card was targeted for revision so that it could be used to identify HIV-exposed babies to facilitate follow-up and the provision of needed care and support.

The child health card is a fundamental child survival tool found in many countries of sub-Saharan Africa. It creates a direct link between parents and health-care workers through an ongoing record of the child’s health during the critical early years of growth and development. It is issued to all children at birth and represents the primary health record for the child from birth until five years of age. Mothers or other caregivers carry the card back and forth from their home to the health center, and as such the card serves as a focal point for each health contact between mother/infant and health-care worker. In Zimbabwe, there is also an antenatal and postnatal follow-up card that is issued by the health facility to pregnant women. This card is used to communicate important health education messages and facilitate appropriate care during the antenatal, labor, and six-week postnatal period.
The relationship between these cards and the continuum of care for mothers and children is shown in Figure 1. Both this card and the child health card undergo periodic revision at the national level to ensure that the content remains in line with continuously evolving recommendations regarding maternal, neonatal, and child health.

Zimbabwe is experiencing a generalized heterosexual HIV epidemic. In this context, MOHCW decided that an integrated approach to messages regarding HIV prevention and care should be used during the next revision of the cards. As part of this plan, information on HIV would be presented on the cards and integrated into sections that would be applicable for both HIV-negative and HIV-positive people. This was intended to help minimize stigmatization while also supporting provision of a continuum of care for HIV-exposed children and their mothers wherever and whenever they access care. It was critical to ensure that cards be maintained for all mothers and children, not just those living with HIV, especially due to the confusion over messages on optimal infant feeding that had developed in recent years. It was therefore necessary to develop simplified, safe, standard infant feeding messages that could be applied and disseminated to all mothers and children, regardless of their HIV status. These messages would also reflect the current conditions in the country to ensure promotion of realistic feeding methods that would be most likely to enhance the HIV-free survival of all infants and children in Zimbabwe. (Note: Although both the mother and child cards were revised, the remainder of this section addresses the child card only.)

The overall objectives of the 2006 version of the child health card are shown in Box 1 (next page). For the first time in the history of the card, information was included on the identification of HIV-exposed infants. The inclusion of information about HIV exposure on the child card was expected to facilitate access to lifesaving care and treatment for HIV-exposed children in the following ways: (1) by encouraging health worker identification of HIV-exposed infants in all clinical settings, including well baby clinics and immunization contacts; (2) by supporting the initiation and supply of cotrimoxazole prophylaxis for all infants identified as HIV-exposed; (3) by promoting formal HIV testing of HIV-exposed infants at the appropriate point in
Box 1. Specific Objectives of the 2006 Zimbabwe Child Health Card

- To record the medical and social history of the child so as to provide a continuous and permanent record of the child’s health. Such background information, when a child is sick, is of great value in diagnosis and treatment.
- To record the birth weight, date of birth, mode of delivery, and other key birth data, as they help in determining the child’s ability to adapt to a new environment and develop normally.
- To record and promote immunization by marking out the schedule for childhood immunization. This also provides a reminder to the guardian as to when the next immunization is due.
- To assist the child’s guardian in understanding the influence of factors such as food consumption and diseases on health and to provide a visual record of the child’s nutritional and health status. In this way, the card contributes to a greater acceptance of responsibility for child care by the mother or guardian and encourages the concept of family self-reliance in health matters.
- To provide health education messages to mothers and guardians, for example, on exclusive breast-feeding, weaning, and how to prepare salt and sugar solution.
- To provide and promote a clearer understanding of the nature of childhood growth and development.
- To enable the health worker to assess child growth and interpret it in terms of health status, as well as to enable the health worker to make decisions regarding appropriate advice for the mother/guardian and how to make the necessary referrals.
- To monitor the growth of children under five years as a means of assessing the quality of nutrition and health status of the community.
- To enable the health worker to identify HIV-exposed infants and offer them appropriate basic care, and to ensure linkages to other care and treatment services if and when needed.

The inclusion of HIV exposure information on the child card also has the potential to support mothers living with HIV by (1) enabling the health-care worker to discuss HIV openly and provide the mother with ongoing care and support for her own HIV infection, including screening for treatment eligibility and referral to appropriate services; and (2) inclusion of an image of a breastfeeding mother and her male partner on the front of the card in an effort to promote shared responsibility for the health of the child and support of the mother by her male partner. It was hoped that this imagery would encourage men to be more involved in the care of their families, thereby changing restrictive gender norms (see Figure 2).

This represents a very important activity, as there is currently no longitudinal care system in place for mothers beyond six weeks postnatally.

The Revision Process

MOHCW led the process of revision, spearheading participation and consultation with multiple stakeholders. The first discussions on including HIV-related information took place at the national level in 2002, prompted by feedback from implementers involved in the pilot projects for PMTCT. Implementers had quickly identified the challenges inherent in providing ongoing care and follow-up for both women and children identified through the new PMTCT program.

A national workshop with representation from all the authorities, each province, and local pediatricians took place in June 2003 to review the existing card and consider the implications of its content in light of evolving knowledge, recommendations, and best practices in maternal, neonatal, and child health. At that time, the implications
Figure 2. The 2006 Zimbabwe child health card (front and back panels)
of the generalized HIV epidemic in Zimbabwe on routine maternal and child health care were also formally considered, and a tentative draft of the new card was developed to include information and messages sensitive to this context.

Concerns were voiced in consultations and policy-level meetings with health-care workers regarding confidentiality and community stigma; discussions focusing on those issues delayed further action for some time. Debate continued as to whether a separate card for HIV-exposed infants would be more stigmatizing and problematic, or whether a “tear-off” section of the overall card should be developed. It was eventually agreed that an acceptability pretest would be performed with both community members and health workers using a prototype of a single, revised card that included HIV information, in an effort to ensure that the card remained applicable to all children. A final decision would then be made on the content of the revised card based on the results of the pretest.

**Methodology and Results of Acceptability Pretesting**

MOHCW’s Health Promotion unit led the pretest, which was designed in collaboration with the National PMTCT (part of the National AIDS and TB Program), National Nutrition, Integrated Management of Childhood Illnesses, Rehabilitation, Expanded Program on Immunization, and National Reproductive Health units. The Pediatric Association of Zimbabwe and the National PMTCT Partnership Forum provided technical support. Representatives from a support group of people living with HIV, consisting of men and women who had participated in PMTCT services in Chitungwiza on the outskirts of Harare, were included in the team to help design, implement, and document the outcomes of the pretest. Implementation of the pretest took place throughout December 2004 and January 2005 and looked at both quantitative and qualitative factors related to the use of the new card.

All sections of the revised card were generally found to be acceptable and well received by community, health-care-worker, and HIV-positive participants. All participants were asked whether anything should be removed from the card. Significantly more health-care workers than community members felt the HIV information should be removed from the card (30.3% versus 13.5%, respectively; \( P < .005 \)), but among the people living with HIV interviewed, only 6.5% (n=4) said that the information related to HIV should be removed.5

**Finalization and Launch of the Revised Card**

MOHCW used all the detailed information from the pretest (regarding both HIV- and non-HIV-related sections of the card) and stakeholder consultations to modify and adapt the card into its current form. Final approval of the revised card was received from the top MOHCW leadership. The card was officially launched June 30, 2006, by the deputy minister of health at a ceremony in Harare. The launch ceremony was accompanied by coverage in the state media, including a prominent article in the main daily newspaper announcing the launch of the new card, with strong statements of support for the revised card and its contents.6

**Procedures to Support Confidentiality**

Quality training of health workers and extensive mobilization and support of communities, along with careful monitoring of impact, were recognized as important components of the roll-out process for the revised card. A procedures manual to accompany the new card for the training of health-care workers was developed with the support of the National PMTCT Partnership Forum and the Pediatric Association of Zimbabwe. The
manual provides updated information on each aspect of care that should be provided to every child at every point of contact. The section related to documentation of the HIV status of the child stresses the importance of obtaining maternal consent prior to completion of these sections. The information related to HIV status and care has also been placed on the card in such a way that when the card is folded, the information is hidden in the inside of the card and cannot be viewed by a casual onlooker. Although stigma is an important issue that cannot be underestimated, a visible increase in demand for HIV services in Zimbabwe has been building over recent years. As such, many felt that it was the right time for this card to be rolled out as a key strategy in helping to address HIV-related stigma once and for all through leadership from the health sector.

ANTICIPATED OUTCOMES
The revised child health card should serve as an important tool for the identification, care, follow-up, and support of HIV-exposed children. The card is also an important tool for enhancing overall child health and facilitating access to care and treatment for women and children living with HIV in Zimbabwe. The results of the pretest in Zimbabwe demonstrated a high regard for confidentiality among health workers. That could be a reflection of health workers stigma regarding HIV, or, more positively, a demonstration of their inherent understanding of the critical need to uphold patient confidentiality. When combined with the high acceptability among people living with HIV, this high regard for confidentiality inspires confidence that the revised child health card will have a positive impact in this area. Concerns over stigma and confidentiality were a key consideration during the revision process, and it will be critical to explore and address these issues going forward through ongoing evaluation.

One of the primary impacts of the card to be monitored is the effect on child health in general (i.e., infant and under-five mortality rates). Specific indicators related to HIV-exposed and -infected children can be collected through the existing health information system, and it is hoped that improvements in these indicators (e.g., number of HIV-exposed infants starting cotrimoxazole, number of infants exclusively breastfeeding to six months, and testing for HIV at any age) will be seen. The number of infants and children formally enrolled in HIV care and treatment services may also rise as a result of effective implementation and use of the card. A study of integrated childhood immunization and HIV-related health services involving household coverage surveys in two rural districts is already under way in Zimbabwe. The revised child health card is being used as one of the key survey tools. MOHCW is leading this process with technical and financial support from its partners.

Systematic documentation of lessons learned over time will also be important to consider when the next version of the card is produced.

LESSONS LEARNED
Issues concerning HIV-exposed children cannot be dealt with successfully in isolation from their mothers, fathers, and siblings. The antenatal care and follow-up card for mothers was revised at the same time as the child card and needs to be used in conjunction with the child card to ensure optimal care for both mother and baby. Addressing HIV as a family disease remains an enormous challenge to be tackled by both the health-care system and communities.

This card belongs to everyone. The process of revising the child health card was taken very seriously in Zimbabwe. The consultation and development process lasted several years because it was essential to obtain input from the wider community and agreement from all levels of the health sector.
respect the principles of confidentiality regarding access to any personal health information, and at the same time should ensure that mothers and caregivers understand what is being written on the card and its potential implications for each individual child and caregiver. The broad task of breaking down HIV stigma in both the community and health sector continues.

RECOMMENDATIONS FOR APPLICATION OF EXPERIENCE IN OTHER SETTINGS

- Successful identification and follow-up of HIV-exposed infants and children requires active development of appropriate tools and a systems-based approach to enable a continuum of care.
- The child health card has a long and accepted history in the Zimbabwean national health system and among community members; it forms the cornerstone of child health in the nation. A card like the 2006 card may be highly useful in other countries with a high HIV prevalence and limited resources as a tool to assist with the identification and follow-up of HIV-exposed babies.
- The process outlined in this chapter is replicable in countries that already have a child health card or child health passport in place, and a formal revision process of an existing card could be defined and embarked upon to update the card with HIV-related information as appropriate. Countries that do not yet use a child health card may benefit from reviewing Zimbabwe’s experiences since 1980, when the card was first issued, and adapting the Zimbabwe card to suit their own needs.
- The Zimbabwe experience demonstrates the importance of a coordinated process led by MOHCW; that process took a considerable amount of time and required contributions and “buy-in” from multiple and diverse stakeholders to ensure a systems-based (not project-based)
approach. Countries undertaking such interventions should aim for a clear participatory and comprehensive process to aid longer-term acceptability and sustainability.

- Additional training of health workers accompanied by enhanced understanding of community members (through better messages and community mobilization with regard to the card) are absolutely essential if the card is to have its intended effect.
- Stigma relating to HIV is not a static entity but is in a state of flux; bold action may be necessary to help reduce stigma and enhance prevention, care, and treatment. However, these approaches need to be undertaken thoughtfully, with respect for individual privacy and participation of key stakeholders (including people living with HIV) in the formulation and implementation of approaches, along with adequate monitoring of impact.

**ACKNOWLEDGMENTS**

This chapter was adapted from a Zimbabwe Ministry of Health and Child Welfare “best practices” document on the national child health card.
REFERENCE LIST


GLOBALLY, AN ESTIMATED 2.1 MILLION children were living with HIV in 2007. In sub-Saharan Africa, the region of the world most severely affected by HIV and AIDS, there were roughly 1.8 million children living with HIV (as of 2007), with the majority of AIDS-related deaths among children worldwide occurring in this region. Antiretroviral therapy (ART) has been widely available for both children and adults in high-income countries since the mid-1990s. The greater availability of ART in these countries has helped to transform a uniformly fatal disease in both adults and children into a chronic, manageable condition, and the impact on reductions in pediatric AIDS mortality in developed countries has been well documented. Yet despite the documented effectiveness of ART in these settings, ART has only recently become accessible to HIV programs in resource-limited settings. The national roll-out of ART in South Africa began in early 2004, with many other African countries starting programs during or after that time. Many factors contributed to the delay in ART access in resource-limited settings, including the high cost of antiretroviral drugs (ARVs), fears of drug toxicity, and the subsequently discredited belief that people in these settings are less likely to adhere to medication regimes. Increasing pressure on pharmaceutical companies to lower the cost of these life-saving medications finally resulted in the release of patents to generic manufacturers, making ART more affordable in developing countries. Yet despite these advances, many countries are still unable to afford the cost of medications and rely heavily on donor assistance to scale up access to treatment for the general population.

Although most developing countries are actively rolling out ART, access to affordable, effective pediatric HIV treatment has lagged behind that of adults in most countries. Several reasons have been cited for the delay in scale-up of pediatric ART, including the following:

- Difficulty in identifying HIV-positive infants and children and enrolling them in treatment, which has been attributed to factors that include poor effectiveness of prevention of mother-to-child transmission (PMTCT) programs (especially in terms of follow-up of HIV-exposed children); poor uptake of PMTCT programs;
and separation of PMTCT and other HIV care services from general primary health-care services (e.g., antenatal care, TB care, routine immunization, etc.).

- Lack of knowledge and confidence among health-care workers to manage pediatric HIV, which can cause them to avoid testing children for HIV and treating young patients.
- Limited availability of ARVs in pediatric-friendly formulations, as well as the perception that ARVs for young patients are more difficult to prescribe and administer.
- Lengthy process of developing and implementing pediatric HIV guidelines because of the scarcity of research in pediatric treatment in resource-limited settings on which to base policy.
- Absent or excessively rigid guidelines. Although guidelines are necessary to set norms and standards for management of patients, they may also become an obstacle to implementation. In the absence of guidelines, health-care workers feel uncertain about how to implement treatment. Yet when guidelines are available, their interpretation may impose rigid limitations, causing delays and- or difficulties in scaling up HIV care for children.

Despite these challenges, data emerging from pediatric programs around the African continent are very encouraging. In Côte d’Ivoire, a two-year survival rate of 98% was reported in children with a CD4 lymphocyte percentage of 5% or more.6 Some ARV facilities in southern Africa have also published data demonstrating the early benefits of ART in children enrolled in treatment programs.7-10

The aim of this chapter is to encourage clinicians to become more comfortable with initiating and managing HIV-positive children receiving ART, despite the many obstacles and challenges that are present in resource-limited setting.

PAVING THE WAY FOR AN EFFECTIVE Pediatric HIV Care Program

An efficient and effective pediatric HIV care program requires the following core components: clearly defined goals; sufficient numbers of adequately trained staff; a system for booking patients, documenting clinical information, and tracking progress or loss to follow-up (paper or computer based); a child-friendly environment; equipment for pediatric care; pharmacy systems that provide consistent supplies of ARVs and other necessary medications; staff capable of drawing blood from infants and children; and a laboratory capable of performing pediatric investigations with reasonable turnaround times.

Although having all these elements in place before a program begins is ideal, the lack of any one component should not prevent services from being offered. Waiting until everything is in place may cause unnecessary delays and lead to significant morbidity and mortality. With the minimum personnel (i.e., a nurse, counselor, and pharmacist or pharmacy assistant) and a consistent supply of ARVs, a facility should be able to initiate most children who are in need of treatment on ART.

To properly plan for the provision of pediatric HIV care, a facility should set targets and timelines in terms of the number of patients it expects to enroll in treatment. This requires knowledge of the demographics of the population served by the facility, including the estimated HIV antenatal seroprevalence rate and the estimated number of HIV-positive children. The latter can be calculated from the antenatal HIV prevalence rates, if available; the number of births in the area; and the estimated rate of vertical HIV transmission, given the effectiveness and coverage of PMTCT programs in the area. Comprehensive data on the proportion and age distribution of vertically infected children...
requiring ART is unavailable in most settings, but it is likely to be high because of the high morbidity and mortality among children living with HIV, especially young infants.11

**Staffing Requirements**

The lack of human resources for health care represents a crisis in resource-limited settings and is one of the most significant obstacles to scaling up HIV-treatment programs.12 The appropriate staff-to-patient ratio has not yet been established for adult or pediatric HIV care,13 but it has been estimated that two physicians, seven nurses, one to three pharmacists, and a variable number of support staff and counselors are needed to provide ART for every 1,000 adult patients.14 Although these targets are far from being reached in most settings, scale-up of quality care for children living with HIV can and must be achieved. Variables influencing the number of personnel a facility will require include task assignments, delivery models, other staff responsibilities, program size, visit schedule, and level of care provided.

Task shifting, in which nurses or laypeople perform tasks outside of their traditional domains (e.g., taking blood samples, providing nutritional counseling, etc.), is one innovative way to address staff shortages. Creative approaches to dealing with increasing patient loads must be sought for programs to remain effective. In Uganda, for example, high school graduates receiving an intensive course in HIV management were successfully employed to lighten the load of more formally trained medical staff.15

Managing HIV infection may require longer consultations for children than it does for adults because of more-complex treatment regimens and the need to consult with caregivers and/or other family members, as well as the patient. For instance, experience at the Tygerberg Hospital Family Clinic (THFC) in South Africa has shown that the average time a doctor requires to see an adult HIV patient is 10 minutes compared with 20 minutes for a pediatric patient (H. Rabie, MD, personal communication, July 2007). Young patients may also have to visit the clinic more frequently than adults for dose adjustments due to frequent growth and/or weight gain.

In many cases, medically stable infants and children can be managed by health-care workers other than doctors, such as nurses or clinical officers with a basic knowledge of HIV. Regardless of what model of care provision is used, family-centered care should be the goal of any pediatric HIV program. Health-care workers must always assess treatment options in light of their appropriateness and accessibility for each patient and the patient’s family.

Pediatric HIV management guidelines (e.g., those from the World Health Organization [WHO], national or regional health authorities, etc.) should be available at all facilities that provide care to children. Training should accompany the implementation of any new or updated guidelines. Basic knowledge of the normal primary care of pediatric patients (i.e., WHO Integrated Management of Childhood Illness [IMCI] strategy) is a necessary prerequisite for health-care workers treating HIV-infected children, because common childhood illnesses are seen more frequently in these patients. Community-based advocates are also essential for tracking children that require home-based support or need to be traced for follow-up.

**Facilities**

Health-care workers should aim to provide a safe and child-friendly environment for children. Play areas containing toys and books and cheerful decoration help to make the facility more welcoming for children and their families. The overwhelming nature of the adult HIV epidemic can often cause facilities to overlook or ignore the unique needs of children. Yet there are some important considerations that must be made for children attending HIV care facilities.
For instance, exposure to harmful organisms may pose a threat to children grouped with large numbers of sick adults in waiting rooms. If possible, waiting and consultation rooms for children should be separate from those for adults. Although effective care can be delivered to both adults and children in a shared space, sensitive issues should always be discussed in private, with the family and/or with the child alone (particularly in the case of adolescents).

**Materials and Equipment**

Following are some essential items specific to the management of HIV infection in infants and children.

- **Scales and weight percentile charts.** Accurate sequential measurement of weight is essential for disease staging, formulating ARV dosages, and monitoring patient progress. Weights should be plotted on WHO weight-for-age percentile charts.

- **Tape measures and head circumference charts.** Neurodevelopmental delay is common in HIV-infected infants and is often underrecognized. Measurement of the head circumference and plotting on a WHO percentile chart is an important component of the neurological assessment in children younger than three years of age.

- **Stadiometer and length/height percentile charts.** Ideally all children need regular measurement of height/length, but it is not essential for HIV management. However, in the case of small infants (i.e., under 5 kg), measuring body length is essential for calculating body surface area, a number used in the calculation of dosages for some ARVs.

- **Appropriate specimen containers, needles, and syringes.** Taking blood specimens in young children will require the appropriate needles and syringes; it may be helpful to use specimen containers that require smaller blood volume. Equipment for gastric lavage for TB diagnosis is also essential. TB specimens should be obtained in well-ventilated areas, and the person administering the test should ideally wear an N95 disposable respirator.

**Drug Supply**

Ensuring a reliable and safe drug supply is one of the most important tasks in pediatric HIV care. Reliable procurement and transportation, maintenance of the “cold chain” (for selected ARVs, such as lopinavir/ritonavir solution, which needs to be stored at temperatures below 25°C), and proper storage conditions are essential.

There should be standard operating procedures in place for tracking and forecasting pediatric drug needs. Drugs close to expiration should be used first. Projected requirements for newly enrolled patients and those already in care should also be taken into account when orders are placed.

**Laboratory Support**

Access to special investigations (e.g., HIV DNA polymerase chain reaction [PCR], CD4 counts, viral loads) often varies among countries and with the level of care provided by the treatment facility. Systems should be in place for managing and tracking both the laboratory specimens and the results. It is imperative that the turnaround time be as short as possible for getting specimens to laboratories, obtaining results, and getting results back to patients. The clinic should develop a system that reviews results as soon as they arrive and addresses abnormalities promptly. The laboratory should be able to inform the clinic immediately of severely abnormal results.

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Clinicians can often proceed with appropriate care, preparing for and initiating ART in the absence of results or while awaiting results, based on clinical parameters. For example, if a child has WHO clinical stage III or IV (moderate or severe) HIV disease, treatment preparation and counseling for the family should occur immediately so that by the next visit, when laboratory results are available, the family may be ready for their child to begin ART.

**Data Capturing**

Systems for booking patients and measuring enrollment and treatment outcomes are essential. Data systems also assist in identifying problem areas and predicting future program requirements. The most basic system is a paper-based register, although more than one type of register can be in use, such as those for PMTCT, infant follow-up, PCR, and ART. Clinics should have access to all the relevant documentation for each patient. Computer-based databases may be helpful in settings that can support the intensive technological requirements and have the necessary capacity for data capturing.

**Referral Networks**

It is important for clinics to develop direct staff contacts and links with the hospitals they refer to and with the smaller clinics that up refer to them. Links with key individuals at various levels of care facilitate the referral process. District networks and regular meetings can be helpful in establishing those links.

**WHEN TO START**

Deciding when to start ART in children requires weighing the risk of disease progression against the development of side effects and resistance in light of the limited availability of pediatric formulations and other resources. Cohort studies from developed countries and recent data from the Children with HIV Early Antiretroviral (CHER) trial in South Africa indicate that starting ART in early infancy, regardless of clinical and immunological staging, is beneficial because it is associated with decreased mortality and lower rates of disease progression.\(^{17,18}\)

**Identification and Diagnosis of At-Risk Children**

The success of early treatment depends on an effective PMTCT program that can identify HIV-positive mothers, can provide optimal ART to prevent vertical transmission, and is linked to an efficient infant follow-up program that includes early HIV DNA PCR diagnosis. Health-care staff at well-baby clinics should be able to offer HIV DNA PCR diagnosis for HIV-exposed infants who have not yet been tested through the PMTCT program. New mothers who may have seroconverted after initial HIV screening or those who may not have been previously tested for HIV should also be tested whenever possible; if they test positive, their infants should be tested by HIV DNA PCR. Identification of infants acquiring HIV through breastfeeding must also be considered.

Methods to improve infant diagnosis are discussed in detail elsewhere in this publication. However, it is important to point out that despite improvements in testing modalities, children living with HIV often go undiagnosed for various reasons, including the following:

- The mother fails to enroll in a PMTCT program and/or refuses HIV testing.\(^{19}\)
- The mother seroconverts during pregnancy.\(^{20,21}\)
- The mother travels to a facility different from her antenatal clinic to deliver the baby where her HIV status is unknown.
- The mother does not give birth in a formal health-care facility and misses being diagnosed with HIV and the opportunities for counseling.
- The infant is lost to follow-up.
- The infant’s HIV exposure status is poorly documented.\(^{22}\)
• Programs are poorly integrated (e.g., poor links between PMTCT and pediatric immunization programs).
• Health-care providers fail to recognize signs and symptoms of HIV or fail to test children suspected of being HIV positive.23

It is imperative that all opportunities to identify and test at-risk infants and children be considered. Infants and children who should be specifically targeted include those
• attending immunization clinics in high-HIV-prevalence settings,24
• suspected of having or diagnosed with TB,
• with HIV-infected parents,
• admitted to hospitals in settings with high HIV prevalence,25
• with malnutrition or recurrent minor childhood infections,
• who have been sexually abused, or
• who are orphaned or otherwise vulnerable.

Factors that can assist in increasing the prevention and diagnosis of HIV in infants include provider-initiated HIV testing for all pregnant women; repeat testing in late pregnancy; dried-blood-spot technology for increasing the ease of specimen collection from infants; integration of PMTCT and immunization programs; validation of rapid tests for use in children26; and standardized training of clinicians, nurses, and laboratory staff.

Infants and children identified as HIV-positive require clinical staging and CD4 evaluation. In a facility with a shortage of physicians, nurses can be trained to perform such evaluations. Children should then be followed up with until they qualify for ART; follow-up should include monitoring of growth and development as well as regular CD4 percentage assessments.

Morbidity and mortality of children who are not on ART can be reduced through a number of simple interventions, including
• cotrimoxazole prophylaxis,27
• nutritional optimization,
• aggressive treatment of infections, and
• diagnosis and treatment of children with TB.

TB diagnosis and treatment is an important component of a successful HIV treatment program because HIV-positive children are more likely to develop TB. In addition, TB is often the sentinel disease with which an HIV-positive child presents to the health-care facility. Every HIV-positive child with confirmed TB exposure requires isoniazid (INH) prophylaxis, regardless of age.28

HIV infection makes TB more difficult to diagnose and reduces the diagnostic value of routine TB tests. For this reason and because of the recent increase in multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB,29 programs should aim to make a bacteriological diagnosis by whatever method possible.

Treatment Initiation

Each of the three major pediatric antiretroviral guidelines, produced by WHO,30 the Pediatric European Network for Treatment of AIDS (PENTA),31 and the U.S. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children,32 provides a slightly different set of clinical and immunological criteria for starting ART. Guidelines from the United States and Europe take into account the viral load. The WHO guidelines for ART initiation, updated in 2006, are the only international guidelines specifically aimed at programs in developing countries.

In the HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS), a large meta-analysis of pooled cohorts of children from the United States and Europe conducted in the era before ART became widely available, CD4 percentage and, to a lesser degree, viral load, were found to be correlated with risk of clinical progression.31 In this analysis, absolute CD4 count correlated well with risk of disease progression in children older than four years,
but was less well correlated in younger children. Total lymphocyte counts also predicted mortality. A similar pooled analysis was performed with data from resource-limited settings, but only for children over 12 months of age. In this analysis, CD4 percentage and count correlated well with risk of disease progression; however, total lymphocyte count was unhelpful. A weight-for-age z (WAZ) score less than –3 and hemoglobin less than 8 mg/dL were found to be highly predictive of mortality, regardless of CD4 count. The association between risk of death and WAZ has been documented elsewhere.

In all analyses, infants were at high risk for death regardless of the clinical or immunological prognostic markers, particularly for those under six months of age. Data from the CHER trial clearly document high mortality in young infants not yet on ART. The CHER trial examined ARV strategies for infants in South Africa. Infants were randomized to start ART either before 12 weeks of age or when they met the WHO CD4 percentage or the clinical criteria for ART initiation. The Data Safety Monitoring Board recommended discontinuing the deferred therapy arm because of a 75% difference in mortality: 4% in the early starters versus 16% in the deferred therapy arm. Infants in the early treatment arm began ART at a median age of seven weeks. All infants in the deferred arm had a CD4 percentage above 25% on entering the study. The deaths occurred in the first six months of life and were not anticipated based on clinical findings; and more than one-third of the deaths occurred at home, implying that the health condition of the children deteriorated rapidly.

The U.S. and WHO pediatric ART guidelines were updated in 2008 and now recommend that all HIV-infected infants under one year of age, regardless of clinical symptoms, start ART as soon as possible (Table 1).

Disadvantages of early therapy initiation in infants include high rates of viral replication and the potential for early resistance and regimen failure, as well as the potential development of side effects caused by lengthy exposure to ART.

Clinical Criteria

WHO recommends that children older than one year of age with moderate to severe disease (clinical stages III and IV) should be initiated on ART regardless of immunological findings. If the stage-III condition is thrombocytopenia, pulmonary TB, lymphoid interstitial pneumonitis, or oral hairy leukoplakia, the decision to start therapy includes consideration of the CD4 count and/or percentage.

Because the risk of disease progression and death changes with age, all the guidelines make recommendations for different age groups. PENTA guidelines divide start criteria into four age categories: infants, 1- to 3-year-olds, 4- to 12-year-olds, and those 13 years of age and over. This categorization becomes complicated for training purposes. Updated WHO guidelines recommend starting ART

| Table 1. WHO Criteria for ART Initiation in Children (2008) |
|-----------------|----------------|----------------|----------------|
| Criteria        | Age            |                |                |
|                 | Infants        | 12 months      | 36 months      | 5 years or over |
|                 | <12 months     | through 35     | through 59     |                |
| CD4 Percentage  | All            | <20%           | <20%           | <15%           |
| Absolute CD4 Count | <750 cells/mm³ | <350 cells/mm³ | As in adults (≤200 cells/mm³) |

Immunological Criteria

Immunological criteria for ART initiation also depend on the age of the child. WHO recommends ART initiation at the absolute and percentage CD4 values corresponding with the definition of severe immunosuppression (see Table 1). The U.S. guidelines are similar to those of WHO for immunological criteria, but PENTA recommends starting ART at higher CD4 percentages. In general, PENTA guidelines recommend treatment of children who have a 5% chance of death and a 10% risk of AIDS (i.e., WHO stage-IV disease) within the following year based on the HPPMCS data. WHO provides guidelines for the use of absolute CD4 count based on data from HPPMCS when CD4 percentage is unavailable.

WHO also provides guidance if no CD4 quantification is possible and recommends using total lymphocyte count (TLC). However, subsequent data have not validated the use of TLC. CD4 percentage ideally should be the investigation of choice for staging children under six years of age based on data from a pooled analysis in both developed and developing countries (Figure 1).

Viral Load Measurements

Viral load is used as an additional criterion for the initiation of ART in developed countries. Viral load was found to predict disease progression in the HPPMCS analysis. Viral load monitoring to determine eligibility for ART is not feasible in many resource-limited settings. Measurement of viral load to monitor patient response to treatment is, however, currently available in South Africa.
Social Criteria
The presence of a reliable caregiver is critical to ensuring that the child adheres to the medication regimen. Living conditions do not always support a young patient’s adherence to ARVs, particularly in settings where there are large numbers of orphaned and/or other vulnerable children or where the caregiver is HIV positive and has not disclosed his or her HIV status to other members of the household. Nevertheless, ART can still be successfully administered through creative planning. Every effort should be made to ensure that even a child with no readily identifiable caregiver has access to ART—for example, by enlisting the help of a neighbor or school teacher.

WHAT TO START
Ideally, treatment combinations for children initiating ART should be selected with the aim of maximizing adherence and minimizing toxicity. Excellent virological outcomes are possible for children with good adherence; ART has been shown to significantly decrease HIV-related morbidity and mortality and optimize growth and neurocognitive development in children.

ART regimens for children are often perceived as being more complex than those for adults for several reasons, including the following:
- Fewer clinical trials have been conducted in children than in adults, resulting in limited treatment options for children.
- Liquid formulations, where available, are often poorly palatable and may need refrigeration or administration in large volumes; thus, it may be difficult for caregivers to transport and administer the medication.
- Often adult tablets are broken or capsules opened for pediatric use; few solid child-friendly preparations are manufactured.
- Few fixed-dose formulations specifically designed for children have been produced to date. Many countries have achieved satisfactory treatment outcomes using adult formulations that are broken into pieces. However, this practice carries a risk of overdosing or underdosing.

Treatment Regimens
A combination of at least three ARVs is the standard of care for first-line ART regimens globally. It is generally accepted that a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third drug, either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) is the most effective combination. Triple-NRTI regimens are less potent. U.S. and PENTA pediatric ARV guidelines recommend either an NNRTI or a PI as the third drug. WHO advocates reserving PIs for second-line regimens except in infants who are required to start ART early and have been exposed to NNRTIs as part of PMTCT, and where PIs are readily available.

The NRTI backbone recommended by WHO for use in children is lamivudine (3TC) in combination with zidovudine (ZDV), abacavir (ABC), or stavudine (d4T) (Box 1). Where available, emtricitabine (FTC) can be used instead of 3TC. 3TC and FTC have a good safety and tolerability profile. WHO recommends that programs ensure that at least two of the other NRTIs are available should...
Two NNRTIs are approved for use in children, NVP and efavirenz (EFV); development of resistance mutations to one usually implies resistance to both. EFV has not been studied in children under three years of age and weighing less than 10 kg. In South Africa, EFV is recommended for children older than three years of age. NVP is recommended in lieu of EFV for adolescent girls, because EFV may have teratogenic effects when used in the first trimester of pregnancy. NNRTIs are not active against HIV-2 and subgroup O virus.

A retrospective review of almost 400 children from Groote Schuur Hospital in Cape Town, South Africa, followed over 36 months suggests that PI regimens may be more effective than NNRTI regimens at achieving virological suppression. The most commonly used PI for children is lopinavir/ritonavir (LPV/r). Dosing and efficacy data are available for children as young as four weeks of age for LPV/r, and a solid formulation of LPV/r has recently been launched that is likely to make dosing for children easier.

There are no good data on what regimens to use for children who fail PMTCT with ART; however, some of these children may also harbor NNRTI-resistant virus. Concerns about the potency of NVP in young infants and the fact that sd-NVP is the standard of care for PMTCT in South Africa have resulted in South African national guidelines recommending LPV/r for first-line therapy in children under three years old. Recognizing that infants who need to start ART early may have been exposed to NVP as part of PMTCT, WHO now recommends that in this situation infants should be started on LPV/r where available instead of NVP. The disadvantages of using a PI for first-line treatment are that currently no potent second-line regimen is available should treatment failure occur, and long-term sequelae of exposure to PIs from early infancy are not known.
Newer PIs (e.g., darunavir) that maintain activity in the presence of high-level PI resistance have recently been approved by the U.S. Food and Drug Administration, and dose-finding trials are in progress for children. New classes of ARV agents (i.e., integrase inhibitors and CCR5 antagonists) are currently entering pediatric clinical trials. These trials offer hope of future potent options for children who fail PI-based regimens.

**Dosing**

Dosing is based either on body surface area (BSA)* or weight. WHO has developed a prototype dosing table that can assist with standardization and calculation of dosing for children.30

WHO and The United Nations Children’s Fund (UNICEF) have convened a working group to develop a harmonized strategy to simplify pediatric ART. Although a few fixed-dose combinations (FDCs) for children have already been developed, the group is calling for the development of solid formulations that will meet the desired dosing ranges as set out in the WHO guidelines.30 The FDCs should be child friendly, readily soluble, crushable or breakable, and available for the smallest infants. A single weight-band-based common dosing schedule suitable for all weights and ages of children has been developed to apply to single-, dual-, or triple-drug FDCs. The numbers of tablets required for any FDC or single ARV tablet formulation will be the same per weight band. Urgent attention needs to be paid to the development of once-daily FDCs because they are likely to enhance treatment adherence in children.

**TUBERCULOSIS TREATMENT AND ART**

In settings where coinfection with TB is prevalent in both adults and children, drug interactions between ART and TB treatment are of concern. Rifampin (RIF), which is a recommended component of first-line TB treatment, is a potent inducer of cytochrome P450 isoenzyme 3A, among others,60 and can cause a decrease in the blood concentrations of PIs and NNRTIs. Rifabutin is recommended as an alternative to RIF because it causes fewer drug interactions. However, rifabutin is costly and not available through most government-run health programs. NVP is not recommended for use in conjunction with RIF because of drug interactions.61

Hepatotoxicity is an issue when either NNRTIs or PIs are administered with TB treatment. Despite concerns about inadequate potency, WHO recommends using a triple-NRTI regimen in conjunction with TB treatment and advises against using boosted PI regimens with TB treatment because of safety concerns in adults.62 Data from a small pilot study demonstrated that boosting LPV/r with additional ritonavir overcomes the effect of RIF.63 Doubling the dose of LPV/r in combination with RIF-containing TB treatment should be avoided as results from a pilot study in South Africa demonstrated that a high proportion of children have subtherapeutic drug levels with this approach.64 Although EFV is recommended for use with RIF,65 there are insufficient data in children, and pilot data show that dosing of EFV in children, with and without RIF, may be inadequate.64 The pilot study, and the general lack of data on drug effects in children, indicate that further research is needed to address the treatment of HIV and TB coinfection in young patients.

**MONITORING CHILDREN ON ART**

Once ART has been initiated, children need to be followed up with on a regular basis (most programs suggest every three months) to monitor clinical, immunological, and, where available, viral progress.

*BSA = square root [body weight (kg) × height (cm) / 3,600]
and to look for development of adverse events. According to South African guidelines, immunological and virological assessment should occur every six months unless the child is ill and requires more intense management.40

In general, the same profile of toxicities experienced in adults occurs in children, often to a lesser extent. Monitoring for toxicity is informed by the side effects likely to occur on a particular regimen (e.g., if AZT is used, regular blood counts will need to be done). Acute infections may mimic drug toxicities and should actively be excluded. If caregivers are well educated about what side effects to expect in children, it is more likely that their patients will adhere to the prescribed regimens.

Toxicity reactions may be mild, moderate, or severe and/or life threatening. If mild, treatment usually does not need to be changed. Moderate reactions (e.g., lipoatrophy associated with d4T) may require single-drug substitution, provided there is viral load suppression. Severe or life-threatening reactions include lactic acidosis, hepatitis, pancreatitis, hypersensitivity, and Stevens-Johnson syndrome. Should any of these reactions occur, ART should cease immediately, supportive management should be implemented, and, when the child recovers, a new regimen should be started without the drug thought to have caused the toxicity.

Clinicians should be familiar with the presentation and management of toxic events, which are outlined in the U.S. pediatric ART guidelines.32 WHO guidelines also include helpful guidance for management of toxicity and provide a toxicity grading system on which to base management decisions.30

SWITCHING TO SECOND-LINE THERAPY
Despite the proven clinical benefits of ART, finding durable regimens remains a challenge, and failure of first-line treatment is not uncommon. ART failure should be considered subsequent to an adequate treatment period (at least 24 weeks), an assessment of adherence, and confirmation that there is no untreated opportunistic infection.30 Data from the United Kingdom (UK) indicate that 22% of HIV-positive children in the UK currently on ART required a regimen change a median of seven years after ART was initiated. There was a large variation in the time to switching as well as the level of viral replication before changing therapy.66 Data from resource-poor settings are limited, although cohort data from the Western Cape of South Africa showed that 3% of children initiated on ART and retained in care required a second-line regimen within three years of initiation.67

In resource-limited settings, clinicians considering a switch of treatment regimens must strike a balance between multiple considerations. For instance, switching regimens early may result in using all available agents in a short time. Yet persisting with failing regimens will lead to the accumulation of resistance mutations, thereby compromising future treatment options.

Various factors can lead to treatment failure. Some potential reasons for failure and their underlying causes are summarized in Table 2.

The decision to switch regimens is further complicated by the good clinical and immunological response many children have in the absence of complete viral suppression. Second-line therapy is often more complicated and more expensive to administer, and the limited number of formulations available for children exacerbates the complexity of treatment.

Drug Selection
The choice of drugs for a second-line regimen depends on drug availability and the patient’s prior treatment exposure. Undesirable and/or dangerous combinations should be avoided. Cross-resistance should be considered as well as the potential for
suggestive of a more severe clinical stage of infection in a child who has been on ART for at least 24 weeks.

Signs of particular concern include the following:
- Lack of or decline in growth rate after initial response on therapy
- Loss of neurodevelopmental milestones or development of encephalopathy
- Development of opportunistic infections or malignancies or recurrence of severe infections

There are certain caveats to the diagnosis of failure based purely on clinical grounds. New opportunistic infections and clinical deterioration, particularly within the first three months after the initiation of ART, may be caused by ongoing immune suppression or immune reconstitution inflammatory syndrome (e.g., 3TC [M184V mutation]). For subsequent changes (i.e., third-line treatment), inexperienced clinicians should consider consulting with an expert.

### DEFINING TREATMENT FAILURE

Treatment failure can be defined as virological, immunological, and/or clinical, and the three types of failure usually occur in that order. In countries with poor access to viral load testing, clinicians rely on clinical and, if available, immunological determinants to diagnose treatment failure.

### Clinical Failure

According to WHO guidelines, clinical failure is defined as the development of new events suggestive of a more severe clinical stage of infection in a child who has been on ART for at least 24 weeks.

### Table 2. Reasons for Treatment Failure and Underlying Causes

<table>
<thead>
<tr>
<th>Reason for Failure</th>
<th>Underlying Cause</th>
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<tbody>
<tr>
<td>Suboptimal plasma levels of ARVs</td>
<td>- Poor or nonadherence to the treatment regimen.68&lt;br&gt;- Drug interactions—in particular, those associated with antituberculous therapy.69&lt;br&gt;- Incorrect dosing of ARVs, especially failure of clinicians to adjust the dosing with increases in weight.69&lt;br&gt;- Genetic polymorphisms and variations in the levels of the cytochrome P450 enzymes; other drug-metabolizing enzymes and transporters are the main pharmacogenetic sources of intra- and inter-individual variations in drug metabolism.70&lt;br&gt;- Malabsorption in HIV-positive children.70</td>
</tr>
<tr>
<td>ART resistance</td>
<td>- Primary infection with a resistant strain of HIV. (Routine surveillance is being conducted internationally for the prevalence in ART-naive patients.)&lt;br&gt;- Can also occur secondarily to a nonsuppressive regimen; resistance mutations to NVP commonly occur subsequent to administration of sd-NVP to mother and baby for prevention of perinatal transmission to the infant.56&lt;br&gt;- Infants and young children have very high viral loads. Although the rate of decline in viral load is the same for children and adults treated with ART, achieving an undetectable viral load may take longer in children. This prolonged replication of HIV in the presence of ARVs may lead to resistance and subsequent treatment failure.72</td>
</tr>
<tr>
<td>Inadequate potency of drug regimen</td>
<td>- Primary infection with a resistant strain of HIV. For example, mono- or dual-therapy regimens or triple-nucleoside regimens may precipitate the development of resistance.</td>
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syndrome (IRIS) rather than failure of ART. In addition, new episodes of pulmonary TB in high-prevalence areas may reflect the high risk of exposure rather than failure of ARVs.

Whether poor clinical and immunological status predicts virological failure in children has yet to be determined. However, in some cases immunological recovery has not occurred despite virologic suppression. In adults, CD4 lymphocyte count and clinical disease poorly predicted virological failure. When viral load is suppressed but clinical or immunological criteria for failure are met, switching regimens is inappropriate. Careful clinical review should be performed to establish possible contributing factors. There are no long-term data to estimate the impact on future treatment outcomes of waiting for clinical deterioration in children before switching regimens. The WHO clinical staging tool for children on treatment also needs to be validated.

Immunological Failure
Immunological failure is defined as a drop in CD4 count below age-related criteria to start treatment after an initial response on ART. However, if treatment is initiated at a normal CD4 count, this level may not increase, but the normal CD4 level should be maintained over time. Some children with severe immunosuppression may not reach normal CD4 levels despite prolonged treatment. Knowledge of baseline CD4 count is essential when using immunological criteria for the decision to switch therapy. No decision to switch should be made on a single CD4 measurement.

Virological Failure
The aim of ART is to reduce viral load and maintain it below detectable levels. In the face of a non-suppressive regimen, resistance mutations develop and accumulate over time. U.S. guidelines provide clear virological criteria for treatment failure but maintain a flexible approach to regimen switching, bearing in mind the limited options for children.

Despite virological failure, many children may remain clinically and immunologically well for some time. As mentioned earlier, the implications of nonsuppressive regimens are yet to be determined but are being investigated in the combined PENTA and PACTG trial (PENPACT 1), a phase II/III randomized, open-label study of combination ARV regimens and treatment-switching strategies in HIV-1-infected, ARV-naive children. The study is looking at infants and children between 30 days and 18 years of age to assess, among other things, the long-term effect of switching regimens when viral load reaches 1,000 copies/mL compared with 30,000 copies/mL. WHO provides no guidance on virological criteria to switch regimens.

Resistance Testing
Resistance testing is expensive, and although the U.S. guidelines recommend this testing for all children failing therapy, data from the PENTA 8 study show that the availability of resistance testing altered NRTI-prescribing practices but not patient outcomes. Despite these findings, the need for widespread access to affordable technology for CD4 (particularly percentage), viral load, and resistance testing must be urgently addressed.

Therapeutic Drug Monitoring
Therapeutic drug monitoring is not readily available in most resource-limited settings, and its role requires further study. However, it may be very helpful in children in whom drug interaction or malabsorption is considered the likely cause of treatment failure.

ADHERENCE
Maintaining children on a treatment regimen on a lifelong basis is challenging for many reasons. For instance, children often rely on caregivers to
supervise and administer their medication. Many children have not been told of their diagnosis, and it is likely that adherence will be more challenging for children who do not know why they need to take medication. In addition, when parents themselves are either gravely ill or have died, a child’s adherence to medication may be compromised by transitional caregivers unaware of the child’s HIV diagnosis. The transition into adolescence can also compromise adherence to medication.

Adherence among children is likely to be improved by the following:

- Fostering a good provider-client relationship between the health-care worker, parent/care-taker, and child
- Disclosure of the child’s HIV status when appropriate
- Caregiver education on pediatric adherence and ongoing support
- Attending to the health needs of the parent/care-taker and ensuring access to ARVs if required
- Simplification of regimens (i.e., use of FDCs in pediatric-appropriate dosages and formulations and switching to solid from liquid formulations as early as possible)
- Addressing the psychosocial needs of adolescents

Constant emphasis on adherence by all members of the multidisciplinary care team should be encouraged. No single adherence tool has been demonstrated to be superior to others. Therefore, clinics should supply caretakers with several tools to facilitate adherence and correctly measure liquid medications.

Pillboxes are invaluable for children on solid formulation and can be used as soon as even one component has been switched from liquid to solid. Color-coding of syringes and drugs is helpful for caretakers, particularly if they are illiterate; uniformity in coding is also helpful. Where available, pediatric fixed-dose formulations should be used to reduce the complexity of dosing. Other tools, such as diary cards, may be helpful but are not essential in implementing a treatment support program. It should be noted that viral load is often used as a surrogate marker of adherence, although few data support that practice.

**ISSUES FOR CLINICIANS**

Following the release of the CHER data, it is clear that HIV-infected infants identified in the early weeks of life should be prioritized for treatment. A pooled meta-analysis of children on combination ART from resource-limited settings shows that mortality is highest in the first few months of ART and that the risk of death after starting ART is independently associated with younger age, lower hemoglobin levels, and severe immunosuppression.

A cost-effectiveness analysis comparing prioritization strategies would help programs deal with resource constraints. Because hospitalization rates are greatly decreased when children are on ART, a decrease in hospitalization costs might mitigate the costs of ART. It may be most cost-efficient to shift resources to ensuring that all eligible children receive ART as soon as possible.

Clinicians in resource-limited settings often must decide whether children living with HIV should have access to scarce resources such as intensive care units (ICUs) or ventilation. However, because HIV has become a chronic rather than a fatal illness, a child living with HIV should have the same opportunity of access to the ICU as a child with any other chronic disorder, such as diabetes.

Initiating children with comorbidities on ART may require ethical debate, particularly where resource constraints exist. Each case should be individually evaluated by a care team, preferably including an ethics committee and other key players, before a treatment decision is made. However, as ART becomes more widely available and affordable, its use as a palliative care aid should not be overlooked.
HIV disease in children is a chronic, manageable condition in all countries with access to ART. To meet the needs of children living with HIV, facilities must set realistic but ambitious targets and timelines. Treatment of children must be demystified; there are many parallels to the treatment of adults, although providers caring for children should be aware of the particular requirements of young patients. Lack of the recommended components of care, outlined in various pediatric treatment guidelines, should not become an obstacle to increasing the numbers of children accessing care. Small adjustments to patient flow, space, and equipment, in addition to task shifting, may result in expanded treatment capacity and better patient outcomes.

Another urgent need is strengthening PMTCT programs to prevent new pediatric infections and identify HIV-infected infants early. Strengthening PMTCT and the identification of HIV-infected infants, together with urgent initiation of these infants on ARVs in the first few months of life, is likely to prevent large numbers of HIV-related child deaths.

Potent first-line and second-line treatment regimens are available for children, although many formulations are not child friendly. Many evidence gaps still exist, and ongoing research should continue to look at ways to optimize first- and second-line regimens, treatment adherence, and monitoring, as well as identifying the most suitable timing for switching regimens. As more evidence becomes available, programs need to have the flexibility to make the necessary adjustments as well as the capacity to rapidly disseminate new recommendations.

To achieve rapid scale-up of treatment for children where human resources are scarce, attention must be paid to simplification of regimens. All formulations developed for adults must be investigated in children to increase treatment options. Scaling up ART services for children to meet the great need that exists is an achievable goal.
REFERENCE LIST


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Follow-Up and Adherence Management for Children and Adolescents Living with HIV

Dorothy Mborig-Ngacha

ANTIRETROVIRAL (ARV) DRUGS ARE becoming increasingly available to children in resource-limited settings and have the potential to greatly improve the survival of HIV-positive children in these settings. A critical factor in the success of HIV treatment programs, both for the individual and for the programs themselves, is adherence to antiretroviral therapy (ART). The World Health Organization (WHO) defines adherence as “the extent to which a person's behavior corresponds with agreed recommendations from a health provider.”1 HIV treatment adherence levels that are greater than 95% result in optimal clinical outcomes and also ensure that individuals are able to stay on their first-line regimens for longer periods by limiting the emergence of resistance. Adherence may be measured either directly or indirectly. Direct methods of measurement include directly observed therapy or measurement of the drug or its metabolite in blood or urine. These methods, though most accurate, are expensive and burdensome to the patient. Indirect methods, such as patient reports, pill counts, pharmacy refill data, and the use of diaries and electronic monitors, though more feasible, are less accurate and more prone to distortion by patients. The most commonly used method of measuring adherence in children is the interviewing of parents or caregivers.

BARRIERS TO ADHERENCE

Despite the critical need for strong HIV treatment adherence, research indicates that many patients have difficulty realizing this goal. A meta-analysis of 59 studies conducted in North America and Africa reported that only 55% (95% CI, 49%-62%) of North American patients demonstrated high levels of ART adherence.2 The percentage of African patients who achieved high adherence was more favorable, at 77% (95% CI, 68%-85%). However, this difference could be attributed to the fact that programs in Africa are relatively new, so patients have been on treatment for shorter periods of time. The proportion of adherent patients could decline over time as patients initiating therapy encounter the challenges of maintaining long-term adherence. The picture for children was not so optimistic. These same studies reported that 40% to 45% of children were not adherent to ART. The most important and prevalent factors that were found to negatively affect adherence in sub-Saharan Africa were cost, lack of disclosure of HIV status, fear of stigma, and complexity of drug regimens.3,4
Factors influencing adherence in children are similar to those in adults. However, maintaining high levels of adherence in children is particularly challenging due to reliance on adult caregivers. Unwillingness to disclose the child’s HIV status may also negatively impact adherence, since children are totally reliant on an adult to ensure that they take their medication. If for any reason the adult caregiver is unavailable, such an event would result in missed doses. In a Ugandan study, Nabukeera-Barungi et al reported that children whose caregivers were unwilling to disclose the child’s HIV status to anyone were three times more likely to be nonadherent to medications (OR 3.4; 95% CI, 1.14-9.82). Adherence in children, more than in adults, may be adversely affected by drug-related factors such as palatability of drugs as well as the type of formulation; young children, in particular, may find it difficult to swallow tablets. HIV disease stage may also influence adherence. Adherence may be better in children with more advanced, symptomatic disease. Nabukeera-Barungi et al reported adherence levels of greater than 95% in children who had been hospitalized at least twice prior to initiation of ART (where repeat hospitalization may be an indirect measure of children with more advanced disease).

Special groups of children in whom adherence management may be particularly difficult include orphans and adolescents. Experience from treatment programs in Africa indicates that orphans living with HIV may face unique challenges related to their care. Due to lack of social services in most resource-limited settings, these children are often taken care of by different adult relatives, making it difficult to provide consistent, ongoing support. Nyandiko et al reported a significantly shorter duration of follow-up among orphaned children, as well as poorer long-term weight gain (an indirect measure of response to therapy). This may point to poorer adherence to follow-up schedules and possibly also to medications. The management of adherence in adolescents is particularly challenging because of the emotional and psychosocial issues that are unique to their developmental stage. There is a paucity of data on strategies for supporting adherence in adolescents in resource-limited settings. However, peer support groups have the potential to be a useful approach, since adolescents value peer relationships the most.

Major barriers to adherence identified in two qualitative studies conducted in developing countries are summarized in Table 1. Important patient-related factors that are relevant to children were fear of disclosure; financial constraints; difficulties understanding treatment instructions and the need for compliance; and the presence of concurrent diseases, including malnutrition. Other barriers identified related to beliefs about medication, including doubts about efficacy and uncertainty about long-term effects of HIV treatment; drug side effects; complex regimens; taste, size, and frequency of dosing; and decreased quality of life while taking medications or feeling too sick.

At the programmatic level, adherence to medication is influenced by accessibility of services, in terms of both geographical access and economic access. Most treatment programs in Africa are now able to offer treatment free of charge to children. However, access is limited by the fact that most children reside in rural settings, while pediatric treatment clinics are often located in higher-level facilities in urban or suburban settings. Transportation costs may therefore be a major barrier to the effective follow-up of children in these clinics. Other program factors that may influence adherence include commodity security as well as the effectiveness of the psychosocial support provided to patients and their caregivers. The patient–health worker ratio in particular will also impact the ability of a particular clinic to offer adequate adherence support to patients and their parents.
Numerous interventions to assist patients with chronic diseases to adhere to medication have been evaluated. These include the provision of verbal and written instructions regarding their medication, counseling about the disease and importance of adherence to therapy, patient reminder tools, and simplified treatment regimens. Whereas these strategies have been used in a variety of settings to improve adherence rates, none has proved effective in all settings, and the most effective interventions have been complex in nature, labor intensive, and costly to the health-care system. Because adherence is determined by multiple factors, a multifaceted approach to enhance adherence is encouraged. Current strategies advocated by WHO to achieve high levels of adherence to ART in resource-limited settings focus on patient education through counseling, enhancing caregiver support by encouraging treatment “buddies,” and disclosure to other trusted members of patients’ networks.

Adherence is dependent upon a number of factors that relate directly or indirectly to communication between health-care providers and families of children in care. Trust must be built between the health professional and the patient to facilitate adherence support as well as adherence reporting. In addition, good communication is crucial to ensure that families are aware of the importance of taking the medications as prescribed. Good communication requires adequate time, which is often lacking in busy clinics in Africa. High patient volumes limit the time spent with each patient and make it impossible to have meaningful interactions with clients for adherence support. This is particularly true at lower-level facilities with fewer staffing levels. Innovation is therefore required to find feasible approaches to address the human resource constraints that are preventing effective adherence support from taking place. Training of lay counselors and, in particular, people living with HIV who have successfully been on treatment has been tried in some programs as a means of improving adherence and will need further evaluation.

### Table 1. Barriers to Adherence from Two Qualitative Studies in Resource-Limited Settings

<table>
<thead>
<tr>
<th>Category</th>
<th>Barrier (# of studies reporting)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-related</td>
<td>- Having a coexisting substance addiction; simply forgetting; financial constraints (2)</td>
</tr>
<tr>
<td></td>
<td>- Fear of disclosure (1)</td>
</tr>
<tr>
<td></td>
<td>- Difficulty understanding treatment instructions and the need for compliance (1)</td>
</tr>
<tr>
<td></td>
<td>- Presence of concurrent diseases or illnesses, including malnutrition (1)</td>
</tr>
<tr>
<td>Beliefs about medication</td>
<td>- Side effects, real or anticipated (1)</td>
</tr>
<tr>
<td></td>
<td>- Complicated regimens (1)</td>
</tr>
<tr>
<td></td>
<td>- Taste, size, and frequency of dosing (1)</td>
</tr>
<tr>
<td></td>
<td>- Having doubts about combination antiretroviral therapy (ART) efficacy (1)</td>
</tr>
<tr>
<td></td>
<td>- Feeling fine or healthy (1)</td>
</tr>
<tr>
<td></td>
<td>- Decreased quality of life while taking medications; feeling too sick (1)</td>
</tr>
<tr>
<td></td>
<td>- Being uncertain about long-term effects of HIV treatment (1)</td>
</tr>
<tr>
<td>Daily schedules</td>
<td>- Trouble incorporating work and family responsibilities with ART (2)</td>
</tr>
<tr>
<td></td>
<td>- Transportation difficulties; long distances to receive treatment (2)</td>
</tr>
<tr>
<td></td>
<td>- Running out of medications or irregular supply (1)</td>
</tr>
<tr>
<td></td>
<td>- Being away from home (1)</td>
</tr>
<tr>
<td></td>
<td>- Too busy or distracted to comply properly (1)</td>
</tr>
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</table>
Additional strategies to improve adherence relate to simplification of regimens through the use of combined fixed-dose drug formulations to reduce the pill burden. The increasing availability of pediatric fixed-dose combinations will be of great benefit to children and should be encouraged by all pediatric programs. Practical aids, including calendars and pill boxes, are also encouraged based on findings from developed-country settings where electronic reminders, pill organizers, and online paging systems have been used with variable results. These reminder systems have been developed based on the observation that simply forgetting is one of the most common reasons cited for missing doses. The medication diary utilizes the same principle and has been shown to improve adherence to a limited extent in adults. The medication diary provides patients a chance to monitor their own adherence during the period between clinic visits by ensuring that a record of daily performance is kept. In addition, unlike electronic reminders, the diary is inexpensive and requires only literacy on the part of the user, making it attractive for evaluation in resource-limited settings.

At the programmatic level, geographical access can be addressed by decentralization of the pediatric care and treatment services to the lowest levels of the health-care system. However, this decentralization will also require ensuring that these lower-level facilities have adequate numbers of health workers who have the capacity to provide care to children living with HIV. Programs in Africa that are decentralizing services should, at the same time, establish networks through which mentorship and ongoing capacity building can be provided to health workers to strengthen their confidence in providing care to children. Commodity security within programs is another important factor in ensuring high levels of adherence to medication. This requires a well-organized logistics management system that will ensure that there are no drug stock-outs. And finally, community-based models for providing adherence support to children should be explored as a strategy for long-term sustainable adherence. Community-based approaches, though more costly, are the most likely to be successful due to their ability to respond to context-specific needs.

Long-term adherence in HIV-positive children is an important strategy, both for optimal clinical outcomes at the individual level and also for the greater good of public health. Partial or poor ART adherence can lead to the emergence of viral strains that are resistant to available ARV drugs. The development and transmission of these drug-resistant HIV strains can limit the treatment options available to newly infected individuals. Drug-resistant HIV can additionally hamper the wide-scale provision of treatment within resource-limited countries by compromising the use of affordable first-line therapies. As treatment programs for HIV-positive children are scaled up, it is crucial that sufficient resources are committed to ensure that these programs are able to provide adequate adherence support to children and their caregivers.
HE MADDOX CHIVAN CHILDREN’S CENTER (MCCC), which opened its doors in February of 2006, offers a multidisciplinary array of services to children living with and affected by HIV in Phnom Penh, Cambodia. Building on community-based approaches to HIV/AIDS and TB care developed by the Cambodian Health Committee (CHC), the goal of the MCCC is to offer medical care and age-specific counseling that is integrated with educational, social, nutritional, and psychological interventions. The CHC, a Cambodian nongovernmental organization (NGO), has developed its TB and HIV/AIDS programs with the support of private donations, as well as grants from various sources including the U.S. National Institutes of Health; the Japanese International Cooperative Agency; and the Global Fund to Fight AIDS, Tuberculosis and Malaria. The placement of the MCCC program within the larger CHC program has provided an opportunity to build upon CHC’s existing infrastructure and approaches while leveraging private donations received to establish the MCCC from the Jolie-Pitt Foundation, the Jeanne and Joseph P. Sullivan Foundation, and other private donors.

In Cambodia, as in other high-HIV-prevalence countries, children who are living with or affected by HIV often fall victim to discrimination, disease, poverty, and a lack of security and future prospects. These children often must deal with the challenges of having ill parents or caretakers and experiencing the death of parents and/or siblings, as well as food shortages and interruptions in their education.

In creating an integrated model of care, the MCCC seeks to address the shared problems of children living with and affected by HIV in a comprehensive way. The rationale behind this approach is that a combination of vigorous efforts to address health and nutritional issues, along with equally strong educational and social interventions, is necessary in order for these children to grow into healthy and thriving adults.

BACKGROUND

There are an estimated 12,000 children living with HIV in Cambodia.19 In 2004, approximately 452 children were receiving antiretroviral therapy (ART) nationwide; this number increased to 1,787 in December 200620 and to 2,372 as of September 2007.21 Access to ART for children increased significantly in June 2005, thanks to a donation of pediatric antiretroviral (ARV) formulations from the Clinton Foundation. Scale-up of ART has been facilitated through programs administered by a variety of international and local NGOs, including Maryknoll Missionaries; Médecins
The MCCC opened in February 2006, and by 2008, 551 children aged 0 to 16 had benefited from the program, which provides medical, nutritional, educational, and psychological support. Of the 551 children who had attended the program during this period, 200 are HIV-positive, and 214 have lost at least one parent. The average age of attendees is eight years, with approximately equal numbers of girls and boys. The program places special emphasis on preschool-age children and teenagers, since young people at these developmental stages are at particularly high risk; successful navigation of these periods requires targeted support in the form of nutrition, education, psychological support, and protection, in addition to health care. These various forms of support are being provided by the center’s multidisciplinary staff, which is comprised of more than 15 people, including a medical doctor, two teachers, a social worker, a psychologist, and a leader of sports activities.

Children are referred to the program by local orphanages and NGOs and are also identified when their adult parents are hospitalized through the CHC-managed TB and AIDS program in the pulmonary ward of the Khmer Soviet Friendship Hospital, the largest public hospital in Cambodia. A medical doctor is on-site at the MCCC and is available for consultation for all children, regardless of their HIV status. For HIV-positive children who are newly diagnosed and are not already receiving medical care at another facility, consultations are performed by the MCCC doctor, along with a doctor and nurse from the pediatric service of Khmer Soviet Friendship Hospital, and with backup support from other CHC physicians. As of February 2008, there...
were 35 children receiving their primary HIV care at the MCCC, and 25 children had been initiated on ART at the center in accordance with national pediatric HIV care guidelines. As of this writing, none of the 19 children receiving ART from the MCCC clinic who were followed for a period of 18 months had a detectable viral load (unpublished data).

Educational support is provided from preschool to grade six and is designed to complement the half-day of public school provided to all Cambodian children. Nearly all of the children attending the MCCC were found to be significantly behind in basic educational skills upon their entry into the program. Many had been out of school for months or years, and all of them were at an inappropriate grade level due to disruptions in their schooling arising from their own illness or that of their parents/caretakers. Many attendees were street children who had been begging or scavenging for food.

The MCCC program has had a positive effect on the educational skills of children attending the program. Significant overall increases in test scores in Khmer language (15%) and in math (10%) for each grade level were observed, for example, between October 2006 to July 2007 (unpublished data). In addition, 45 children who were not regularly attending school were reintegrated into the appropriate grade for their age. A random assessment among 75 parents/caretakers looking at the program’s impact on their own and their children’s lives revealed that 91% of parents observed an improvement in their children’s school results, 89% believed their children’s behavior had improved, and 88% noticed an improvement in communication with their child after they started the MCCC program.

The MCCC incorporates a number of different approaches to psychosocial support, such as art therapy, individual therapy, and peer group counseling. These activities are particularly geared toward children facing critical life situations and events, such as abandonment, the death of caregivers, and domestic violence. The goal of this psychosocial support is to enable them to better cope with these traumas and to decrease the risk of depression.

A particular focus has been placed on medical counseling for children and parents about HIV/AIDS and drug adherence. Many of the HIV-positive children cared for at the MCCC come from unstable families, live with aging caregivers (such as grandparents who may not understand the treatment process), or stepparents or more distant relatives who are not invested in or may not pay particular attention to the child’s health issues. To provide quality counseling and ensure the best medication adherence, the care team has developed age-specific developmental-level protocols and teaching materials (e.g., cartoons, stories, drawings) to educate children about their treatment, their HIV status, and the importance of adherence and medical follow-up.

Social support is also provided to families and caregivers to increase the program’s positive impact. For example, an immediate intervention is provided for families facing specific crises, such as the death of a family member, which can be both emotionally and financially challenging. In such cases, short-term financial and/or logistical support may be provided in order to prevent the deterioration of family living conditions, which are often marginal even before any additional challenges arise.
The emphasis is on helping the family to maintain stability (such as through the retention of housing), ensuring that children continue to attend school, and ensuring that basic daily living necessities, such as adequate food and clean water, are available. In 2007, for example, 57 families received support for emergency housing, funeral fees, schooling fees, clothing, and transportation.

When caregivers such as HIV-positive, widowed mothers have accessed treatment and are medically stable, the MCCC social team will assist them with job placement or will help them to develop a small business through training and small loans. The center also assists these women by providing a safe haven for their children during the day. This gives them time to reorganize their lives and to look for work without having to worry about the safety of their children.

Other activities such as art, sports, life-skills workshops, computer and English classes, and museum field trips are included in the program to expose the children to other activities and environments. Lunch and a morning and afternoon snack are provided to all children in attendance and to any family member who is at the center.

LESSONS LEARNED
The overall success of the MCCC model is evidenced by improvements in children's health status, including demonstrable decreases in patient viral load and increases in total lymphocyte percentages. Other positive outcomes include improved nutrition, educational performance, and behavior, and increased requests for children to attend the program.

Our experience demonstrates the following:

- Medical consultation, social support, and psychological counseling are all critical, interdependent activities to address the multitude of issues facing children living with or affected by HIV.
- When children are hospitalized, provision of food is particularly important. We have found that many children who were hospitalized and extremely sick were refusing to eat. The inclusion of nutritious and appetizing food in their medical plan has been a positive contribution.
- The follow-up of HIV-positive children is facilitated by a structure that involves routine attendance by the child for a variety of nonmedical activities. Such a model decreases patient and caretaker stress associated with medical consultations and allows staff to be quickly alerted to any problems (e.g., a child’s extended absence from the program) that may impact treatment adherence, as well as any social or medical situations affecting the child or caretaker; the ability to observe problems as they occur allows team members to intervene in a timely fashion.
- Medical counseling is particularly important for children who come from families that are experiencing multiple social and economic problems. Materials and concepts traditionally used for adult HIV/AIDS counseling are not generally appropriate for use with children. For example, disclosure of HIV status is a very different process for adults as compared to children. For adults, disclosure is often the starting point for treatment. For children, disclosure is a long-term process,
with the goals of helping the children to cope with their disease while developing an identity in the context of their chronic illness and helping them become active partners in their own treatment. Thus, counseling must be adapted to meet the needs of each child’s developmental and cognitive stage.

- Children living with or affected by HIV often suffer discrimination, malnourishment, interruption of school attendance, and the death of family members, with their identities strongly influenced by these experiences. At the MCCC, children are considered first and foremost as children and are not defined by their diagnosis or by the fact that HIV/AIDS has touched their family. Our experience suggests that this approach helps to overcome problems of self-esteem and to restore children’s self-confidence. In other words, the center is a place where children have the opportunity to be like other children among peers who share similar difficulties.

- With better access to treatment, the number of surviving teenagers living with HIV has increased. This vulnerable group requires specialized approaches to help them make a successful transition to adulthood. Sports, art, life-skills workshops, field trips, and vocational training, as well as peer support, are all helpful in this regard.

- Given proper support for families and caregivers, orphaned children are able to remain in their homes and can achieve long-term treatment success.

- Networking with existing pediatric health services increases capacity to treat children living with HIV in a sustainable way. Also, linking the MCCC to existing TB and HIV/AIDS services in a major urban ward for adult HIV/AIDS and TB has been an effective way to identify at-risk children who can benefit from the services provided at the center.

- When services are offered, children and their families are anxious to take advantage of them and have demonstrated that they can achieve impressive gains in the medical, educational, and behavioral status of children.
REFERENCE LIST


The goal of nutritional care for HIV-affected infants and children (up to the age of 14 years) is to improve clinical outcomes as well as to prevent and/or treat underlying or HIV-associated malnutrition. These clinical outcomes include HIV-related symptoms and disease progression, other non-HIV morbidities, infant and child growth, and normal activity (e.g., school attendance), as well as survival. Appropriate actions to achieve said outcomes include nutritional assessment and counseling, as well as support for the mother or primary caregiver. All actions should address the overall quantity and quality of macro- and micronutrients in the diet or supplements to augment the diet and meet nutritional requirements. Responsive feeding and caring behaviors (for well, sick, asymptomatic, and symptomatic children) that have been found to be useful in clinical and home care of both HIV-negative and HIV-positive infants and children should also form part of the prevention and treatment plan. Improving access to food, social grants, and community support as well as other non-nutritional interventions such as exercise, hygiene, and deworming can improve nutritional status and thereby quality of life.

Malnutrition increases the likelihood of child and infant death and is associated with more than half (54%) of all childhood mortality in resource-limited settings. For this reason, establishing and maintaining appropriate and adequate diets and micronutrient status for children living with or affected by HIV in these settings is imperative in order to prevent malnutrition, common childhood illnesses, and opportunistic infections, as well as to support continued growth and development. Other preventive measures that can improve the health status of children affected by HIV include basic childhood immunizations; hand washing and general hygiene by caregivers; routine cotrimoxazole; and periodic, routine well baby care. For children on antiretrovirals (ARVs), appropriate and adequate nutrition is needed to achieve the full benefits of therapy. Nutritional care (with or without food and micronutrient supplements, depending on local needs) should be included as a critical component of the essential care package for HIV-affected children.
NUTRITION AND HIV/AIDS IN CHILDREN FROM BIRTH TO 14 YEARS

There is a paucity of information from carefully conducted research studies on pediatric HIV disease progression and treatment in resource-limited settings. A 2005 study in Tanzania found that HIV infection was a strong determinant of mortality among children six months to five years of age who were hospitalized with pneumonia, and that undernutrition (i.e., wasting and stunting), anemia, and inadequate water supply contributed significantly to infant and child mortality, independent of HIV infection. Studies in resource-limited settings have shown that infant and child mortality are independently associated with maternal HIV status and maternal death, and that HIV-positive children have up to a fourfold increase in mortality by two years of age compared to their HIV-negative counterparts. The types of morbidities observed in HIV-positive children in resource-limited settings are similar to those seen in HIV-negative children; however, the rates, severity, complications, and recurrence of morbidities are all greater among children living with HIV. There is also some evidence that progression to AIDS may be more rapid among children living in resource-limited settings.

The implication of these and other data is that routinely monitoring something as simple as weight is a valuable way of monitoring disease progression in HIV-positive children. In resource-limited settings, studies of the relationships between nutrition and HIV disease are complicated by absolute food insufficiency or minimal dietary diversification, as well as a much greater burden of infectious diseases than exists in better-resourced settings. Yet despite these challenges, a number of studies have demonstrated a link between nutritional care and improved health outcomes among children living with HIV. A 2002 controlled clinical trial in Tanzania found that vitamin A supplementation improved the weight and length/height of infants six months to five years of age infected with HIV and malaria, and decreased the risk of stunting associated with persistent diarrhea. Several recent reviews suggest that provision of micronutrients and routine nutritional counseling, care, and supplements (with or without antiretroviral therapy [ART]) could significantly reduce pediatric HIV-related morbidity and mortality. However, most reviews are based on trials and well-conducted studies among adults. For children, there is limited evidence to support micronutrient supplementation, with the exception of vitamin A. Studies also suggest that routine nutritional (anthropometric) and neurodevelopmental assessments are useful in determining the appropriate initiation, management, and monitoring of ART. Insufficient intakes of energy and micronutrients have their own detrimental impact on immune function independent from HIV infection, and the positive impact of food or micronutrient supplementation on immune function will be more significant in HIV-positive individuals having a nutritionally deficient diet. In summary, while little research has been done on the specific benefits of nutritional care and supplementation in children living with HIV, existing data suggest that the health of these children would benefit from proven nutritional support interventions. This is reflected in the 2007 World Health Organization (WHO) guidelines for nutritional care for HIV-positive children aged six months to 14 years, which recommend early advice and active support to ensure that adequate energy, protein, and micronutrient intakes are met at all stages of HIV disease, despite the fact that research has not been conducted to demonstrate that early nutritional support delays the progression to AIDS.
A study of growth patterns among HIV-positive children in Europe demonstrated that, even in a high-resource setting, growth faltering is apparent. HIV infection affected both weight and height (although weight differences were more pronounced), and overall differences between HIV-positive and HIV-negative children increased with age. Children with more advanced HIV disease also had much poorer growth at all ages. In the United States, neither prematurity nor low birth weight is associated with perinatal exposure to HIV, but there is evidence from resource-limited settings that these outcomes are affected by the HIV status of the mother. Growth failure and other nutritional problems have been documented in HIV-infected infants (or infants of HIV-positive mothers) from many resource-limited settings (the Democratic Republic of the Congo, Kenya, Malawi, Rwanda, Tanzania, and Uganda), with reports of low birth weight, prematurity, intrauterine growth retardation (IUGR), stunting, underweight, and wasting.

Common nutritional problems for HIV-positive children include poor growth compared to peers and a higher risk of becoming malnourished. Reductions in length or height of HIV-positive children are common, and poor growth (slow weight gain or decreasing weight) is often apparent even before opportunistic infections or other AIDS symptoms appear. When children living with HIV infection become malnourished, they tend to lose more muscle compared to malnourished children who are HIV-negative. These nutritional outcomes, while important in themselves, can also lead to increased risk of common morbidities and mortality. A 1995 study in Malawi found that the most frequent causes of death for HIV-positive children were diarrhea, pneumonia, and failure to thrive. It is unclear whether growth retardation is an aggravating factor, a consequence (and thus a possible marker) of pediatric HIV disease progression in resource-limited settings, or both, as part of a vicious cycle.

The pattern of weight and height recovery in HIV-positive children is dependent on many things. Linear growth is not only dependent on nutritional factors but may also be impaired by changes in growth-hormone receptor sensitivity. Acute inflammatory proteins from whatever cause can also impair linear growth even if there is adequate energy and micronutrient intake.

It is common for HIV-positive children to have low blood levels of micronutrients, which reflects poor nutritional status and also the effect of acute inflammatory proteins. Children whose HIV disease is advanced are often severely malnourished, with poor muscle mass, low fat reserves, and low levels of all vitamins, minerals, and other essential trace elements. When ART is initiated in these children, the children’s appetites tend to increase dramatically, with resulting improvements in weight, growth development, and function (such as school attendance) as well as life expectancy. Adequate nutritional intake does not guarantee nutritional recovery, even in the presence of ART.

Common problems in HIV-positive children that can complicate pediatric nutrition and health care include diarrhea; nausea; vomiting; poor appetite (anorexia); difficulty eating during or after an illness; a sore mouth or throat caused by thrush, herpes, infections, or other conditions; and changes in the taste or texture of foods or food cravings due to illness or side effects of medications. Anorexia is likely to be an effect of acute inflammatory proteins on the appetite center; therefore, when tackled via antibiotics or ART, appetite improves. HIV-positive children, like their adult counterparts, often experience a large increase in appetite when initiated on ARVs—which is a positive outcome, particularly in resource-limited settings where anorexia may be a major cause of malnutrition even in HIV-negative children. An increased appetite can, however, create enormous demands on caretakers, since children are dependent on others for food acquisition,
When a child is determined to be HIV-positive, certain dietary approaches are recommended that reflect the current evidence base. HIV-positive infants and children have increased nutritional requirements compared to HIV-negative children of the same age. Requirements will vary according to nutritional status, age, HIV-related symptoms, and comorbidities. Additional energy requirements for HIV-positive children can range from a 10% increase per day for asymptomatic children who are well nourished, to a 20%-30% increase for HIV-positive children with poor weight gain or HIV-associated conditions such as chronic lung disease, malignancy, or, especially, concurrent TB, to a 100% increase for severely malnourished infants (whether or not they are on ARVs). These energy requirements are summarized in Table 1. Protein should contribute 10% to 15% of total energy intake.

<table>
<thead>
<tr>
<th>Age</th>
<th>HIV-negative</th>
<th>HIV-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kcal/daya</td>
<td>Asymptomatic: 10% additional energy (kcal/day)</td>
</tr>
<tr>
<td>6–11 mos.</td>
<td>690</td>
<td>760</td>
</tr>
<tr>
<td>12–23 mos.</td>
<td>900</td>
<td>990</td>
</tr>
<tr>
<td>24–59 mos.</td>
<td>1,260</td>
<td>1,390</td>
</tr>
<tr>
<td>6–9 yrs.</td>
<td>1,650</td>
<td>1,815</td>
</tr>
<tr>
<td>10–14 yrs.</td>
<td>2,020</td>
<td>2,220</td>
</tr>
</tbody>
</table>

*Based on average of total energy requirements for light and moderate habitual physical activity levels for girls and boys by age group.

Source: Adapted from WHO12 and Joint Food and Agriculture Organization of the United Nations.13

**NUTRITIONAL REQUIREMENTS FOR CHILDREN LIVING WITH HIV**

When a child is determined to be HIV-positive, certain dietary approaches are recommended that reflect the current evidence base. HIV-positive infants and children have increased nutritional requirements compared to HIV-negative children of the same age. Requirements will vary according to nutritional status, age, HIV-related symptoms, and comorbidities. Additional energy requirements for HIV-positive children can range from a 10% increase per day for asymptomatic children who are well nourished, to a 20%-30% increase for HIV-positive children with poor weight gain or HIV-associated conditions such as chronic lung disease, malignancy, or, especially, concurrent TB, to a 100% increase for severely malnourished infants (whether or not they are on ARVs). These energy requirements are summarized in Table 1. Protein should contribute 10% to 15% of total energy intake.
Micronutrient supplementation studies to date among HIV-positive children are limited to vitamin A, and one study about zinc.\(^5\)\(^,\)\(^14\) Due to the limited availability of data, WHO guidelines suggest providing the same additional micronutrients to HIV-positive children as those recommended for daily intake in HIV-negative children. These guidelines also state that in settings where diet typically lacks adequate diversity, a minimum of one recommended daily allowance (RDA) should be provided to HIV-positive children; this often necessitates micronutrient supplementation, such as a daily multivitamin.

Recommendations for specific micronutrient supplementation in the general pediatric population (that also apply to HIV-positive or HIV-affected children) include routine vitamin A supplementation every six months (100,000 IU for children 6-12 months and 200,000 IU for children 12-59 months). Vitamin A given to HIV-positive children reduces morbidity and all-cause mortality,\(^5\) and therefore regular vitamin A supplements are justified. Determining the benefits of iron supplementation is somewhat more complicated, and the most recent WHO guidelines suggest that iron should only be given to HIV-positive children if there is an indication of iron deficiency. South African guidelines for the management of children living with HIV\(^15\) recommend one course of empiric iron without formal iron assessment studies, with subsequent referral for additional care and supervision in cases of persisting anemia. Micronutrients are also useful as part of treatment protocols for specific disease episodes (e.g., vitamin A as part of treatment for diarrheal disease and measles, zinc supplementation during diarrheal disease episodes).

**Special Considerations for Children 0 to 24 Months**

For children younger than two years of age born to mothers known to be HIV-positive, recent WHO guidance on infant feeding\(^16\) recommends that feeding options and local recommendations should be governed by infant and child survival, and not just avoidance of HIV transmission (i.e., HIV-free survival). Exclusive breastfeeding or, when AFAS (acceptable, feasible, affordable, sustainable, and safe), exclusive replacement feeding (using commercial infant formula), are the recommended options for the first six months for infants of HIV-positive mothers. The choice between these two options should be made based on a thorough assessment of the mother’s individual and family circumstances, and in addition, consideration of the availability and quality of local health and counseling services. Mixed feeding should be avoided in infants less than six months of age.

**Infants (0 to 6 Months)**

Young infants who have been identified as HIV-infected need the immune and nutritional protection that breastfeeding affords. HIV-infected infants who are breastfed display better growth and survival than formula-fed infants, and the risk of reinfection with additional strains of HIV during breastfeeding is extremely low.\(^16\) In resource-limited settings, the vast majority of infants of unknown status born to HIV-positive women will be breastfed. For these infants, WHO recommends exclusive breastfeeding for the first six months to minimize risk of HIV transmission and increase survival, with complementary feeding to be introduced according to national recommendations for the general population.

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\(^{a}\)Complementary feeding is defined as the process starting when breast milk alone is no longer sufficient to meet the nutritional requirements of infants, and therefore other foods and liquids are needed, along with breast milk. The target age range for complementary feeding is generally considered to be 6 to 24 months of age, even though breastfeeding may continue beyond two years.\(^7\)
PREVENTION AND MANAGEMENT OF NUTRITIONAL PROBLEMS IN CHILDREN LIVING WITH HIV

Nutritional Monitoring

Routine monitoring of the growth of pediatric patients is recommended so as to detect any growth faltering and begin supportive action before a child becomes malnourished. Any child who has experienced poor growth (compared to standard reference curves), has trouble eating, or has lost weight since a previous clinic or home visit is in need of additional care. Since weight and growth both accurately reflect disease progression, monitoring weight and growth is an inexpensive and valuable tool for determining nutritional status that can be used in virtually any setting.

New growth reference standards for infants and children from birth to 14 years of age (separately for boys and girls) have recently been released by WHO. In many programs in developing countries, children under 2 years of age are being targeted for frequent growth monitoring because this is the period when malnutrition typically occurs. WHO recommends focusing on this “critical window” between birth and 2 years of age to ensure adequate nutrition and prevent malnutrition.

WHO also recommends that HIV-positive children up to 14 years of age have their growth and nutritional status monitored at least every three to six months. It is standard practice in most countries to promote monthly growth monitoring for all infants and young children from birth to 2 years of age; this level of routine follow-up is even more critical for infants and young children living with HIV.

To prevent growth faltering, monthly monitoring of weight gain in children is ideal. Monitoring weight does not prevent growth faltering but assists in early detection and management. In

In cases where it is AFASS for an infant to be replacement fed, commercial breast milk substitutes (formula) are recommended over diluted animal milks or other replacement feeding options, due to the complexities of meeting the nutritional requirements of young infants who are not breastfed.

Infants and Young Children (6 to 24 Months)

Continued breastfeeding combined with complementary feeding from six months to at least two years of age is the general recommendation for optimal infant feeding practices for children in this age group, including infants of mothers who are HIV-negative or of unknown status.

Infants and young children of HIV-positive mothers who are 6 to 24 months of age who were breastfed in the early months should continue to be breastfed until replacement feeding meets the AFASS criteria. Replacement-fed infants of HIV-positive mothers who are 6 to 24 months of age should continue to be replacement fed with commercial infant formula until at least 12 months of age, ideally up to 2 years. Complementary foods should be introduced starting at 6 months of age for all children (breastfed and nonbreastfed) to meet the additional nutritional requirements of children at this age.

Older Children

Currently there is little information on the nutritional management of older children from 6 to 14 years of age. Evidence and guidelines for preventing and managing malnutrition in this age group come primarily from data on children from birth to 5 years of age.
some growth-monitoring programs, children who are losing weight or not gaining weight have become the focus—not just those who are severely malnourished. This is an improvement over previous practices that identified only malnourished children as needing attention; however, pediatric HIV care providers must be informed of and advise mothers on what optimal weight gain should be for children at different ages to ensure that early growth faltering is detected. According to the most recent WHO growth charts, boys 0-5 months of age should be gaining 0.7 kg/month to stay at the median weight for age (or 0.583 kg/month to stay at the 15th percentile), while boys 6-11 months need to gain 0.25 kg/month (or 0.22 kg/month to stay at the 15th percentile). While infants may not meet this target for weight gain every month and may exceed this target in some months, care providers should be able to look at overall weight gain over a two- to three-month period to detect a problem in weight gain. Length monitoring is of less routine value, as it is difficult to perform correctly. If a child is on ART, it is important to monitor weight in order to recognize when an increase or change in ARV dosages may be needed.

**Assessment of Nutritional Status**

All HIV-positive children should have their nutritional status assessed to screen for malnutrition. Weight-for-height indices are the most accurate tool for this assessment but are generally hard to apply and therefore not used extensively. A weight for height of less than 70% (less than 3 z scores) of the median WHO reference value, severe visible wasting, or edema of both feet is a sign of severe malnutrition. Mid-upper-arm circumference (MUAC) provides a useful alternative for initial screening of nutritional status, as it is simple, requires less equipment, and is a good indicator of lean body mass. MUAC cutoffs for severe malnutrition are as follows: less than 110 mm for infants and children under 5 years, less than 135 mm for children 6-9 years, and less than 160 mm for children 10-14 years of age. MUAC is useful for screening and identifying moderate or severe malnutrition but is not very good for monitoring recovery, as the body tends to reestablish truncal tissue first and only then peripheral or limb tissue, such as upper arm tissue. Guidelines for determining whether a child is severely malnourished are included in Box 1. Any child who is classified as severely malnourished requires immediate therapeutic care (see following section on nutritional counseling and support). Children who are identified as moderately malnourished, have slow growth, or are losing weight should also be provided with additional care.

**Nutritional Counseling and Support**

Nutritional management in children is more challenging than in adults. Children have smaller stomachs and thus need to eat more frequently. Their smaller size makes accurate nutritional assessment and monitoring more challenging as well. Children are dependent on others for food, feeding, and care, and often cannot communicate their own needs effectively to caregivers. Active or responsive feeding has been shown to be an important part of optimal complementary feeding practices for children 6-24 months of age. In addition, dietary management in children is often complicated by wider socioeconomic factors such as inadequate food availability, lack of dietary diversity, and extreme poverty.

*For the Child with Normal Growth*

The 2007 WHO guidelines on the nutritional care of HIV-infected children emphasize giving positive feedback to the mother or primary caregiver...
Box 1. Determining whether a Child Has Severe Malnutrition

In children 6–59 months of age, severe malnutrition is present when any one of the following criteria applies:
- Weight for height is less than 3 $z$ scores below the median World Health Organization (WHO) reference value.
- There are signs of severe visible wasting.
- Edema of both feet is present.
- Mid-upper-arm circumference (MUAC) in children up to 59 months of age is less than 110 mm.

In children 6–14 years of age, there is less experience with screening for severe malnutrition. The following criteria can be used for screening and diagnosis:
- Weight for height is less than 3 $z$ scores below the median WHO reference value.
- There are signs of severe visible wasting.
- Edema of both feet is present.
- The following MUAC values apply (the most appropriate cutoff values still need to be determined for this age group, and these still require formal validation but may be helpful for screening):
  - In children 6–9 years of age, a MUAC less than 135 mm (~$-3$ $z$ scores for 7-year-old)
  - In children 10–14 years of age, a MUAC less than 160 mm (Integrated Management of Adult and Adolescent Illness [IMAI] guidelines)

If weight for height and MUAC have not been measured and a child is found to have a very low weight (i.e., weight for age is less than 3 $z$ scores below the median WHO reference value) and there are no visible signs of severe malnutrition, then he or she should be assessed carefully for other problems and admitted for investigation, if the cause of very low weight has not been explained or diagnosed.

Other indications that the child is at risk of undernutrition:
It is better to identify infants and children who are at risk of undernutrition, or who have poor growth, before they become severely malnourished. Therefore, if any of the indicators listed below are present, the child should be examined for visible signs of malnutrition (e.g., very little subcutaneous fat and muscle, particularly obvious on the upper arm and the thighs and buttocks, or sagging skin, with or without bipedal edema). If signs of severe visible wasting are not present, the child can be given nutritional support at home with early follow-up (five to seven days) and assessed for ART and/or other medical problems.

Possible indicators of undernutrition include the following:
- The mother reports that her child is failing to gain weight.
- The child has had a poor appetite recently.
- The child is not gaining weight and his or her growth curve is flattening.
- The child is losing weight and the growth curve is dropping downward.
- The child’s MUAC is reduced but not yet at the cutoff for diagnosing severe malnutrition, that is:
  - 120 mm in infants 6–12 months*
  - 130 mm in children 1–5 years*
  - 145 mm in children 6–9 years*
  - 185 mm in children 10–14 years*
- Changes have taken place with regard to the child’s caregiver or home circumstances.

*These cutoffs are based on 2 $z$ scores below median WHO growth reference values and are not clinically validated.

Source: Adapted from WHO.\(^7\)
to reinforce good feeding practices. The guidelines specifically suggest the following:

- Encourage the mother or caregiver by stating that the child is growing well. Explain the growth chart and how to follow progress.
- Ask if there have been any major changes in the child’s circumstances from the last visit that might put the care of the child at risk, including access to food.
- Explain to the mother or caregiver why additional food (energy) is needed in children (and adults) living with HIV infection (approximately 10% more).
- Counsel on continued breastfeeding if the mother is well. (Check national guidelines regarding breastfeeding policy and the age of the child.)
- Counsel on complementary feeding and replacement feeding (frequency of meals, amount and type of food per meal, responsive feeding). Reinforce and encourage good practices.
- Counsel on feeding a variety of foods such as milk, fruit, vegetables, whole grains, cereals, and meat/chicken or fish based on local diets (i.e., food sources that are high in vitamin A, iron, calcium, etc., and other locally produced foods).
- Review safe food preparation, food and water storage methods, and hygiene issues (e.g., keep hands, utensils, and food preparation areas clean; separate raw and cooked foods; cook food thoroughly; keep food at safe temperatures; ensure cleanliness and safety of water and food).
- Check whether there are other sources of good foods such as community gardens or other local resources.

For the Child Whose Growth Is Faltering or Who Is Losing Weight but Is Not Severely Malnourished

In cases where a child is experiencing growth faltering or weight loss, WHO guidelines’ recommend checking for morbidity and opportunistic infections as well as adherence (if the child is on ART). WHO also recommends checking to see if there have been any recent changes in caregiving or social circumstances. Box 2 summarizes these recommendations.

Feeding during Illness and Recuperative Feeding

Care for HIV-positive children should stress the need for continued feeding and increased breastfeeding and intake of other fluids during illness episodes, as well as recuperative feeding after illness episodes, at least until the time when the child has regained his or her weight prior to illness—this is a key period for weight recovery. If the child fails to gain weight during this period, he or she may permanently drop to a lower weight or weight-for-height centile. Nutritional support may be needed if the child lives in a food-insecure household. Rollins et al found better weight gain after an episode of severe diarrhea when HIV-positive infants received continued nutritional support for eight weeks during and after hospitalization. For children who were undernourished prior to the illness episode, recuperative feeding should continue until the child’s nutritional status (weight and weight for height) is no longer considered malnourished. These guidelines are consistent with the Integrated Management of Childhood Illness (IMCI) guidelines and the related protocols commonly used in many resource-limited settings.19

Food and Micronutrient Supplementation

It is often wrongly assumed that distribution of food is synonymous with nutritional support. Although food supplementation may have a very important role to play in nutritional support for individual patients or populations, food is not a
Box 2. Guidelines for an Integrated Approach to the Nutritional Care of HIV-Positive Children Aged 6 Months to 14 Years

The following steps and accompanying key messages have been developed to guide health-care providers in the nutritional care of HIV-positive children.

I. Assess, Classify, and Develop a Nutritional Care Plan

Step 1. Assess and classify the child’s growth
- Regular and careful assessment of a child’s growth helps monitor HIV disease progression and can identify complications early, providing an opportunity to intervene.

Step 2. Assess the child’s nutritional needs
- The nutritional needs of HIV-positive children for growth, development, and immunological function depend on HIV disease stage and history of recent complications such as persistent diarrhea or opportunistic infections.

Step 3. Develop a nutritional care plan
- The nutritional needs of HIV-positive children vary according to their age, disease stage, presence of acute and/or chronic infections, and current treatment. Nutritional needs are best met through balanced and varied food intake in adequate quantities. When this is not achievable, additional nutritional support may be needed.

II. Implement the Nutritional Care Plan

Step 4. Identify what the child eats and drinks
- Implementing a nutritional care plan starts with understanding what the child presently eats and drinks. The type of food given, and how it is prepared, can be as important as the amount and frequency of food eaten. In most situations a balanced diet (i.e., a variety of foods) is better than specialized supplements.

Step 5. Discuss who gives the child his or her food and how the child eats
- Children should be fed with care and patience. Before offering information and suggestions, first find out who is the main caregiver for the child and who else is involved with feeding and care. This helps clarify the quality and consistency of care practices.

Step 6. Assess whether there is sufficient food and income at home
- All children need regular, adequate, and appropriate foods in order to grow, develop, and maintain optimal body function. Nutrition is not just food but includes the entire process of having access to food, the quantity and quality of food, and how it is given to a child, as well as how the body uses it.

Step 7. Discuss exercise and avoid risk factors for malnutrition
- Physical activity and play help children develop and maintain strong muscles and improve their sense of well-being. Maintaining good nutritional status enables HIV-positive children to fight and avoid infections such as diarrhea. Preventive measures such as good hygiene, immunizations, and regular vitamin A supplements similarly protect the child against infections and undernutrition.

Step 8. Decide whether to refer and when to review
- HIV-positive children should be referred to other health-care facilities when specific needs are identified or when health workers with other skills or other resources are required. The frequency of and interval between reviews depends on the condition and needs of the child.

III. Children with Special Considerations

Step 9. Address the special needs of HIV-positive children
- HIV-positive children commonly experience weight loss and poor appetite and suffer from mouth sores and diarrhea. In spite of these problems, children can often still be managed at home if the correct help is offered early.

Step 10. Address the special needs of children on antiretroviral treatment
- Appropriate and adequate nutrition is needed to achieve the full benefits of ART. Children’s growth while on ART is a good indicator of response to treatment and ongoing adherence. Although ART can change the way the body uses fats, proteins, and energy, these metabolic changes can generally be managed without needing to stop the ART.

Source: Adapted from WHO.7
substitute for appropriate nutritional care of HIV-positive children. The need for food supplements may be assessed on an individual basis after determining whether the child’s family is able to comply with a nutritional care plan (see Box 2). The need for food supplements may also be determined on a population basis, for example, in areas (or at times of the year) where food or income insecurity is common. Therapeutic feeding for severely malnourished children will require appropriate selection of foods, and the treatment of choice is usually a specialized food product or ready-to-use therapeutic food (RUTF), such as F-100 or F-75 (provided by the United Nations Children’s Fund [UNICEF]) and Plumpy’nut.

Supplementation and food support present a complicated set of issues, and it may be preferable to differentiate between a nutritional supplement (to enhance energy density or increase caloric intake), a micronutrient supplement (to ensure micronutrient intake), and food support (where there is a basic lack of food in the household). The choice of what support to offer will depend on the resources available, the scale of the HIV epidemic locally, the level of food insecurity, and the level of malnutrition in the general population.

In programs where free infant formula is available for distribution (on a limited basis and for specific cases, such as when a mother has died or when replacement feeding is AFASS) to infants of HIV-positive mothers, an appropriate and equivalent (in nutritional content and in economic value) food alternative should be provided to breastfeeding mothers or infants for whom it is not AFASS to stop breastfeeding until all AFASS criteria are met.14 Some countries have developed strategies that allow for continued breast-milk feeding of HIV-positive children using methods that can reduce or eliminate the risk of HIV transmission. These include the use of an HIV-negative wet nurse (e.g., HIV-negative grandmothers or other HIV-negative women from the same community), heat-treating of breast milk, and/or the use of pasteurized breast-milk banks.

**Treatment of Severely Malnourished Children**

Standard treatment guidelines for the therapeutic care of severely or acutely malnourished infants and children should be used in the care of infants and children living with HIV. In addition to therapeutic feeding, these children should also be assessed and treated as indicated for concurrent morbidity (e.g., diarrhea or septicemia and other opportunistic infections, especially TB), and assessed for ART eligibility (or adherence if they are already on ART). The 2007 WHO guidelines7 and the 2007 Joint Statement on Community-Based Management of Severe Acute Malnutrition22 both contain useful guidance for clinical and community-based nutritional care for severely malnourished infants (Figure 1).

Management of severe acute malnutrition in infants and children can be challenging for caretakers, whether it is undertaken at home or in health facilities. According to WHO,7 severely malnourished infants can often be managed at home if they still have a good appetite. The presence or absence of appetite and the availability of RUTFs will impact the success of any approach to nutritional management and are critical determinants of whether the child should be managed in the hospital or at home. Diarrhea, nausea, vomiting, and anorexia are common in malnourished infants and children and will also need to be effectively managed.

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1Therapeutic feeding is a curative nutritional intervention used to rehabilitate a severely malnourished patient.
At this time, there are very few examples of best practices or lessons learned since pediatric treatment of HIV and AIDS in children in resource-limited settings is just getting under way. Based on some early experiences and existing research and evidence, and drawing upon the extensive experience in treatment and prevention of malnutrition in resource-limited settings and emergencies, WHO has recently released practical guidelines and clinical support tools to assist in the nutrition care of HIV-infected children aged six months to 14 years. In addition, a two-day training course is under development.

The WHO guidelines and related tools were field tested by clinical staff and community workers at a district hospital in Kenya and at two HIV treatment/referral hospitals in South Africa in late 2006 and early 2007. The field testers found that the guidelines were useful and clear and filled a much-needed gap in pediatric HIV care (Randa Saadeh, WHO, personal communication, March 2007).

A number of African countries have been implementing strategies for infant feeding and nutritional care of children under two years of age, including Côte d’Ivoire, Cameroon, Rwanda, South Africa, Zambia, Mozambique, Tanzania, and Zimbabwe. The Elizabeth Glaser Pediatric AIDS Foundation and PATH have collaborated on

**BEST PRACTICES AND LESSONS LEARNED**

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many of these efforts, which incorporate a number of activities, including training of health workers using an adapted WHO Integrated Training Course on Infant Feeding and HIV; development, adaptation, and diffusion of tools and materials (e.g., clinical AFASS algorithms, as well as counseling and information, education, and communication materials); development and dissemination of technical materials and tools for nonbreastfed and older children; strengthening of systems to routinely follow up with HIV-exposed children through the first two years of life; and extending the reach and impact of clinical services by mobilizing communities around supporting HIV-positive mothers and caretakers of young children to access available infant feeding and nutrition services for themselves and their children.

Over the past several years, a number of groups have worked together with the World Food Program (WFP), attempting to link individual (or, more commonly, family) food supplementation with prevention of mother-to-child transmission (PMTCT) or ART programs. These efforts have had mixed success, as WFP assistance is primarily targeted at food- or income-insecure households, not specifically at those living with HIV. The United Nations and the U.S. government have begun working to introduce and establish food and nutrition models for people living with HIV and their families in six countries (Ethiopia, Kenya, Nigeria, Tanzania, Uganda, and Zambia) based on the small-scale “food by prescription” (FBP) model originally developed in Kenya. An FBP program typically allows for the provision of supplementary food for specific populations (e.g., infants 6-24 months born to HIV-positive women, HIV-positive pregnant and lactating women, people living with HIV with low body mass indexes); procurement, distribution, and management of food; and clinic staff training, job aids, and counseling materials, as well as other forms of support for nutritional care.

Several HIV/AIDS programs in Africa and Asia are providing micronutrient supplements to adults as part of HIV care and treatment, and vitamin A to children older than six months as part of routine care.

Findings from a program providing nutritional care for HIV-positive adults in Zambia may have lessons for pediatric care as well. A 2005 evaluation of nutritional support provided by Catholic Relief Services (CRS) in Zambia, in partnership with the Catholic dioceses of Solwezi, Mongu, and Monze, looked at the effectiveness of the provision of a family ration of nutritional supplements to HIV-positive home-based care clients not on ART who met certain criteria for targeted nutritional supplementation. The evaluation assessed the impact of the program on home-based care clients 18 years of age and older and showed that nutritional supplements led to improvements in nutritional status (as measured by MUAC), number of meals eaten per day, physical status (reduced average number of AIDS-related symptoms and amount of time clients required assistance from a caregiver), household food security, and several quality-of-life indicators (improved mental outlook, increased participation in activities of daily living and work, and reduced number and severity of negative coping strategies employed by a client’s household).
REFERENCE LIST


Treatment and Prevention of Opportunistic Infections in Children Living with HIV

Maxensia Owor, a Mary Glenn Fowler, a,b Heather Jaspan, c,d Helena Rabie, c
Mark Cotton, c and Philippa Musoke a,e

CHILDREN LIVING WITH HIV ARE AT a high risk of acquiring opportunistic infections (OIs) due to their immature and compromised immune systems. Routine care of these children should include prevention and treatment of OIs, as the risk of developing OIs is directly related to the degree of immunosuppression. In high-income countries, the incidence of Pneumocystis pneumonia has decreased dramatically following early diagnosis of HIV infection in children, widespread use of potent combination antiretroviral therapy (ART), and routine prophylaxis. In resource-limited settings, however, children living with HIV continue to experience a high burden of OIs due to delayed diagnosis of HIV, delayed presentation to medical professionals, and limited access to antiretroviral medications (ARVs).

The spectrum and presentation of OIs in children is varied, as the infections affect different body systems. Pneumocystis jiroveci infection is a highly fatal OI still seen in infants born to women with unrecognized HIV infection. Tuberculosis (TB), serious bacterial infections, toxoplasmosis, cryptococcal meningitis, cytomegalovirus (CMV) infections, and candidiasis are other common OIs still regularly seen in developing countries. Cryptosporidium and microsporidium infections also persist, and contribute significantly to chronic diarrhea in severely immunocompromised HIV-infected children in resource-limited settings.

This chapter outlines the recommendations for treatment and prevention of the most common opportunistic infections among children living with HIV in resource-limited settings.

PNEUMOCYSTIS PNEUMONIA

Epidemiology
Pneumocystis pneumonia (PCP), which is caused by the yeast-like fungus P. jirovecii, is the most common AIDS-defining illness in children living with HIV and is associated with high mortality. Since the introduction of cotrimoxazole (trimethoprim-sulfamethoxazole [TMP-SMX]) prophylaxis in 1995, the frequency of PCP in developed countries has declined remarkably.

Clinical Findings
PCP incidence is highest in the first year of life and peaks at three to six months of age. Onset is

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usually abrupt, with low-grade fever, cough, dyspnea (i.e., difficult or labored respiration), tachypnea (i.e., increased rate of respiration), and poor feeding. Occasionally, the onset may be insidious. Auscultation reveals a clear chest or diffuse, fine crepitations (i.e., grating or crackling sounds). Chest radiograph often shows diffuse bilateral interstitial infiltrates but may be normal. Hyperinflation is common. The presence of any one of the following signs should raise a high index of suspicion for PCP:

- Known or suspected HIV infection
- Ordinary pneumonia that does not respond to treatment
- Age of three to six months
- Hypoxia (oxygen deficiency)/cyanosis
- Tachypnea and respiratory distress out of proportion to chest findings

**Diagnosis**

Definitive diagnosis requires demonstration of the organisms in sputum or tissue. Sputum can be collected through induction of sputum, nasopharyngeal aspirates, and bronchoscopy. Useful stains for identifying PCP include immunofluorescence, silver methenamine, toluidine blue, and Giemsa stain. Polymerase chain reaction (PCR) is used mainly in research settings. Lactate dehydrogenase (LDH), a nonspecific indicator of lung disease, may be very elevated in individuals with PCP. In resource-limited settings, however, diagnosis cannot be made definitively and treatment has to be presumptive with clinical diagnosis.

**Treatment**

The drug of choice for treating PCP is intravenous TMP-SMX. Recommended dosage is trimethoprim 15–20 milligrams per kilogram of body weight per day and sulfamethoxazole 75–100 milligrams per kilogram of body weight per day in divided doses every six hours intravenously for 21 days (see Table 1). Children with mild to moderate disease can be given TMP-SMX orally.

Pentamidine 4 mg/kg once daily intravenously is an alternative drug for children with intolerance or treatment failure to TMP-SMX. If improvements are seen after five to seven days of intravenous treatment, the remaining course of treatment can be administered orally with atovaquone. Pentamidine should not be administered with the nucleoside reverse transcriptase inhibitor didanosine, because both drugs cause pancreatitis.

Although experience with use of clindamycin-primaquine, trimetrexate glucuronate, and dapsone-trimethoprim in children is limited, recommendations are extrapolated from adult studies. Surfactant may offer a possible treatment strategy in very ill infants.

Steroids are indicated if the patient has moderate to severe PCP. The benefits of steroids include decreased morbidity and mortality, reduced respiratory failure, and decreased ventilatory requirements. Steroids should be started within 72 hours of initiating TMP-SMX. The recommended dose of methylprednisolone is 1 mg/kg/day administered intravenously every six hours for one week and then weaned off over the subsequent 10–14 days.

**Prevention**

HIV-infected infants with relatively high CD4 counts can still develop PCP. The recommendation is that all HIV-exposed and infected infants younger than one year should start on PCP prophylaxis, regardless of their immune status (see Tables 2, 3, and 4 for treatment recommendations and dosing guidelines). Recommendations for prophylaxis in older pediatric patients are based on definition of HIV infection status, age, and CD4 count.
### Table 1. Recommended Treatment of PCP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Possible Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)</td>
<td>Drug of choice</td>
<td>Trimethoprim 15–20 mg/kg/day IV + sulfamethoxazole 75–100 mg/kg/day IV every 6 hours for 21 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For oral therapy, give loading dose of 20 mg/kg followed by 5 mg/kg after 6 hours and 6 hourlya</td>
<td>Rash, neutropenia, anemia, nausea, vomiting, diarrhea, raised liver enzymes</td>
</tr>
<tr>
<td>Pentamidine-isethionate</td>
<td>Intolerance to TMP-SMX or treatment failure</td>
<td>4 mg/kg IV once daily for 21 days</td>
<td>Pancreatitis, hypoglycemia, renal dysfunction, fever, hyperglycemia, hypotension, neutropenia</td>
</tr>
<tr>
<td>Clindamycin-primaquine</td>
<td>Contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency</td>
<td>Clindamycin 10 mg/kg/day IV in 3–4 divided doses + primaquine 0.3 mg/kg PO daily for 21 days</td>
<td>Rash, hemolytic anemia, nausea, neutropenia, <em>Clostridium difficile</em>–associated colitis</td>
</tr>
<tr>
<td>Dapsone-trimethoprim</td>
<td>Limited data in children</td>
<td>Dapsone 2 mg/kg PO once daily + trimethoprim 5 mg/kg PO every 8 hours daily for 21 days</td>
<td>Methemoglobinemia, hemolytic anemia, neutropenia, thrombocytopenia</td>
</tr>
</tbody>
</table>

### Table 2. PCP Prophylaxis for HIV-Exposed or Infected Children

<table>
<thead>
<tr>
<th>Indications</th>
<th>First Choice</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected or exposed infants aged 1–12 mo</td>
<td><strong>Trimethoprim-sulfamethoxazole (TMP-SMX)</strong></td>
<td><strong>Dapsone (children older than 1 month)</strong></td>
</tr>
<tr>
<td>HIV-infected children 1–5 yr with CD4% &lt; 15%</td>
<td>150 mg/m²/day TMP + 750 mg/m²/day SMX in 2 divided doses orally for 3 consecutive days</td>
<td>2 mg/kg/24 hr (max 100 mg)</td>
</tr>
<tr>
<td>HIV-infected children 6–12 yr with CD4 count &lt; 200 cells/mm³ or CD4% &lt; 15%</td>
<td>or Single dose orally for 3 consecutive days or 2 divided doses orally every other day for 3 days</td>
<td>or <strong>Pentamidine (children older than 5 yr)</strong> 4 mg/kg every 2–4 weeks IM/IV or 300 mg monthly via Respirgard nebulizer system</td>
</tr>
<tr>
<td></td>
<td>or <strong>Atovaquone (children older than 24 months)</strong></td>
<td>or <strong>Atovaquone (children older than 24 months)</strong></td>
</tr>
<tr>
<td></td>
<td>30 mg/kg/day orally or (4 to 24 months) 45 mg/kg/day orally</td>
<td></td>
</tr>
</tbody>
</table>

*aIM = intramuscularly; IV = intravenously; PO = perorally*
Cryptosporidiosis and Microsporidiosis

Epidemiology
Cryptosporidiosis is caused by *Cryptosporidium* parasites, enteric pathogens that can cause life-threatening, persistent diarrhea in immunocompromised individuals. The common species that cause disease in humans are *C. hominis*, *C. parvum*, and *C. meleagridis*. Cryptosporidiosis is more common in HIV-infected children living in resource-limited settings than in those living in developed countries. Children with CD4 percentages of less than 25% are more likely to have cryptosporidiosis. Coinfection with *Enterocytozoon bieneusi* is common in HIV-infected children with cryptosporidiosis. The route of transmission is fecal-oral, and important sources of infection include animals, contaminated drinking water, food, and day-care centers.

Clinical Findings and Diagnosis
Chronic, profuse, watery diarrhea with resultant weight loss is the most common presentation. Abdominal cramps, fever, vomiting, anorexia, and dehydration may also occur. Additional intestinal complications include cholecystitis, sclerosing cholangitis, pulmonary cryptosporidiosis, and central nervous system (CNS) disease.

Diagnosis
*Cryptosporidiosis*
Stool specimens are concentrated and stained with Kinyoun acid-fast stain and inspected for oocysts. At least three separate stool specimens should be evaluated. Other tests that are more sensitive and more specific than staining technique include PCR and monoclonal antibody-based fluorescein stain.

### Table 3. Primary Prophylaxis for HIV-Associated Infections in HIV-Exposed or HIV-Infected Infants and Children (WHO)

<table>
<thead>
<tr>
<th>HIV Infection Status</th>
<th>Age</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-exposed</td>
<td>Birth to 4–6 weeks</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>From 4–6 weeks until</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td></td>
<td>HIV infection can be</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ruled out</td>
<td></td>
</tr>
</tbody>
</table>
| Newly diagnosed      | 1–4 years            | Prophylaxis if WHO stage II, III,
| infection            | or IV, regardless    |                                 |
|                      | of CD% or            |                                 |
|                      | CD4% < 25%           |                                 |
|                      | > 5 years            | Adult guidelines                |

**Secondary PCP Prophylaxis**
Any child with a history of prior PCP should continue with prophylaxis of 6–8 mg/kg/day of trimethoprim (TMP) daily for life. Because the safety of discontinuing secondary prophylaxis for HIV-infected children has not been extensively studied, World Health Organization recommends continuing prophylaxis indefinitely. Breakthrough PCP can occur despite prophylaxis. The drug of choice for treatment remains TMP-SMX.

**Stopping Prophylaxis**
TMP-SMX prophylaxis should only be discontinued for children who are found to be HIV-negative after they have stopped breastfeeding for at least three months. HIV-infected children and HIV-exposed children whose infection status remains unknown should continue to receive PCP prophylaxis indefinitely. The safety of discontinuing prophylaxis in children receiving ART has not yet been established, though some studies suggest that prophylaxis can safely be discontinued once the CD4 count has increased above the age-appropriate Centers for Disease Control and Prevention (CDC) threshold.
**Cryptosporidiosis**

Nitazoxanide*

Children 1–3 years: 100 mg perorally (PO) twice a day (BID)

Children 4–11 years: 200 mg PO BID

*Only for approved use in HIV-negative children but HIV-infected children may respond to a higher dosage for a longer period (until 3 tests in stool are negative). (22.5mg per kg twice a day has been used)  

Paromomycin

25–35 mg/kg in 2–4 divided doses PO (maximum 2 g daily)

**Microsporidiosis**

Microsporidiosis is detected through thin smears of unconcentrated stool in formalin suspension or duodenal aspirates stained with trichrome.

**Treatment**

Treatment with ARVs resulting in immune reconstitution is the best intervention for the reduction of cryptosporidia. Although the drugs listed here have been used to reduce symptoms, their effectiveness is limited, and recommended treatment duration is unknown.
Azithromycin
10 mg/kg PO on day 1, then 5 mg/kg PO daily from day 2 to day 10

**Microsporidiosis (other than Enterocytozoon bieneusi)**

- Albendazole
  - 7.5 mg/kg PO BID (maximum dose 400 mg BID) for 4 weeks
  - or
  - Fumagillin (no data)

**Prevention**

Possible interventions include boiling all drinking water and avoiding contact with all human and animal feces.

**TOXOPLASMOSIS**

**Epidemiology**

Toxoplasmosis is caused by *Toxoplasma gondii*, an intracellular parasite found worldwide. Although infection with *T. gondii* is generally asymptomatic, infection can cause severe symptoms in infants born with congenital infection or in an immunocompromised host. In these circumstances, the parasite can invade the CNS and other organs, including the liver and spleen.

Congenital toxoplasmosis infection can occur among both HIV-exposed and nonexposed infants, though risk may be higher among HIV-exposed infants due to reactivation of latent maternal disease. Congenital toxoplasmosis is acquired via transmission across the placenta, generally among mothers who have primary infection during pregnancy. In the case of HIV-infected pregnant women, transmission can also occur with reactivation of infection. The overall rate of congenital infection is about 30% but varies according to trimester of exposure, with extremely low risk during the first trimester, rising to close to 90% in the third trimester. Maternal acquisition can occur from handling cat feces, eating inadequately cooked meats, or being exposed to contaminated soil.

Acquired or reactivated toxoplasmosis may also lead to symptomatic disease and is seen among severely immunosuppressed children and adults living with HIV due to environmental exposure or ingestion of inadequately cooked meats that have tissue oocytes. Primary prevention of toxoplasmosis is through the avoidance of cat feces, undercooked meat, and unwashed vegetables. Widespread use of TMP-SMX for PCP prophylaxis has the unanticipated benefit of preventing toxoplasmosis.

**Clinical Findings and Diagnosis**

Congenital toxoplasmosis can be symptomatic or asymptomatic. Symptomatic newborns may have CNS findings, including microcephaly, chorioretinitis, hydrocephalus, encephalitis, and seizures. Other findings may include small size for gestational age, low birth weight, and hepatosplenomegaly. Although the majority of infected newborns are asymptomatic on physical examination, they may have intracranial calcifications on neuroimaging, as well as ocular findings of chorioretinitis. Over time and without early treatment, a substantial number will develop chorioretinitis and impairment of vision. Congenitally infected children are also at risk for developmental delay, seizures, and secondary microcephaly.

Older HIV-infected and/or immunosuppressed children may manifest new onset neurologic findings due to acquired or reactivated toxoplasmosis. Presentations in HIV-infected children can include headache, focal neurologic signs, diffuse encephalitis, seizures, or decreased vision. Disseminated toxoplasmosis infection may involve the liver, lung, eyes, and heart.
Definitive diagnosis of congenital toxoplasmosis infection is based on serology using immunoassays or immunosorbent assays for toxoplasma-specific IgM, IgA, or antibodies, or PCR detection of organisms. Neurologic exam, including funduscopic examination and neuroimaging for calcifications, can be useful when congenital toxoplasmosis is suspected. In some settings, newborn screening with dried blood spots is routinely done, as this allows for early identification and treatment, which can significantly decrease later sequelae. Definitive diagnosis is based on cytology or histology.

### Treatment and Follow-Up

During pregnancy, mothers identified as having primary infection based on seroconversion are treated with spiramycin. The treatment for congenital toxoplasmosis is pyrimethamine given in combination with sulfadiazine and folic acid for 12 months (see Table 5). Likewise, older HIV-infected children with acquired toxoplasmosis are given pyrimethamine and followed up for clinical improvement over a six-week period. Alternative therapies include atovaquone and azithromycin with pyrimethamine. Following initial treatment, lifelong suppressive therapy is necessary.

Where pyrimethamine and sulfadiazine are unavailable, many clinicians use Trimethoprim-sulfamethoxazole at 20 mg/kg per day in 4 divided doses for 3 to 4 weeks followed by same dosage as for PCP prophylaxis.

Follow-up evaluations should include complete blood count (CBC) monitoring during treatment, developmental and neurologic exams, and ophthalmology exam (every 3 months for the first 18 months of life, then every 6–12 months).

### Prevention

Prevention is based on avoidance of exposure to oocysts, such as cat feces and contaminated soil, as well as avoidance of undercooked or raw meat.

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Initial Treatment</th>
<th>Suppression</th>
<th>Primary or Secondary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Pyrimethamine 2 mg/kg/day for 3 days, then 1 mg/kg/day for 2–6 months, followed by 1 mg/kg 3x a week for 12 months plus Leucovorin 10 mg 3x a week with each dose of pyrimethamine plus Sulfadiazine 100mg/kg/day for 12 months</td>
<td>Chronic suppression at lower doses of pyrimethamine and sulfadiazine</td>
<td></td>
</tr>
<tr>
<td>Acquired, older children, and adolescents</td>
<td>Pyrimethamine 25–100 mg/day for 3–4 weeks plus Sulfadiazine 1–1.5 g 4x daily (QID) for 3–4 weeks (Steroids may ameliorate ocular complications.) plus Atovaquone with or without pyrimethamine</td>
<td>Chronic suppression at lower doses of pyrimethamine and sulfadiazine</td>
<td>Trimethoprim-sulfamethoxazole: 150 mg TMP and 750 mg SMX/m² body area</td>
</tr>
</tbody>
</table>
CRYPTOCOCCAL DISEASE

Epidemiology
Cryptococcal infection in humans is generally caused by Cryptococcus neoformans, an encapsulated yeastlike fungus found in soil contaminated by avian feces. Primary human acquisition results from inhaling fungal particles, with resultant pulmonary infection. In immunocompetent hosts, pulmonary infection is generally mild but can lead to cough and fever. In immunosuppressed individuals, including those with severe HIV infection, dissemination to the CNS and other organs can occur. CNS infection, though sometimes showing a slow course, is fatal without treatment.

In resource-limited settings, cryptococcal meningoencephalitis is one of the most frequent OIs seen in adults living with HIV; in some parts of Africa, it is the primary etiology for community-acquired meningitis. In studies from Zimbabwe and Malawi, close to half of adult meningitis cases were due to cryptococcal infection. In a follow-up study of a cohort from Rakai, Uganda, cryptococcal disease accounted for 17% of all deaths seen among HIV-infected adults.

Despite being common in adults, cryptococcal meningitis is relatively rare among HIV-infected children. Usually, infection in children is detected due to the reactivation of latent pulmonary infection, with subsequent dissemination to the CNS. Secondary spread from an infected individual to others has not been reported.

Clinical Findings and Diagnosis
Initial presentation is usually meningoencephalitis with headache and fever. Signs of acute meningitis, as well as new onset seizures, may be seen (e.g., fever, neck stiffness). Disseminated cryptococci can also be seen, with associated skin papules that resemble molluscum contagiosum. Clinical pulmonary disease is uncommon but can occur.

Diagnosis of CNS disease is based on isolation of the organism from cerebral spinal fluid (CSF). CSF microscopic examination is often normal in terms of cells, chemistries, and protein but with elevated opening pressure. India ink wet mounts of the CSF are useful for diagnosis, as are fungal cultures of CSF and blood. Cryptococcal antigen titers in the CSF can also be measured and may help diagnose treatment failure or relapse. Involvement of the lungs is diagnosed based on bronchoalveolar washings and India ink staining, as well as on culture and antigen assays.

Treatment
Treatment guidelines for HIV-infected children with cryptococcal disease (see Table 6) are based on adult studies. Amphotericin B, combined with flucytosine or fluconazole, is used for to treat both meningoencephalitis and severe pulmonary disease. Combination therapy is given for 2 weeks, followed by fluconazole for at least 10 weeks or longer, depending on whether CSF cultures are negative at 2 weeks (about 60%–80% will be negative at that point). Following successful treatment, lifetime suppressive therapy with fluconazole is required. It is not known whether, following immune reconstitution in children, secondary prophylaxis may be discontinued; current recommendations are for lifetime maintenance to prevent relapse. With early ART intervention, it is anticipated that cases of pediatric cryptococcal infection will be increasingly rare.

Fluconazole or itraconazole can be used to treat moderate or mild pulmonary disease, followed by lifetime suppressive therapy.

Prevention
Primary prevention is based on avoidance of contaminated soil. Lifetime secondary prophylaxis with low-dose fluconazole is recommended for children with HIV infection who have completed initial therapy. (Data are not currently available
for HIV-infected children as to whether secondary prophylaxis can be safely stopped following ART leading to immune reconstitution.)

**BACTERIAL INFECTIONS IN CHILDREN LIVING WITH HIV**

**Epidemiology**

Bacterial coinfections are a major source of comorbidity in children infected with HIV. These infections cause a wide spectrum of diseases, many of which are included in the WHO and CDC staging systems. In fact, bacterial infections are so prominent in pediatric HIV that the CDC staging system was revised in 1987 to include them.28

Since the widespread availability of ART, there has been a marked decrease in morbidity and mortality associated with bacterial infections in both developed and developing countries. In the United States, pneumonia is still the most common bacterial infection in HIV-infected children on ART. However, with an incidence rate of 2.15 events per 100 person years, this is far less than the 11.1 events in the same (albeit younger) children pre-ART (Table 7).29 In a California cohort followed from 1994 to 2001, bacterial infections accounted for 60 hospitalizations for 64 children in 1994, but only 8 hospitalizations for 101 children in 2001.30 The hospitalization rate for serious bacterial infections was only 14.2 per 100 person years for a Thai cohort of children initiated on ART between 2002 and 2005.31 Nevertheless, bacterial infections remain the most common reason for hospitalization among HIV-infected children.

**Responsible Organisms**

The relative prevalence of most bacterial pathogens is similar to that of HIV-uninfected children. However, in a large Kenyan study, *Streptococcus pneumoniae, Haemophilus influenzae*, nontyphoid salmonella, and *Escherichia coli* were more common in HIV-infected children.32 These organisms were frequently seen in malnourished children in the pre-HIV era. *Streptococcus pneumoniae* is the most common organism, with *Staphylococcus aureus*, salmonella species, and gram-negative *Enterobacteriaceae* occurring commonly.33,36–38 *Pseudomonas aeruginosa* is also seen occasionally.

Table 8 shows the relative frequencies of specific bacterial isolates from blood cultures of HIV-infected children from various settings. Depending on the study’s design, the frequencies quoted are representative only of community-acquired isolates,
or a combination of both community- and hospital-acquired infections. The proportion of *H. influenzae* has been influenced by the introduction of the *H. influenzae* type B (Hib) vaccine—in 1991 in the United States and in 1999 in South Africa.

**Clinical Findings and Diagnosis**
The burden of disease for bacterial infection includes almost every organ system, including the central nervous system (i.e., meningitis), lung, mastoid, bone and joints, and gastrointestinal tract. Concomitant bacteremia is common. Abscess formation in internal organs and skin can also occur (see Table 7). Otitis media (OM) and acute sinusitis are also common.

**Pneumonia**
By far, the most frequent cause of bacterial morbidity in all HIV-infected children is pneumonia. This is true both with and without TMP-SMX prophylaxis.35 Although HIV-infected children have a greater risk of bacterial infections than their HIV-negative counterparts,32 the relative prevalence of these infections does not seem to be significantly different in HIV-positive and HIV-negative children, though some have suggested that meningitis tends to be less common in HIV-infected children.33 It is clear, however, that bacterial infections are more invasive, more likely to disseminate, and have worse outcomes in HIV-infected children.33,39 In addition, HIV-infected children often have multiple diagnoses and polymicrobial infections.33,39

**Acute and Chronic Otitis Media**
In various cohorts from different settings, including the United States,42 Thailand,43 and Africa,44 acute OM and chronic OM have been common in HIV-infected children. In a Nigerian cohort of HIV-infected children, almost all of whom were receiving ART, 11% had discharging ears, 86% of which were chronic serious otitis media (CSOM).44

<p>| Table 7. Incidence of Serious Bacterial Disease in HIV-Infected Children from Different Settings |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Description</th>
<th>United States a n=2767</th>
<th>United States b n=2767</th>
<th>S. Africa c n=141</th>
<th>Zambia d n=534</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multicenter cohort</strong></td>
<td><strong>Multicenter cohort</strong></td>
<td><strong>Inpatient cohort</strong></td>
<td><strong>Randomized prospective study</strong></td>
<td></td>
</tr>
<tr>
<td>Bacteremia/ septicemia</td>
<td>220 (8%)</td>
<td>25 (0.9%)</td>
<td>74 (52%)</td>
<td>19 (3.6%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>698 (25%)</td>
<td>123 (4%)</td>
<td>95 (67%)</td>
<td>159 (30%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>13 (0.5%)</td>
<td>&lt; 4</td>
<td>4 (3%)</td>
<td>13 (2.4%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>68 (2.5%)</td>
<td>27 (1%)</td>
<td>15 (11%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Skin or soft tissue, incl. abscess</td>
<td>5 (0.2%)</td>
<td>&lt; 4</td>
<td>2 (1.5%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Osteomyelitis or septic arthritis</td>
<td>17 (0.6%)</td>
<td>&lt; 4</td>
<td>1 (0.7%)</td>
<td>3 (0.6%)</td>
</tr>
</tbody>
</table>

*Pre-ART: These represent events ever occurring in the cohort.33
Post-ART era: These represent first-time events only. Only diagnoses with four or more events are reported.29
Spectrum of disease in HIV-infected children hospitalized for bacterial infections33
Causes of death and hospitalization only. Half received TMP-SMX versus placebo. It is unclear whether the arthritides were infectious.35*
Sinusitis

The prevalence of sinusitis in cohorts from resource-limited settings is slightly lower than in the United States,42 probably due to underrecognition in these settings, where sinusitis must be diagnosed clinically. In a U.S. cohort of 376 children prior to ART, there were 95 episodes of sinusitis, 67% of which presented with persistent nasal discharge and 55% with nocturnal or persistent cough.37 Therefore, in children living with HIV, there should be a high index of suspicion for diagnosing and treating sinusitis, even in the absence of

Table 8. Bacterial Isolates from HIV-Infected Children from Different Settings with Serious Bacterial Infections*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>20 (37)</td>
<td>41 (50)</td>
<td>21 (23)</td>
<td>24 (39)</td>
</tr>
<tr>
<td>S. aureus</td>
<td>8 (15)</td>
<td>10 (12)</td>
<td>14 (16)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>E. coli</td>
<td>—</td>
<td>7 (9)</td>
<td>5 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>—</td>
<td>—</td>
<td>11 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. influenza</td>
<td>2 (4)</td>
<td>19 (35)</td>
<td>8 (9)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Salmonella species</td>
<td></td>
<td>3 (4)</td>
<td>12 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other streptococci</td>
<td></td>
<td>9 (17)</td>
<td>1 (1)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>—</td>
<td>—</td>
<td>2 (2)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>5 (9)</td>
<td>—</td>
<td>5 (6)</td>
<td>—</td>
</tr>
<tr>
<td>Other gram negatives</td>
<td></td>
<td>2 P. aeruginosa</td>
<td>1 Neisseria meningitidis</td>
<td>1 P. aeruginosa</td>
</tr>
<tr>
<td></td>
<td>1 Kingella kingae</td>
<td>1 acinetobacter</td>
<td>4 acinetobacter</td>
<td>1 Serratia marcescens</td>
</tr>
<tr>
<td></td>
<td>1 Clostridium perfringens</td>
<td></td>
<td></td>
<td>1 campylobacter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 acinetobacter</td>
</tr>
</tbody>
</table>

*aCoagulase-negative staphylococcus excluded
*bBacterial isolates from any culture-confirmed infections. Half of the children received intravenous immunoglobulin (IVIG), and some received TMP-SMX.36
*cBlood cultures from children with community-acquired pneumonia.40
*dBlood culture results in hospitalized, HIV-infected children with sepsis, lower respiratory tract infection (LRTI), or meningitis.41
*ePositive blood cultures in hospitalized children with severe LRTI. Culture results may be biased due to handling of cultures.39

retrospective cohort analysis from South Africa, Karpakis et al documented otorrhea in 104 (32%) of 326 children who did not have ready access to ART.46 The median CD4 percentage in children with otorrhea was 17.5% (8.3%–23%) versus 21% (14%–28%) in those without otorrhea (P=004). In a Brazilian cohort, all of which were on ART, 33% of the children had OM, either acute, chronic, or serous; 14% had sinusitis; and 8% had tonsillitis. In addition, a handful of these children had serious sequelae, such as peritonsillar abscesses, mastoiditis, and cholesteatoma.46
acute symptoms, such as headache, facial pain, or fever. It appears that the risk of OM decreases with improved immunological status; however, the risk of sinusitis is independent of CD4 count.37,42

**Diagnosis**

Pneumonia can be diagnosed based on clinical and radiological findings. Otitis media can be diagnosed by direct visualization of the ear. Sinusitis can be diagnosed based on history, ranging from prolonged purulent nasal discharge to fever and facial pain.

**Antimicrobial Treatment**

The empiric treatment of bacterial infections in HIV-infected children in resource-limited settings should take into account the region’s antimicrobial susceptibility patterns (see Table 9). Recommended empiric therapy for HIV-infected children in Cape Town, South Africa, is shown in Table 10. The clinician must be certain to include viral, fungal, and mycobacterial infections in the differential diagnosis of bacterial infections and must treat accordingly.

**Prevention of Bacterial Infections**

The most effective public-health approach to improving infectious disease burden is through vaccination. However, children living with HIV mount immune responses of variable efficacy to vaccines.47 These responses are particularly poor pre-ART, though they generally improve after immune reconstitution.48-50 Effective vaccines are licensed for Hib and S. pneumoniae. Both are polysaccharide protein conjugate vaccines. The Hib vaccine is now widely available in developing countries. Although the estimated efficacy of the Hib vaccine is decreased and the risk for vaccine failure is increased in HIV-infected children,51 the introduction of the Hib vaccine into countries with high HIV prevalence has greatly decreased the Hib disease burden.52 In 2000, a pneumococcal conjugate vaccine (PCV) was licensed in the United States. Although PCV is less immunogenic in HIV-infected children than in uninfected children,54 its efficacy also seems to improve in children receiving ART.55 A similar nine-valent PCV has been extensively studied in South Africa, and similar efficacy is seen in these HIV-infected infants.55,56 Unfortunately, PCV is not yet widely accessible to children in developing countries.

**TUBERCULOSIS AND HIV**

**Epidemiology**

The HIV pandemic has led to a resurgence of TB in both adults and children in regions where there is a high prevalence of both infections, such as sub-Saharan Africa.57 Childhood TB contributes to significant morbidity and mortality, with more than 800,000 children diagnosed with TB globally in 2000, representing more than 10% of the world’s total TB cases. HIV-infected children run a high risk of acquiring TB from an adult household member with sputum-positive TB. For example, a household contact study in Uganda reported that 10% of the children and 1.9% of the adults developed TB infection after exposure to an adult with sputum-positive TB.58 Young age, immunosuppression due to HIV, and malnutrition lead to progressive primary TB with increased morbidity and mortality.59

The prevalence of TB in HIV-infected children depends on the prevalence of TB in the adult population. The seroprevalence of HIV in childhood TB cohorts from different regions varies from between 10% in West Africa to as high as 60% in southern Africa. In hospitalized children with culture-confirmed TB from South Africa, 49% were HIV-infected, as opposed to 19% of similar children in Côte d’Ivoire.60,61 Studies of HIV-exposed cohorts have documented a 10-fold increase in the incidence of TB in HIV-infected versus HIV-uninfected children.62 A Zambian autopsy study of HIV-infected children found
### Table 9. Antibiotic Susceptibilities of the Most Common Organisms Isolated from Blood Cultures of Children with Serious Bacterial Infections in South Africa and Uganda

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Country</th>
<th>S. pneumoniae</th>
<th>H. influenzae</th>
<th>S. aureus</th>
<th>E. coli</th>
<th>Salmonella species</th>
<th>Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin/ampicillin</td>
<td>Uganda</td>
<td>58</td>
<td>0</td>
<td>65</td>
<td>17</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>46</td>
<td>89</td>
<td>—</td>
<td>14</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>25*</td>
<td>100</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>Uganda</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>0</td>
<td>26</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>52</td>
<td>94</td>
<td>40</td>
<td>14</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>0*</td>
<td>0</td>
<td>33</td>
<td>—</td>
<td>—</td>
<td>28</td>
</tr>
<tr>
<td>Cloxacillin/methicillin</td>
<td>Uganda</td>
<td>62</td>
<td>—</td>
<td>60</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>23</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cefotaxime/ceftriaxone</td>
<td>Uganda</td>
<td>73</td>
<td>100</td>
<td>68</td>
<td>100</td>
<td>91</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>89</td>
<td>—</td>
<td>86</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>45</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Uganda</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>97</td>
<td>—</td>
<td>61</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Uganda</td>
<td>43</td>
<td>50</td>
<td>88</td>
<td>83</td>
<td>83</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>19</td>
<td>—</td>
<td>—</td>
<td>45</td>
</tr>
<tr>
<td>Amikacin</td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>80</td>
<td>86</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>100</td>
<td>—</td>
<td>—</td>
<td>90</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>69</td>
</tr>
<tr>
<td>Meropenem</td>
<td>South Africa</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>100</td>
</tr>
</tbody>
</table>

*Percent susceptible given for HIV-infected and HIV-negative malnourished children

*Percent susceptible given for HIV-infected children only

*For HIV-infected children only

*50% had intermediate sensitivity

**Only one organism tested; resistance was 90% for nasopharyngeal isolates

— = not tested
have a negative tuberculin skin test due to the underlying immunosuppression.

TB remains the major OI, presenting as immune reconstitution inflammatory syndrome (IRIS) in children initiating ART. It usually presents within the first two months after initiation of therapy.68,69

Clinical Findings and Diagnosis
The clinical presentation of TB is similar in HIV-infected and uninfected children, with pulmonary TB (PTB) being the most common form. However, disseminated and extrapulmonary TB (EPTB) are more prevalent in HIV-infected children.65 Persistent or recurrent fever, chronic or intermittent cough, weight loss, and failure to thrive are the most common presenting symptoms. However, because of the nonspecific nature of the signs and symptoms, many children with TB are not diagnosed or are diagnosed late, leading to a delay in treatment and a high rate of mortality. On the other hand, overdiagnosis of TB in children coinfected with HIV also occurs frequently because of the other HIV-related pulmonary manifestations, such as lymphoid interstitial pneumonitis, bronchiectasis, and Kaposi's sarcoma. These conditions may mimic TB but may also occur concurrently with pulmonary TB.66

Generalized lymphadenopathy may be due to disseminated TB or HIV; the correct diagnosis can only be confirmed with a lymph node aspirate, biopsy for mycobacterial culture, or histopathological diagnosis. Many different clinical scoring systems have been developed to assist in the diagnosis of childhood TB. However, most scoring systems for childhood TB diagnosis exhibit low sensitivity and poor correlation between the different systems.67 The Mantoux skin test is considered positive at greater than or equal to 5 millimeters in HIV-infected children. However, most HIV-infected children with TB have a negative tuberculin skin test due to the underlying immunosuppression.

Laboratory Diagnosis
The gold standard for TB diagnosis is a positive mycobacterial culture from body fluid, including sputum, gastric aspirates, ascitic fluid, pleural fluid, cerebrospinal fluid, bone marrow aspirate, or other sterile sites. However, most childhood TB is diagnosed from a variety of signs and symptoms combined into a clinical algorithm. In most childhood TB studies, less than 50% of sputum cultured is positive for mycobacteria.60-62,65 Three early-morning gastric aspirates or an induced sputum are recommended for diagnosis of pulmonary TB, though the sensitivity still remains low at 30% to 50%. However, one induced sputum has been found to be as sensitive as three early-morning gastric aspirates, regardless of the child's HIV status.70

The sputum is cultured on Lowenstein-Jensen or Middlebrook 7H10 (solid media) or Middlebrook 7H9 (liquid media / mycobacteria growth indicator tube [MGIT]). Standard mycobacterial cultures require six to eight weeks for mycobacterial growth; however, the BACTEC system from Diagnostic Systems enables mycobacterial growth within 10 to 14 days. When available, ultrasound and computed tomography (CT) scan of the chest, abdomen, and/or head to visualize enlarged lymph nodes and granulomatous lesions may assist in the diagnosis of EPTB.

Newer blood tests, including the whole-blood interferon gamma assay (QuantiFERON) and the TB ELISPOT assays, have been developed and tested in the field. Some studies have reported that
**Table 10. Empiric Therapy for Selected Severe Bacterial Infections in Children with Proven or Suspected HIV Infection in Cape Town, South Africa**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Antibiotic</th>
<th>Alternatives</th>
<th>Consider Adding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis (community acquired)</td>
<td>Ampicillin + gentamicin*</td>
<td>Ceftriaxone, if intrinsic renal impairment</td>
<td>Plus cloxacillin for community-acquired sepsis or vancomycin for hospital-acquired sepsis if <em>S. aureus</em> suspected*</td>
</tr>
<tr>
<td>Sepsis (hospital acquired)</td>
<td>Piperacillin/tazobactam + amikacin*</td>
<td></td>
<td>Vancomycin if staph suspected</td>
</tr>
<tr>
<td>Lower respiratory tract infection (community acquired)</td>
<td>Ampicillin + gentamicin*</td>
<td>Cefuroxime</td>
<td>Add erythromycin if suspected atypical* Plus cloxacillin if <em>S. aureus</em> suspected</td>
</tr>
<tr>
<td>Lower respiratory tract infection (hospital acquired)</td>
<td>Piperacillin/tazobactam + amikacin*</td>
<td></td>
<td>Vancomycin if <em>S. aureus</em> suspected</td>
</tr>
<tr>
<td>Meningitis (community acquired)</td>
<td>Ceftriaxone</td>
<td></td>
<td>Amoxicillin if &lt; 2 months old plus Vancomycin if high prevalence of resistant pneumococcus or fever not responding after 48–72 hrs in the absence of other cause</td>
</tr>
<tr>
<td>Meningitis (hospital acquired)</td>
<td>Ceftriaxone</td>
<td>Meropenem (if <em>Enterobacteriaceae</em> suspected)</td>
<td>Vancomycin*</td>
</tr>
<tr>
<td>Urinary tract infection (inpatient)</td>
<td>Gentamicin or cefuroxime</td>
<td>Ceftriaxone (if renal impairment)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection (outpatient)</td>
<td>Amoxicillin + clavulanate or cefuroxime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute osteomyelitis/septic arthritis</td>
<td>Cloxacillin</td>
<td>If younger than 2 yr: ceftriaxone; switch to cloxacillin if <em>S. aureus</em> cultured</td>
<td>Clindamycin or vancomycin*</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Amoxicillin/ clavulanate</td>
<td>Ceftriaxone</td>
<td></td>
</tr>
</tbody>
</table>

*Until isolates and susceptibilities known

*Peak and trough levels after 24 hours

*Consider *S. aureus* if there is an indwelling catheter, thrombophlebitis, breakdown, empyema, and so forth. Consider methicillin-resistant *Staphylococcus aureus* (MRSA) if recent hospitalization.

*Peak and trough levels after 24 hr if MRSA confirmed, to prevent vancomycin resistance

*Strongly consider high-dose TMP-SMX for *Pneumocystis jirovecii* pneumonia in hypoxic infants under 12 months of age
the ELISPOT assay in the field is more sensitive for TB latent infection than the standard tuberculin skin test.\textsuperscript{71}

**Treatment**

The recommended treatment for TB in children who are smear negative is three drugs—isoniazid (INH), rifampicin (RIF), and pyrazinamide (PYZ)—for two months, followed by four months of RIF and INH, to complete a total course of six months. If the child has smear-positive TB, then the recommendation is to initiate treatment with four drugs, including INH, RIF, PYZ, and ethambutol (ETH) for two months, followed by four months of INH and RIF. The six-month short-course regimen is still recommended by WHO, regardless of the child’s HIV status.\textsuperscript{72} However, many experts have recognized the high relapse rates and thus recommend extending the length of treatment to nine months. Schaff et al reported nine second episodes of TB (relapse and reinfection) among 56 HIV-infected children who had culture-confirmed TB and who were followed for a median duration of 39 months.\textsuperscript{73}

Currently, there are no completed studies to confirm the most appropriate duration of TB treatment in HIV-positive children coinfected with TB. Poorer TB treatment outcomes, including slower response to anti-TB treatment and higher mortality, have been reported in HIV-infected children. In addition, multidrug-resistant TB is on the rise, especially in HIV coinfected adults, leading to an increased risk in children.\textsuperscript{74-77}

**Prevention**

There is clear evidence that Bacille Calmette-Guérin (BCG) vaccination reduces the incidence of severe TB in children. Thus, BCG is still widely implemented during the neonatal period in many developing countries where both HIV and TB are prevalent. In 2006, WHO recommended that infants who are known to be HIV infected should not receive BCG vaccine, even if they are asymptomatic.\textsuperscript{72} The basis for this new recommendation was the increasing number of reports of disseminated BCG disease in HIV-infected children who received BCG vaccine at birth, even when they were asymptomatic. However, most infants are of unknown HIV status when immunized at birth, making these recommendations difficult to implement in most resource-limited settings.

Prophylaxis with INH is recommended by WHO, as well as by most national TB guidelines, for all children under five years who are exposed to a sputum-positive adult. However, because of the logistics and costs of implementing this intervention, many developing countries do not comply with these guidelines. Furthermore, there is a concern about the potential risk of treating active TB disease with one drug leading to emergence of drug resistance. Zar et al\textsuperscript{64} reported the benefit of INH prophylaxis in a randomized control trial in HIV-infected children who received INH or placebo and documented a 50% reduction in mortality in the INH arm versus those on placebo.

**SUMMARY**

- HIV-infected children in high-TB and high-HIV-prevalence settings are at a high risk of acquiring TB because of their young age, underlying immunosuppression, and the high prevalence of TB in their environment.
- The clinical presentation of TB in children is similar, regardless of HIV status, with pulmonary TB remaining the most common manifestation.
- Response to treatment tends to be poor and mortality higher in HIV/TB coinfected children. However, some children who do not respond to treatment may present with other pulmonary manifestations of HIV that mimic TB.
• Although clinical scoring systems have been developed to assist in the screening and diagnosis of childhood TB, most lack specificity and have not been validated in HIV-infected children. The Mantoux skin test is less sensitive and chest X-ray is less specific for diagnosis of TB in these children.
• The new blood tests, including QuantiFERON and TB ELISpot assays, have been developed for diagnosis of latent and active TB but are not yet used routinely in the field.
• The WHO-recommended duration of treatment for pulmonary TB in HIV-infected children is six months; however, some experts and guidelines recommend an extension to nine months.
• Preventive INH therapy is effective in reducing the incidence of TB and associated mortality in HIV-infected children.
• The management of the HIV-infected child coinfected with TB includes timely diagnosis and appropriate and prompt treatment of HIV infection and TB.
REFERENCE LIST


50. Abzug MJ, Pelton SI, Song LY, et al. Immunogenicity, safety, and predictors of response after a pneumococcal conjugate and


Globally, there are 1.7 billion young people aged 10 to 24 years, representing one-quarter of the world’s population, with over 85% living in developing countries. While young people in developing countries have a mortality rate of less than 3%, HIV and AIDS have reduced their chance of surviving to age 60 by 20% in the hardest-hit countries. At present, young people represent the fastest-growing cohort of new HIV infections globally, accounting for roughly 40% of new HIV infections among people aged 15 and over in 2007; over 5 million young people are currently living with HIV, and more than 5,000 young people between the ages of 15 and 24 years are newly infected every day. These global figures likely underestimate the total burden of HIV borne by young people, as there has been no systematic evaluation of the numbers of youth who are long-term survivors of perinatal infection.

The previously held belief that long-term survival of perinatally infected children is exceptional has recently been challenged. New programmatic evidence and estimations of the effect of HIV on child mortality show that up to 13% of perinatally infected children may survive until 10 years of age, the majority of whom present to health services with signs and symptoms of chronic HIV infection. Given that the global scale-up of prevention of mother-to-child transmission (PMTCT) programs, especially in high-burden countries, has occurred only in the last decade, it is likely that this cohort may contribute significantly to the estimates of young people living with HIV. Despite dedicated efforts to scale up HIV prevention, it is likely that the numbers of youth living with HIV will continue to increase. This is due to continued transmission of HIV (i.e., via mother-to-child transmission, sexual transmission, and injection drug use), the increasing long-term survival of HIV-positive children and young people due to investments in and roll-out of pediatric HIV care and treatment programs globally, and the challenges of scaling up successful prevention strategies for young people.

The current estimates of young people living with HIV do not, however, reflect the unequal regional burden of disease or the underlying national and regional drivers of the pandemic: sub-Saharan Africa is home to almost two-thirds of all young people living with HIV, followed by Asia. In Eastern Europe and Central Asia, young people account for the largest proportion of the overall...
number of HIV infections, where nearly half of the people living with HIV are younger than 25 years (see Table 1).³

While historical data point to unprotected heterosexual sex and mother-to-child transmission (MTCT) as the primary drivers of the HIV epidemic in sub-Saharan Africa, there is increasing documentation of both noninjection and injection drug use, and related HIV risk and transmission.⁸⁹ It is unclear, however, to what degree this affects young people living in sub-Saharan Africa. The centrality of high-risk behaviors, such as noninjection and injection drug use, commercial sex work, and unprotected sex between men, is especially evident in the HIV epidemics of Asia, Eastern Europe, and Latin America.

Given the significance of young people in the global HIV pandemic, the past decade has seen an increased focus on articulating key goals and commitments by the global community to address youth in the context of HIV.

While promising steps have been made toward achieving the Millennium Development Goals and UN General Assembly Special Session on HIV/AIDS prevention targets for comprehensive, correct knowledge of HIV and the use of condoms during high-risk sexual activity, efforts to systematically address the care and treatment needs of HIV-positive youth have been largely absent from global and national programming.³¹⁰ Despite young people’s increased risk of HIV infection and the commitment of the international community to address this vulnerable population, the needs of young people are often overlooked when national HIV/AIDS strategies are designed and implemented.³¹³ Where youth-centered national policies do exist, implementation challenges often negatively impact their operationalization at the service delivery level.³¹⁴

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**Table 1. Global Epidemiology of HIV Infection in Young People**

<table>
<thead>
<tr>
<th>Main Modes of Transmission</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asia and Pacific</td>
<td>IDU, SW, MSM</td>
<td>110,000 (18%)</td>
<td>450,000 (79%)</td>
</tr>
<tr>
<td>Eastern Europe (CEE/CIS)</td>
<td>IDU, SW</td>
<td>100,000 (29%)</td>
<td>240,000 (71%)</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>Heterosexual unprotected sex, IDU</td>
<td>47,000 (58%)</td>
<td>35,000 (42%)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>Heterosexual unprotected sex, MTCT</td>
<td>2,500,000 (78%)</td>
<td>780,000 (24%)</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>MSM, heterosexual sex</td>
<td>140,000 (33%)</td>
<td>280,000 (67%)</td>
</tr>
<tr>
<td>South Asia</td>
<td>Heterosexual sex, IDU, SW, MSM</td>
<td>270,000 (38%)</td>
<td>440,000 (62%)</td>
</tr>
<tr>
<td>Totals</td>
<td>3,167,000 (57.4%)</td>
<td>2,225,000 (40.7%)</td>
<td>5,321,000</td>
</tr>
</tbody>
</table>

CEE = Central and Eastern Europe; CIS = Commonwealth of Independent States; IDU = injection drug use; SW = sex work; MSM = men who have sex with men; MTCT = mother-to-child transmission

Source: Adapted from United Nations Children’s Fund (UNICEF).³
GLOBAL GOALS ON YOUNG PEOPLE AND HIV

The need to give specific attention to young people has already been endorsed by governments in a range of international forums, including the five-year follow-up to the Cairo International Conference on Population and Development (ICPD+5), the Millennium Summit, the 2001 United Nations (UN) General Assembly Special Session on HIV/AIDS and its five-year review, as well as the 2002 UN General Assembly Special Session on Children and the 2002 Youth Employment Summit. Specific targets have been agreed on to reduce global HIV prevalence among young people by 25% by 2010. Beyond this, the 2001 UN General Assembly Special Session on HIV/AIDS committed to ensuring that by 2010, at least 95% of young men and women should have access to the information, education, and youth-specific services necessary to reduce their vulnerability to HIV infection.11 Regarding the path to achieving these goals, the declaration from the 2006 UN High-Level Meeting on AIDS explicitly urges heads of governments and their representatives to “commit ourselves to addressing the rising rates of HIV infection among young people to ensure an HIV-free future generation through the implementation of comprehensive, evidence-based prevention strategies, responsible sexual behavior, including the use of condoms, evidence- and skills-based, youth-specific HIV education, and the provision of youth-friendly health services.”12

In many settings, young people encounter significant obstacles to accessing health-related information and services. Legal barriers, such as laws regarding age of consent, may prevent many young people from accessing services such as voluntary counseling and testing (VCT).15 A review of access to HIV counseling and testing services for youth in developing countries revealed that the legal age of consent is often set at the age by which the majority of youth are already sexually active. Oftentimes, criteria such as pregnancy, marriage, or sexual activity may “emancipate” the minor for purposes of consent.16 Further, while some countries, such as Brazil and Uganda, allow medical professionals to provide care to clients under the age of medical consent if health-care workers deem the service in the best interest of the young person, this is not the norm. This exclusion is compounded by the fact that youth are disproportionately poor and unemployed and, thus, often lack a voice to make their interests and concerns known to policymakers.17 Case studies have shown that due to their age and cultural barriers, young people may be denied access to the full range of information and services needed to protect themselves against infection. Where services do exist, youth are often discouraged from utilizing these services due to poor treatment by facility staff and the judgmental attitudes of health providers.18-20 In addition, youth often hesitate to access services close to their homes out of fear of inadvertently encountering family or community members.21

Given the centrality of young people in the global HIV pandemic, halting the spread of HIV will require the implementation of a more robust, systematic, and evidence-based approach to care and support for young people at risk of and living with HIV, with key attention to overcoming the barriers to access and utilization of health services by young people. The challenges of providing youth-centered
HIV services require a strategic country-specific approach that is inclusive of young people in terms of both coverage and acceptability. While a significant body of evidence has been generated over the past decade on programming for young people, this has been largely limited to sexual and reproductive health services. Key lessons can be gleaned from this large body of work, but without adequate implementation and evaluation of this body of work as it relates to HIV, it is uncertain to what degree these lessons will be able to inform programming for HIV-positive young people. In light of the vital importance of a multi-sectoral response to HIV for young people, this chapter will focus on the contributions of the health sector in addressing HIV and AIDS among this often invisible population affected by the HIV and AIDS pandemic.

**PATTERNS OF INFECTION**

In addition to understanding the type of HIV epidemic and its drivers, it is also important to understand how the mode of HIV transmission may affect both clinical and individual responses to care and treatment services. Vertically infected youth have unique clinical and programmatic challenges that are reflective of many other chronic illnesses. There is evidence from cohorts of perinatally infected children in the United States, and emerging evidence from Africa, that not all perinatally infected children experience rapid deterioration of clinical status, and that many will survive into adolescence, presenting with signs of chronic infection such as failure to thrive, delayed puberty, or recurrent respiratory tract infections, skin complaints, and diarrhea. Perinatally infected youth who have been on long-term antiretroviral therapy (ART) are more likely to be in advanced stages of HIV disease and immunosuppression; have a history of opportunistic infections (OIs) with complications or disabilities; have a significant antiretroviral (ARV) exposure history, associated drug resistance, and sequelae of long-term ART (e.g., lipodystrophy, etc.); require combination ART to control viremia; and have a greater dependency on caregivers due to physical and developmental disabilities with resulting greater difficulty in achieving functional autonomy. Innovative evidence from a recent study of perinatally infected adolescents aged 15 to 19 in Uganda who were aware of their HIV status provided key insights into the sexual and reproductive needs of this unique population. The study results revealed that many of these young people were dating, and the majority who were not currently parents had the desire to have children later in life. Approximately 33% of interviewed youth had had intercourse, and 39% were in a serodiscordant relationship; only 44% of sexually active youth were using some form of contraception on a regular basis. In addition, of those youth in relationships, 62% had never discussed their HIV serostatus with their current partner and 67% did not know the HIV status of their current partner. This research, the first of its kind, underscores the imperative to move programming for vertically infected youth beyond the medical model to support young people in navigating their sexual and reproductive health needs responsibly.

In contrast, young people infected horizontally through high-risk behaviors (e.g., unprotected sex, sex work, injection drug use) are more likely to be in earlier stages of HIV disease, more likely to have fewer complications of OIs, less likely to require ART, and more likely to achieve functional autonomy. In addition, studies of horizontally infected youth in the United States and Europe have demonstrated a significant immunologic reserve, which indicates that they may have a fuller response to ARV or immune-based therapies, compared to that seen in adults.
In working to promote the health of young people worldwide, it is also crucial to recognize that not all young people are the same. Young people’s experiences vary according to their age, gender, marital status, school status, and socioeconomic status, among other variables.

**Age and Developmental Differences**

Adolescence, commonly divided into three general stages (i.e., early, middle, and late), is a developmental phase defined by a variety of physical, cognitive, and psychosocial changes (Table 2). Physical development refers to the process of puberty and the acquisition of physical maturity. Cognitive development refers to the transition from concrete thinking to more abstract thought. Psychosocial development refers to a variety of tasks, including separation or independence from family, and the achievement of educational or vocational goals.

**Gender Differences**

Gender plays an integral role in determining a young person’s vulnerability to HIV infection and his or her ability to access care, support, or treatment. Global data have shown that more than half of all young people aged 15–24 living with HIV are women. Research has demonstrated that HIV prevalence in young women in certain settings is up to six times that in sexually active men aged 15–19 and up to three times that in men aged 20–24. The heightened biological susceptibility of young women (e.g., immaturity of the genital tract in young girls) and higher prevalence of ulcerative sexually transmitted infections such as herpes simplex virus type 2 in young women can account for some of this increased vulnerability. While there has been progress in achieving many global goals for prevention among young people, a gender differential still places many young girls at higher risk due to lower levels of comprehensive knowledge about HIV and a lower percentage of condom use as compared to same-age boys. The influence and contribution of structural inequities cannot be underestimated as a significant contributor to the risk of HIV acquisition in young women. Gender norms often dictate that women and girls be ignorant and/or passive about sex, which greatly constrains their ability to negotiate safer sex or access appropriate services. Similarly, gender norms often cast women as being primarily responsible for reproductive and productive activities within the home, in contrast to men, who are often cast as the primary economic actors and producers outside the home. Such gender stereotypes can result in young women having much less access than young men to key resources such as education, income, and employment; this significantly reduces their power to negotiate the use of protection (i.e., condoms) with their partners and their ability to access care, treatment, and support services.

**Marital Status Differences**

Globally, there have been declines in early marriage (prior to 18 years of age) for young women, but the number of girls married by the age of 18 is still substantial. While the numerous negative consequences of early marriage for adolescent girls have been well documented, the needs of married adolescents have been largely neglected by HIV researchers and programmers, despite the fact that they represent a sizable proportion of adolescents at risk for HIV. This is partly because the adolescent policy and programming agenda, in its brief history, has been framed by the priorities and cultural experience of developed countries, where the proportions of married adolescents are relatively low. However, new research indicates that in most of the 26 countries worldwide that collect data on sexual activity among married and unmarried adolescents, the majority of sexually active girls between the ages...
of 15 and 19 years are married. Of equal or greater relevance to the spread of HIV is the fact that sex within marriage in these countries is overwhelmingly unprotected. For example, across the 26 countries, 80% of unprotected sexual encounters among young people occurred within marriage. Married adolescents are also more likely to have older partners, who in turn are more likely to be HIV-positive as reflected in a study conducted in Kisumu, Kenya, in which 30% of male partners of married adolescent girls were HIV-positive, while only 11.5% of the partners of unmarried girls were HIV-positive.

<table>
<thead>
<tr>
<th>Table 2. Stages of Adolescence</th>
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<tbody>
<tr>
<td><strong>Category of change</strong></td>
</tr>
<tr>
<td>10–13 to 14–15 years</td>
</tr>
<tr>
<td><strong>Growth</strong></td>
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<td></td>
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<tr>
<td><strong>Cognition</strong></td>
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<tr>
<td><strong>Psychosocial</strong></td>
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<td></td>
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<tr>
<td><strong>Family</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Peer group</strong></td>
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<td></td>
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<td></td>
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<tr>
<td><strong>Sexuality</strong></td>
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</table>

Source: Adapted from World Health Organization (WHO), Commonwealth Medical Association Trust, and UNICEF.
School Status Differences
School is the institution, aside from the family, that plays the most important role in the socialization of the young and also has the power to influence the behavior of young people both directly and indirectly. For example, research in a variety of developing-country settings has shown that adolescents who are not in school are much more likely to engage in risky sexual behavior. Further, studies show that young people who are already sexually active and enrolled in school are much more likely to use contraceptives and condoms than are sexually active young people who are not in school.
There are multiple pathways by which the school can influence young people's behaviors, and more research is needed to clearly reveal these trajectories. For instance, it may be that the school creates a safe and supportive environment for young people, where they are free from the exploitation and abuse that they may face at home. It may also be that school is the one place where young people learn about HIV and the behaviors that transmit HIV through the implementation of life skills-based education. However, as some studies suggest, it could also be that poverty is the underlying factor that exacerbates young people's vulnerability to HIV, and that those who are poor are simply less likely to be in school.

FRAMEWORK FOR A COMPREHENSIVE RESPONSE
An effective and comprehensive response for the prevention and treatment of HIV among young people requires commitment from all sectors of the national government. It is imperative that youth be included in the development and implementation of national policies, guidelines, and training materials. In addition, government commitment is required to ensure that adequate resources (financial, human, etc.) are dedicated to address the need for youth-friendly HIV-related services and activities.

Adults such as community leaders and caretakers often serve as the gatekeepers for access to health and other services for young people. For young people to adequately access HIV-related information and services, dedicated efforts to mobilize community support for these services are needed.

There is also an urgent need for accurate, relevant, age- and developmentally appropriate, and nonjudgmental health information targeting young people. This material can support increased treatment literacy, promote HIV counseling and testing, support behavior change, and provide information for parents, caregivers, and guardians of youth infected and affected by HIV. This represents an important opportunity to engage other sectors in this effort. While the health sector can lead the development of facility-based information, education, and communication material, other sectors, such as education, the media, and the community, can play a key role in these efforts due to their frequent interaction with young people.

The Health Sector Response: Youth-Friendly Services
To be effective in preventing and treating HIV among young people, the health sector must carry out three important tasks: (1) provide youth-friendly health services; (2) mobilize and offer technical support to other sectors of the government and civil society; and (3) collect, analyze, and disseminate information about the spread of HIV among young people.

There is no one-size-fits-all approach to providing health services to young people. There are some guiding principles, such as linking prevention and care, linking HIV services with services relating to other adolescent sexual and reproductive health problems and interventions, and making existing services more responsive to the specific needs of young people. However, different
interventions and delivery strategies are likely to be needed to provide prevention and care services in different types of epidemics, and specific outreach strategies will usually be necessary for reaching the adolescents and youth most at risk. In addition, it is essential to ensure adequate referral systems within the health sector (from VCT to clinics, from clinics to hospitals, from general practitioners to specialized services, etc.) and between the health sector and other sectors and organizations.

Regardless of the country or cultural setting, one of the key ingredients that has been shown to be effective in providing health services to young people is ensuring that they are youth- or adolescent-friendly.

Defining Youth- or Adolescent-Friendly Health Services

There are many variations of the definition of adolescent- or youth-friendly health services. Simply stated, “Adolescent-friendly health services have policies and attributes that attract adolescents to the facility or program, provide a comfortable and appropriate setting for adolescents, meet the needs of adolescents, and are able to retain their adolescent clientele for follow-up and repeat visits.”

For services to be considered “youth-friendly,” the World Health Organization (WHO) has agreed upon a set of overarching characteristics:

- **Accessible and equitable.** All adolescents are able to use the services if they wish. All the essential health services that adolescents need are being provided in ways that make it possible for all adolescents to use them.
- **Acceptable.** Adolescents are willing to use the services that are available. Health workers and health facility staff are trained to provide services to young people in a way that is respectful and that ensures client privacy and confidentiality.
- **Appropriate.** Health services at the point of service delivery meet the needs of adolescent clients. If an adolescent client seeks help for the management of a sexually transmitted infection and these services are not being provided, the point of service delivery is not meeting the individual’s needs.
- **Effective.** The services make a difference in improving the health of adolescents. The necessary skills, equipment, and supplies are in place to provide quality services for adolescents.

Table 3 provides a detailed list of youth-friendly characteristics that are essential for every health facility or program that intends to reach out to adolescents. They are organized according to the five broad characteristics listed above.

Models of Youth-Friendly Services

While there is little documentation of youth-friendly HIV care and treatment services, significant work by national governments and local and international partners has focused on the implementation and evaluation of youth-friendly sexual and reproductive health services, and many of these lessons learned may be applicable in programming for HIV-positive youth. Youth-friendly services can be provided in a variety of contexts, including specialized adolescent health centers, community-based health facilities (including stand-alone units or adolescent corners and providers), school-based health services, community-based centers (which may offer other services such as health information, recreation, or help with literacy or mathematical skills), pharmacies and shops, and outreach services for marginalized young people.

While there are several different models for youth-friendly services, not all are cost-effective, and not all increase service utilization. In reality, there is no imperative to creating parallel systems and facilities. The global consensus is that the greatest benefit comes from improving existing health services in local...
In line with this recommendation, HIV services for young people can be integrated into pediatric clinics, adult clinics, or, where resources are available, stand-alone clinics (Box 1). While pediatric HIV care models are often family-centered (i.e., care is offered in a discreet, child-friendly manner), teen services are generally seen as supplemental to existing services. The issue of HIV status disclosure, and young people’s right to confidentiality and/or consent, is a key issue in the treatment of adolescents. Services

### Table 3. Essential Characteristics of Youth-Friendly Health Services

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EQUITABLE:</strong> Services are provided to all people who require them.</td>
<td></td>
</tr>
<tr>
<td>Policies and procedures do not restrict the provision of services.</td>
<td>There are no policies or procedures that restrict the provision of health services to adolescents on the basis of age, sex, social status, cultural background, ethnic origin, disability, or any other area of difference.</td>
</tr>
<tr>
<td>Health-care providers and support staff treat all adolescent clients with equal care and respect, regardless of status.</td>
<td>Health-care providers and support staff administer the same level of care and consideration to all adolescents, regardless of age, sex, social status, cultural background, ethnic origin, disability, or any other difference.</td>
</tr>
<tr>
<td><strong>ACCESSIBLE:</strong> Ready access to services is provided.</td>
<td></td>
</tr>
<tr>
<td>Policies and procedures ensure that health services are either free or affordable to adolescents.</td>
<td>All adolescents are able to receive health services free of charge or are able to afford any charges that might be in place.</td>
</tr>
<tr>
<td>The point of service delivery has convenient working hours.</td>
<td>Health services are available to all adolescents during times of the day that are convenient to them.</td>
</tr>
<tr>
<td>Adolescents are well informed about the range of reproductive health services available and how to obtain them.</td>
<td>Adolescents are aware of what health services are being provided, where they are provided, and how to obtain them.</td>
</tr>
<tr>
<td>Community members engage in respectful and participative discussion with health-care providers, creating a shared understanding of adolescent health and development and increased support for reproductive health service provision.</td>
<td>Community members (including parents) are well informed about how the provision of health services could help their adolescents. They support the provision of these services as well as their utilization by adolescents.</td>
</tr>
<tr>
<td>The provision of health services by selected community members, outreach workers, and peer-to-peer educators is implemented in a way that effectively reaches adolescents.</td>
<td>Efforts are made to provide health services in close proximity to where adolescents are located. Depending on the situation, outreach workers, selected community members (e.g., sports coaches), and adolescents themselves may be involved in these efforts.</td>
</tr>
</tbody>
</table>
### Table 3. Essential Characteristics of Youth-Friendly Health Services (cont.)

**ACCEPTABLE:** Care meets the expectations of the people who use the services.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policies and procedures guarantee client confidentiality.</td>
<td>Policies and procedures maintain adolescent confidentiality at all times (except where staff are obligated by law to report incidents—such as sexual assaults, road traffic accidents, or gunshot wounds—to the relevant authorities). Policies and procedures address the following:</td>
</tr>
<tr>
<td></td>
<td>- Registration—information on the identity of the adolescent and the presenting issue or complaint is gathered in confidence</td>
</tr>
<tr>
<td></td>
<td>- Consultation—confidentiality is maintained throughout the visit at the point of delivery (i.e., before, during, and after a consultation)</td>
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<td></td>
<td>- Record keeping—case records are kept in a secure place, accessible only to authorized personnel</td>
</tr>
<tr>
<td></td>
<td>- Disclosure of information—staff do not disclose any information given to or received from an adolescent to a third party (e.g., family members, school teachers, or employers) without their consent</td>
</tr>
<tr>
<td>The point of service delivery ensures privacy.</td>
<td>The point of service delivery is located in a place that ensures the privacy of adolescent users. Its layout is designed to ensure privacy throughout an adolescent's visit. This includes the point of entry, the reception area, the waiting area, the examination area, and the patient-record storage area.</td>
</tr>
<tr>
<td>Health-care providers are nonjudgmental, considerate, and easy to relate to.</td>
<td>Health-care providers do not criticize their adolescent patients even if they do not approve of their words or actions. They are considerate to their patients and reach out to them in a friendly manner.</td>
</tr>
<tr>
<td>The point of service delivery ensures that consultations occur within a short waiting time, with or without an appointment, and that referrals (where necessary) are provided swiftly.</td>
<td>Adolescents are able to consult with health-care providers at short notice, regardless of whether they have a formal appointment. If their medical condition requires that they be referred elsewhere, the referral appointment should also take place within a short time frame.</td>
</tr>
<tr>
<td>The point of service delivery has an appealing and clean environment.</td>
<td>The point of service delivery is welcoming, attractive, and clean.</td>
</tr>
<tr>
<td>The point of service delivery provides information and education through a variety of channels.</td>
<td>Informational materials that are relevant to the health of adolescents are available in different formats (e.g., posters, booklets, and leaflets). They are presented in a familiar language, are easy to understand, and are eye-catching.</td>
</tr>
<tr>
<td>Adolescents are actively involved in the assessment and provision of health services.</td>
<td>Adolescents are given the opportunity to share their experiences in obtaining health services and to express their needs and preferences. They are involved in certain appropriate aspects of health service provision (e.g., peer education).</td>
</tr>
</tbody>
</table>
Table 3. Essential Characteristics of Youth-Friendly Health Services (cont.)

**APPROPRIATE:** Required care is provided, and unnecessary and harmful care is avoided.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>The required package of health care is provided to reflect and fulfill the individual needs of all adolescents, either at the point of service delivery or through referral linkages.</td>
<td>The health needs and problems of all adolescents are addressed by the health services provided at the point of delivery, or through referral linkages. The services provided meet the special needs of marginalized groups as well as the general population.</td>
</tr>
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</table>

**EFFECTIVE:** Care produces positive change in the health status or quality of life of the client.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health-care providers have the required competencies to work with adolescents.</td>
<td>Health-care providers have the required knowledge and skills to work with adolescents and to provide them with the required health services.</td>
</tr>
<tr>
<td>Health-care providers use evidence-based protocols and guidelines.</td>
<td>Health service provision is based on protocols and guidelines that are technically sound and of proven usefulness. Ideally, they should be adapted to the requirements of the local situation and approved by the relevant authorities.</td>
</tr>
<tr>
<td>Health-care providers are able to dedicate sufficient time to deal effectively with their adolescent clients.</td>
<td>Health-care providers allow for sufficient time to deal with their adolescent clients.</td>
</tr>
<tr>
<td>The point of service delivery has the required equipment, supplies, and basic services necessary to deliver the essential care package.</td>
<td>Each point of service has the necessary equipment, supplies (including medicines), and basic services (e.g., water and sanitation) needed to deliver the health services for which it is required.</td>
</tr>
</tbody>
</table>

Source: WHO.40

for young people are often provided in the context of adult clinics, where providers do not have specific training in the care of young patients. Since these adult clinics tend to be quite large, newly diagnosed young people and those transitioning from pediatric care can often “slip through the cracks.”

**Key Considerations for Implementing Youth-Friendly Health Services**

When developing youth-friendly services for the prevention and treatment of HIV among young people, it is important to take a number of factors into consideration.

In any given community, it is important to recognize differences among young people and to be prepared to adjust programming to respond to these differences. Age, gender, marital status, and socioeconomic status often influence how health services are accessed and used by young people. While global data show that there are lower levels of investment in the health, nutrition, and education of young girls, multicountry service utilization data on youth-friendly reproductive health services indicate that young women aged 19 to 24 are more likely to visit government facilities than are young men; young men aged 20 to 24 utilized services more than
**Box 1. Service Delivery Models for Youth-Friendly Services**

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult clinics</strong></td>
<td>In Colombia, PROFAMILIA (Asociación Pro-Bienestar de la Familia Colombiana) began basing youth-friendly services inside adult clinics after dedicated youth facilities proved costly and difficult to sustain. PROFAMILIA now offers youth-friendly services in 35 cities and towns across Colombia. Where young clients are numerous, managers set aside space and assign personnel exclusively for young people. Elsewhere, young people share clinic space and providers with adult clients. Regardless of the service model, all staff members are trained on young people’s special reproductive health and family planning needs.</td>
</tr>
<tr>
<td><strong>Youth clinics</strong></td>
<td>The Pediatric Infectious Disease Clinic at Mulago Hospital in Kampala, which is managed by the Baylor-Uganda Children’s Foundation, cares for more than 5,000 children and adolescents. Following a needs assessment in 2003, an outpatient adolescent HIV clinic was established; it now cares for over 800 HIV-positive young people between the ages of 12 and 24, the majority of whom were infected through MTCT. Young people are seen on designated days of the week and benefit from comprehensive health services that include sexual and reproductive health services and a robust psychosocial support program that is designed to address the needs of early, middle, and late adolescence (S. Kitaka, e-mail communication, June 12, 2008). The Health and Education Alternatives for Teens (HEAT) Program, established in 1992 with funding from the New York State Department of Health AIDS Institute through the Research Foundation of the State University of New York, is the only program of its kind in Brooklyn, New York, to offer comprehensive medical care, supportive services, and access to clinical research for HIV-positive and at-risk youth aged 13 to 24. HEAT provides age- and developmentally appropriate, culturally competent care for heterosexual, lesbian, gay, bisexual, and transgender black and Latino youth. The full-service clinic embraces a philosophy of “one-stop shopping,” where all HIV-related care is provided by an interdisciplinary team, eliminating the barriers that youth often face when trying to access health care. HEAT’s adolescent-focused model puts the young person in the center of his or her care and involves the client in all decisions about his or her treatment and other services. The program supports both on-site and outreach HIV counseling and testing, outpatient medical care, and mental health and case management, and emphasizes transition to adulthood by helping young people build the necessary life skills to maximize their potential to live productive lives. These include financial skills such as budgeting, skills for independent living (housing, education, and career), knowledge and responsibility for health care, social skills, developing a social network, responsible sexual behavior, and the ability to use community resources (J. Birnbaum, e-mail communication, May 22, 2008).</td>
</tr>
<tr>
<td><strong>Youth corners</strong></td>
<td>In Zimbabwe, the Family Planning Service Expansion and Technical Support (SEATS) project collaborated with the Gweru City Council to establish youth corners at adult clinics. These spaces were located away from the busiest parts of the clinic to give young people a private place to talk with peer educators and to read informational materials. Peer educators could refer young people who wanted clinical services to nurses who were specially trained in youth-friendly services.</td>
</tr>
</tbody>
</table>
### Box 1. Service Delivery Models for Youth-Friendly Services (cont.)

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Social franchising</td>
<td>In Madagascar, a franchised network of more than 120 private youth-oriented clinics offers young people family planning and sexually transmitted infection services, and in some cases HIV/AIDS counseling and testing. TOP Réseau franchise members share a brand name and business strategy. Flexible hours, discreet locations, inviting surroundings, and subsidized fees help make the clinics youth-friendly, while special training, job aids, on-site supervision, and regular monitoring ensure good quality of care.45,46</td>
</tr>
<tr>
<td>Workplace clinics</td>
<td>In Bangladesh, adolescent girls make up most of the workforce at many garment and fish-processing factories. Teams of providers from the Marie Stopes Clinic Society offer family planning, antenatal care, and treatment of sexually transmitted infections and gynecological problems along with health education at over 140 of these factories; employers subsidize the cost of services.47</td>
</tr>
<tr>
<td>Outreach services for disadvantaged, displaced, and marginalized young people</td>
<td>The Uganda Youth Development Link (UYDEL) offers services such as family planning, treatment of sexually transmitted infections, and HIV counseling and testing to street children and adolescent sex workers at conveniently located drop-in centers and mobile outposts. Teams of health providers make weekly visits to the outposts, which are placed at clubs, restaurants, and other places where youth congregate.48,49</td>
</tr>
<tr>
<td>Youth-friendly retail outlets</td>
<td>Cities across Mexico are replicating the youth-friendly pharmacies pioneered in Guanajuato, Mexico, by the Centro Latinoamericano para Salud y Mujer (CELSAM). The project trained pharmacy staff on adolescent reproductive health, stocked the pharmacies with posters and informational materials, and promoted the youth-friendly outlets in schools, cafés, bars, and discos, as well as via a telephone hotline and a Web site.50</td>
</tr>
<tr>
<td>Multipurpose youth centers</td>
<td>Youth centers offer recreational and vocational activities such as games, movies, and computer training, along with information, counseling, and services on pregnancy prevention and the prevention and diagnosis of sexually transmitted infections, including HIV. Program evaluations in Latin America and sub-Saharan Africa, however, have cast doubt on their sustainability and cost-effectiveness. Most young people use youth centers for recreation rather than services; those using services tend to be older, and recreational activities raise costs.51,52</td>
</tr>
</tbody>
</table>

Source: Kols.53

Young men aged 15 to 19, with the youngest age groups (10 to 14) having the fewest visits.54–56 The traditional location of these services within maternal and child health clinics may explain some of these differences.

Subpopulations of young people, such as out-of-school youth; street youth; youth using drugs or alcohol; gay, lesbian, bisexual, and transgendered youth; sex workers; and youth with mental and physical disabilities, may tend to engage in behaviors that put them at higher risk for pregnancy, sexually transmitted infections, and HIV infection. Specific strategies, which may include the implementations of both static facilities and outreach campaigns, are required to reach these groups with information and services.57
C HILDREN LIVING WITH HIV struggle with many psychosocial issues that could be effectively dealt with through competent basic counseling and support. While psychosocial support is commonly mentioned as an important component of comprehensive care for children living with HIV infection, it is often vaguely defined, given lip service, or perceived as an “add-on” activity. In addition, there has been a lack of training curricula and job aids to enable health-care workers to provide meaningful psychosocial support to children in need.

A number of issues affect children’s psychological and social well-being. As parents and caregivers, we often misread children’s attempts at communicating intense feelings and worries, and in the process children’s voices go unheard or are misunderstood. Many children do not know their HIV status; receive conflicting messages about their chronic health-care needs; and are dealing with parents’ deaths, property grabbing, stigma, and discrimination. This breakdown in communication can affect a child’s ability to trust and develop positive self-esteem as well as his or her confidence and ability to problem solve. To address this gap, a new psychosocial care and counseling training program has been developed and field-tested in a number of African countries by CRS AIDSRelief, a President’s Emergency Plan for AIDS Relief (PEPFAR)–funded care and treatment program.

Special Considerations for HIV-Positive Young People and Those Most at Risk of HIV Infection

Sexual and Reproductive Health

The further development of youth-friendly health services in resource-limited settings must address the unmet reproductive and sexual health needs of young people. Efforts are increasingly focused on ways to provide youth-friendly HIV care together with youth-friendly sexual and reproductive health services. When these services are combined, youth can receive the full spectrum of care required to both prevent and treat HIV and other sexually transmitted infections, while other important issues such as reproductive health and PMTCT for young mothers are addressed as well.

Psychosocial Support

Numerous factors contribute to the psychological health of HIV-positive children and adolescents. First and foremost is the challenge of managing a serious and at times life-threatening chronic illness within the context of the already demanding developmental tasks and changes associated with adolescence. Most adolescents with chronic illnesses face the constant threat of their illness interfering with their psychosocial as well as physical development. Taking medications on a regular schedule, a task so important to the control of their infection, becomes an additional challenge, as many children and adolescents whose families may have been disrupted by the illness end up living with surrogate caregivers who may not understand the importance of adherence to therapy.
This may be compounded by frequent changes in living environments and conditions.

Second, there is the inherent stigma of the disease for both the patient and his or her family. This is most clearly evidenced in the constant struggle these patients and families face surrounding the issue of disclosure. This can be a challenge both within the family and outside the family. “Who should know?” and “How much should they know?” are common questions asked by families. Children and adolescents living with HIV face enormous stigma, and the range of reactions resulting from this stigma can have serious, long-lasting impacts on their lives. For example, many children have been disowned and isolated by their family members and friends, marginalized by those closest to them in life because of their HIV-positive status. Often stigma arises from a lack of knowledge regarding how the disease was contracted and how it may be transmitted. To avoid unintended disclosure, many youth resort to hiding medications from family members and disguising the true intent of their medical appointments. The demands of complex drug regimens coupled with the potential side effects are quite burdensome for youth; the need to hide their diagnosis makes the proper management of their health even more challenging.

Parental influence often creates further challenges for youth; many parents do not want their children to know their own status for fear that the children will then know the parents’ HIV status. Many parents experience a profound sense of guilt for transmitting the virus to their child or for not protecting the child.

This course is meant to be adapted and modified to fit the local context and priority needs of local health-care workers and counselors. For example, in the first training conducted in Zambia, the curriculum was adapted to include time for the creation of simple tools to improve communication with children, such as dolls, puppets, modeling clay, rattles, and mobiles, as these were not commonly available in the clinic setting. Also, a job aid on the benefits of disclosure was developed through group work and made into a handout for each participant.

Participants have described the course as “an eye-opener” and as “a milestone in my life!” as they learned to help children tell their stories and make their own decisions. When asked about specific skills gained, people expressed simply, “how to say it,” “talking with rather than to children,” “speaking the language that the children are familiar with,” and “active listening with the eyes, ears, and heart!”

Developed as a two-week training program entitled “Psychosocial Care and Counseling for HIV Positive Children and Adolescents,” the course includes a series of modules as well as an accompanying video. The 14 modules cover key topics such as child development, family systems, communicating with children, disclosure, and adherence, as well as legal and ethical issues. The video, developed for educational purposes only, includes actual sessions with HIV-positive children and adolescents as they work through difficult issues such as disclosure, stigma, and sexual abuse. The course explores and challenges common barriers to pediatric care and treatment (such as caregivers’ fear and reluctance to disclose an HIV-positive diagnosis to a child), discussing adolescent sexuality and practical issues such as inadequate legislation governing the rights of children.

In partnership with the African Network for the Care of Children Affected by HIV/AIDS (ANECCA),

Developed as a two-week training program entitled “Psychosocial Care and Counseling for HIV Positive Children and Adolescents,” the course includes a series of modules as well as an accompanying video. The 14 modules cover key topics such as child development, family systems, communicating with children, disclosure, and adherence, as well as legal and ethical issues. The video, developed for educational purposes only, includes actual sessions with HIV-positive children and adolescents as they work through difficult issues such as disclosure, stigma, and sexual abuse. The course explores and challenges common barriers to pediatric care and treatment (such as caregivers’ fear and reluctance to disclose an HIV-positive diagnosis to a child), discussing adolescent sexuality and practical issues such as inadequate legislation governing the rights of children.
from other causes of infection (e.g., sexual abuse). Furthermore, the child becomes responsible for maintaining the secrecy regarding who in the family is HIV-positive. The secrecy and lack of family discussion regarding HIV has further implications as these children reach puberty and begin dating. In many cultures, sex and sexuality are not discussed within the family, which means youth are not getting information regarding ways they can engage in normal adolescent development as a responsible, HIV-positive adolescent. These overwhelming factors can lead to depression, further impacting adherence to treatment regimens and medical care. Unfortunately, these youth have few if any opportunities to sort through the challenges related to being HIV-positive, since in many resource-constrained settings, mental health services are either unavailable or under-resourced.

Transitions to Adolescent and Adult Care and Treatment Services

Transitioning, as it relates to HIV-positive young people moving to adult care settings, can be defined as the purposeful, planned movement of adolescent and young adults with chronic physical and medical conditions from child/adolescent-centered to adult-oriented health care systems.

—Miles et al

Transitioning to adult services poses many challenges for young people living with HIV. The higher patient load typical of adult care settings is often accompanied by decreased time with health-care workers, which can negatively impact the development of the personal bonds and trust that are critical for young people. The loss of trusting relationships with health-care workers in pediatric/adolescent clinics can be compounded by the lack of youth-friendly skills of many providers in adult services. New service locations, exposure to diverse patient populations in adult services, and the challenges of increased responsibility for their own health can pose significant barriers to successful transitions.

While there is a lack of robust evidence to outline the ideal time and best models for transitioning HIV-positive young people to adult-oriented services, several principles derived from experience with transitions from other disease programs can help guide this process (Box 2).

Health Service Providers

While the increasing recognition of adolescent medicine as a pediatric subspecialty has increased the ranks of specialized providers in the United States and several European countries, scaling up services staffed by dedicated service providers for young people is not feasible in most resource-limited settings. Therefore, a variety of service providers at multiple levels of the health system need to be engaged and oriented to provide high-quality and effective HIV prevention, care, and treatment services for young people. Consideration should be given to government health workers at all levels, those providing services for young people through nongovernmental organizations, private practitioners, and community caregivers (including traditional healers). In addition, youth should have a role in the planning, support, and promotion of these services, to ensure buy-in and relevance to the target population, and to partially relieve the burden on overstretched staff.

Research from both developing and developed countries indicates that the most important factors cited by young people as real or perceived barriers to accessing sexual and reproductive health services are a lack of provider competency and discriminatory attitudes. This is not surprising, given that the basic principles and practices of working with adolescents are not a routine part of health worker preservice and in-service training, leaving providers ill equipped to appropriately address the health issues of young
To address the gap in training materials focused on adolescent issues, various organizations and international bodies have developed training curricula for health-care workers who provide services for young people. These training curricula are intended to increase provider competency in the provision of youth-friendly services and address topics such as normal adolescent development, adolescent sexual and reproductive health, counseling skills (that address provider biases), and clinical care guidelines for young people. In addition, these curricula highlight key issues in working with adolescents.

### Box 2. Key Elements of Transitional Care

**Beginning Early**

When children enter the pediatric service, they should know what to expect and when they can expect to leave it. It is important to understand, however, that transitioning ideally takes place during a stable time when patients are chronologically as well as behaviorally and psychologically ready.

**Fostering Independence**

Many adolescents with chronic conditions are at higher risk than their peers for unnecessary dependency, developmental difficulties, and psychosocial delay. To support increasing autonomy and self-reliance, greater emphasis can be placed on providing opportunities for young people to take an increasingly active role in their health care. New responsibilities can include activities such as self-management, scheduling appointments, refilling medications, finding transportation, and discussing educational and vocational goals. Skills training in areas such as communication, decision making, problem solving, assertiveness, self-care, and self-advocacy can also support the development of autonomy to support successful transitions.

**Transition Planning**

Having a designated professional to help facilitate the transition is invaluable to support the young person and his or her family in making a successful transition. The development of detailed transition plans and an accompanying portable, accessible, medical summary can help ensure a smooth transition between services and health-care providers.

**Partnership with Adult Services**

Partnerships between adult and pediatric/adolescent services can facilitate the successful transition to adult health services. Training programs for adult health-care providers that address transitional care and that provide orientation regarding working with young people is a key element of this partnership. Gradual introduction of young people to adult providers through group visits to the adult clinic and/or joint consultations with adult and pediatric/adolescent providers can also help in this process.

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TRACY’S STORY: LIFE AS AN HIV-POSITIVE TEENAGER

Tracy is a perinatally HIV-infected 15-year-old girl. She is one of seven children. Tracy has been on antiretroviral medications since age six, and failed first-line treatment approximately two years ago. Her biological father does not live in the home full-time, as he travels to find work. Thus, Tracy is responsible for a significant amount of care for her younger siblings, including providing meals and supervision. She has numerous chores to tend to in the home and is expected to help out where needed. Her mother is often delayed in getting home from work, as she must comply with her employer’s requested hours to maintain her job. Tracy and her family live on limited resources; feeding the family can be a day-to-day challenge that often ends in relying on community members for food. Tracy describes herself as a good student; she explains how she is very disappointed when she is unable to attend school, but unfortunately this is a common occurrence.

Tracy is on a twice-a-day dosing schedule, but given the requirements regarding food intake with certain medications and the amount of time that needs to elapse between the two doses, she must wake up at 5:30 a.m. to eat and receive her first dose of medication. Her evening dose begins at 5:30 p.m.; she uses the start of a local TV show to remind her that it is time to take her medication. Tracy explains how she is tired of taking her medications, and the fatigue is overwhelming for her. Through teary eyes she acknowledges how much she misses her father and the role he has played in keeping her motivated to stay on treatment. She talks about being tired of this way of living but not knowing any other way; she often questions whether

with HIV-positive youth, such as the differences between vertically and horizontally infected youth and how these differences influence health-seeking behaviors and clinical needs, disclosure to vertically infected young people, disclosure of HIV status to sexual partners, prevention for positives (including harm-reduction strategies), and the challenges of adherence to care and treatment regimens.

It is important that health providers for youth are prepared and willing to screen for adolescent risk behaviors and age-appropriate developmental curiosities. The clinic visit is a unique opportunity to provide adolescents with accurate health information that they might otherwise not receive. As a part of the education process, it is important to address issues that may be sensitive or difficult for them to talk about, in language that is understandable and adolescent friendly (i.e., the tone should be informative and friendly rather than judgmental). Care providers need to appreciate that adolescents are developing young adults, most of whom will need to manage their health care independently. As such, including them in decisions related to the management of their illness and encouraging independent decision making facilitates their development into responsible adults. This empowerment can have a positive impact on their adherence to medication and compliance with medical appointments. Often caretakers will need to be involved in this process, many of whom will require some reeducation regarding adolescent development and how to deal constructively with the adolescent’s
Tracy continues to display very good immunologic signs in relation to her HIV infection. However, it is clear that there are numerous factors potentially impacting her adherence to treatment and the management of her illness. Likewise, her emotional well-being is strained, and there are no outlets or resources to help her address the numerous psychosocial difficulties present in her life.

Unfortunately, Tracy’s story is not unique. Many teens around the world face very similar circumstances, with limited resources to address them. Adolescent-friendly interventions are increasingly necessary, as vertically infected children are aging into adolescence due to the effectiveness of antiretroviral medications. Adolescent risk behaviors, such as unsafe sexual practices, are yielding more HIV-positive adolescents, and nonconsensual sex is being forced upon young girls. Due to these and other factors, the number of HIV-positive adolescents is increasing worldwide.

Tracy often stays with relatives for varying periods of time, where she is not allowed to let them know her HIV status. Under these circumstances it becomes quite difficult to be adherent to her medication regimen, as she must hide her medications. She struggles with this same issue when staying over with friends. Tracy explains how secrecy is a constant part of her illness management. When it comes to her friends, she does not disclose to anyone. She says she has a boyfriend who does not know her status. When asked whom she talks with about the challenges of being a teenager and trying to manage her social life, she replies that there is no one; conversations about sex are completely off limits. Tracy admits to having sex with her boyfriend but is certain to use condoms each time. She describes her family and the broader culture as a place where sex is almost a taboo subject. “I don’t even tell my doctor about that,” she explains.

Emerging independence. This may include coaching the caretakers about appropriate language to use when talking to their child about sensitive topics such as sex.

A Minimum Package of Services

A growing body of evidence shows that there are a range of services that can be provided through the health system to contribute to the prevention, care, and treatment of HIV among young people.

These services include the following:

- **Information and counseling** to help young people develop the skills needed to abstain from sex, limit their numbers of partners, use condoms correctly and consistently, and strengthen their ability to avoid infection
- **Condoms** for young people who are sexually active and **sterile injecting equipment** for those who are injecting drugs
- **Diagnosis of and treatment for sexually transmitted infections** to decrease HIV infection and to identify individuals who are having unprotected sex so that they can receive HIV counseling and testing
- **HIV testing and counseling**, which is an essential entry point for young people to access HIV-related services
- **Care, support, treatment, and prevention for young people living with HIV and AIDS**
- **Adult male circumcision**, as there is now compelling evidence that male circumcision is protective against HIV transmission from women
to men,† and that it is an important intervention to consider, particularly in countries where there is a high HIV prevalence and a low circumcision rate.‡

In selecting a package of adolescent care services for a particular country, it will be important to have baseline HIV/AIDS data from this group, as well as details on risk behaviors and what types of health services are currently being accessed by young people. Some specific factors to consider in defining the package of services include the following❼:

- The estimated HIV-related morbidity and mortality among the population as a whole, and the share of this burden that falls on adolescents, as well as unhealthy practices adopted during adolescence that could result in morbidity and mortality later in life
- The feasibility and cost of the recommended interventions (especially in the context of going to scale)
- The provision of health services as part of other initiatives to address problems and needs identified (e.g., national programs addressing HIV/AIDS that are not focused on a particular age group)

Each health system will need to select a package of services that reflects the specific needs of the young people in the target setting. In most countries, however, services should include

- information and counseling to reduce risky behavior;
- interventions to reduce the harmful effects of risky behavior; and
- testing, treatment, and care of young people with sexually transmitted infections, including HIV.§

With national and regional considerations in mind, it is important to clearly articulate a comprehensive package of services that is to be provided for HIV-positive young people (see Table 4). While the majority of the elements of the package are identical to services for adults or younger children, providing services in an age- and developmentally appropriate manner and ensuring that the services are responsive to the particular population of young people is critical. In addition, to the degree that it is feasible, providing the convenience of integrated services can help attract and retain young clients.

**Health System Policies and Standards**

**Policies**
The health sector needs to contribute to and disseminate a broad evidence base for effective interventions for HIV prevention and care. However, there are some policy issues that are of specific importance to the provision and use of health services for HIV prevention by young people and that may either facilitate or obstruct access to the services by those who need them. These include policies and laws that restrict the provision of services and commodities to young people, and those that have an impact on young people’s ability to use the services that are provided. For example, policies relating to consent and confidentiality for minors are particularly relevant for those seeking VCT services. It is important that a systematic review of existing laws and policies affecting the provision and use of services be included when a situation analysis is carried out.

**Standards**
The past decade has seen the development of programs to define and implement standards for health services in both developed and developing countries. The development of standards can help in

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<table>
<thead>
<tr>
<th>Minimum Package of Services</th>
<th>Minimum Plus (in addition to the minimum package)</th>
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<tbody>
<tr>
<td><strong>HIV testing and counseling</strong></td>
<td></td>
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<tr>
<td>Treatment for:</td>
<td></td>
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<tr>
<td>- OIs, including PCP, TB, and candidiasis</td>
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<tr>
<td>- Diarrhea (ORS)</td>
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<tr>
<td>- Malaria</td>
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<tr>
<td>- Deworming</td>
<td></td>
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<tr>
<td><strong>Prophylaxis (primary/secondary) for:</strong></td>
<td><strong>Prophylaxis (primary/secondary) for:</strong></td>
</tr>
<tr>
<td>- OIs, including PCP and cryptococcus</td>
<td>- TB</td>
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<tr>
<td>- Malaria (IPT, mosquito nets)</td>
<td>- MAC</td>
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<tr>
<td><strong>ARVs (first and second line)</strong></td>
<td><strong>ARVs (third line/experimental)</strong></td>
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<tr>
<td><strong>PMTCT and antenatal care</strong></td>
<td></td>
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<td>Complete history and clinical examination</td>
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<tr>
<td>- including weight and height</td>
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<tr>
<td>- including a focus on STI signs and symptoms</td>
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<tr>
<td><strong>Sexual and reproductive health</strong></td>
<td><strong>Termination of pregnancy</strong></td>
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<tr>
<td>- Condoms/contraception/emergency contraception</td>
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<td>- Family planning</td>
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<td>- Pregnancy options and support</td>
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<td>- Sex education</td>
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<tr>
<td><strong>Prevention with/for positives</strong></td>
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<tr>
<td>- Counseling for prevention</td>
<td></td>
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<tr>
<td>- Positive (healthy) living</td>
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<tr>
<td>- Family testing</td>
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<td>- PEP</td>
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<tr>
<td>- Condoms</td>
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<tr>
<td>- Substance abuse counseling</td>
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<tr>
<td>- Clean needles and syringes for injection drug users (i.e., access to harm-reduction services)</td>
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<tr>
<td><strong>Psychosocial counseling</strong></td>
<td></td>
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<tr>
<td>- Mental health screening and referral</td>
<td></td>
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<tr>
<td>- Adherence counseling</td>
<td></td>
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<tr>
<td>- Disclosure counseling</td>
<td></td>
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<tr>
<td>- Clinic-based peer support group</td>
<td></td>
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<tr>
<td><strong>Nutrition counseling</strong></td>
<td><strong>Nutrition support</strong></td>
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<tr>
<td>- Pregnancy</td>
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<tr>
<td>- Hemoglobin</td>
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<tr>
<td>- Syphilis</td>
<td></td>
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<td>- Sputum</td>
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<tr>
<td>- CD4 lymphocyte count</td>
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<tr>
<td>- Pap smear</td>
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<tr>
<td>- Viral load</td>
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<tr>
<td>- Resistance testing</td>
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establishing and maintaining youth-friendly HIV prevention, care, and treatment services and can serve as a foundation for ongoing quality improvement processes at institutional and national levels.40,41 The development of criteria is a critical element of this process, as a means to assess whether the developed standards have been attained. Evidence from an assessment of South Africa’s National Adolescent Friendly Clinic Initiative (NAFCI) has shown that setting and implementing standards and criteria improves the quality of adolescent services in clinics.72

Facility Changes

There is ample programmatic evidence to show that changes made in facilities can increase young people’s utilization of health services.73,74 These changes may include increasing the physical accessibility of health services by holding clinics in special youth centers or in places that are regularly accessed by young people; offering services in places that are easily accessible through public transportation; and extending clinic hours to evenings or weekends, when young people are not working or in school. Creating physical surroundings that provide a welcoming environment (e.g., the paint on the walls, posters, chairs, clear advertisement of the clinic, a separate entrance for youth) is another important component of making a facility more adolescent-friendly. In addition, it is vital to ensure that privacy and confidentiality are upheld when young people enter the health facility and meet with their health providers.75

As cost can create a significant barrier to young people’s ability to utilize health services, free or subsidized services are preferable. Evidence indicates that the utilization of cash transfers and programmatic vouchers to subsidize the cost of services may provide a useful approach to increasing health service utilization and to providing services to young people.45-47,76-79

The Role of Family and Community

In addition to improving the supply of health services, it is also important to generate demand from

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Table 4. WHO Recommended Minimum Package of Services for Young Client (cont.)

<table>
<thead>
<tr>
<th>IEC materials</th>
<th>Immunizations</th>
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<tbody>
<tr>
<td>■ Prevention</td>
<td>■ Hepatitis B</td>
</tr>
<tr>
<td>■ Treatment literacy</td>
<td>■ Pneumococcal</td>
</tr>
<tr>
<td>■ Disease literacy</td>
<td>■ Human papillomavirus</td>
</tr>
<tr>
<td>■ Living positively</td>
<td>■</td>
</tr>
<tr>
<td>■ Existing legal rights (as they apply locally)</td>
<td></td>
</tr>
</tbody>
</table>

Effective referral system with follow-ups
- Linkages with family, community, NGO services
- Linkages with other youth services
- Connections with legal institutions

Immunizations
- Tetanus toxoid
- Hepatitis B
- Pneumococcal
- Human papillomavirus

OI = opportunistic infection; PCP = Pneumocystis jirovecii pneumonia; TB = tuberculosis; ORS = oral rehydration salts; IPT = intermittent preventive treatment; ARV = antiretroviral; STI = sexually transmitted infection; PEP = postexposure prophylaxis; NGO = nongovernmental organization; MAC = mycobacterium avian complex; VCT = voluntary counseling and testing; PMTCT = prevention of mother-to-child transmission; IEC = information, education, and communication

Source: WHO and UNICEF.20
the youth in the community. To do this, families and communities need to be informed about the availability of services through a range of channels, including youth groups, the media, and schools. This information needs to include not only details about the availability of services (when and where), but also information about why young people should use the services, and information to allay young people’s anxieties about using them. As there is considerable stigma surrounding HIV and sexuality among young people, community acceptance of HIV-related services can be critical to their success. It may be necessary to find some respected “champions” in the community (e.g., religious leaders, youth leaders, local government officials, etc.) to support the provision and use of health services by young people for HIV prevention and care. For services involving treatment and care, support groups will be required in the community.

A number of innovative approaches have been devised to increase the demand from young people who do not currently use services but who may be vulnerable and in need of such services.

- Outreach. Outreach is necessary for any at-risk population that cannot be reached through existing health centers and that is not being

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**SOUTH AFRICA AND THE NATIONAL ADOLESCENT FRIENDLY CLINIC INITIATIVE: STANDARDS FOR CERTIFICATION**

In South Africa, the Department of Health and the loveLife program—a national HIV prevention program for youth—have developed and implemented national standards for youth services that include clinic policies, the range of services, staff training, and the assessment and care of clients. Participating clinics form a quality improvement team that includes all categories of staff to assess youth-friendliness, identify needed improvement, and develop a plan of action for implementing changes. The National Adolescent Friendly Clinic Initiative (NAFCI) has articulated 10 key standards by which adolescent-friendly clinics are evaluated:

1. Management systems are in place to support the effective provision of adolescent-friendly health services.
2. The clinic has policies and processes that support the rights of adolescents.
3. Appropriate adolescent health services are available and accessible.
4. The clinic’s physical environment is conducive to the provision of adolescent-friendly health services.
5. The clinic has the drugs, supplies, and equipment necessary to provide the essential service package for adolescent-friendly health care.
6. Information, education, and communication promoting behavior change are provided, consistent with the essential service package.
7. Systems are in place to train staff to provide effective adolescent-friendly health services.
8. Adolescents receive an adequate psychosocial and physical assessment.
9. Adolescents receive individualized care based on standard case management guidelines or protocols.
10. The clinic provides continuing care for adolescents.
HE NYERI YOUTH HEALTH Project is an intervention for young people implemented by the Family Planning Association of Kenya in collaboration with representatives from the community that took place from 1998 to 2000 with the goal of addressing the unmet reproductive health needs of 14,000 unmarried young people aged 10–24 living in the Nyeri municipality in Kenya’s Central Province. Formative research revealed that both young people and parents preferred that sexual and reproductive health information be provided by trusted adults rather than peers. Based on this research, the Nyeri Youth Health Project enlisted respected young parents living in the community to give young people sexual and reproductive health information and referrals for services. The counselors, known as Friends of Youth (FOY), received a month of training on HIV/AIDS, sexual and reproductive health, behavior change, and communication skills, among other basic skills. The FOY also gave young people in need of services coupons to visit participating providers; the coupons were subsidized by the providers and the Family Planning Association of Kenya. The counselors made more than 40,000 contacts with young people and 5,800 contacts with parents during the project. Simultaneously, providers (mainly from the private sector) were given training on youth-friendly service provision. Evaluation of the project showed a significant increase in the proportion of young people reporting healthy behaviors, as seen in the decrease in sexual activity and the number of partners and the increase in the percentage of young people reporting condom use during their last sexual encounter, abstention from sexual activity, and discussion of a sexual or reproductive health topic with a parent or other adult.
While the results of a recent survey of the literature on community-based peer education programs targeting youth in lower-income communities showed positive changes in the knowledge, attitudes, and behaviors of young people that would help reduce the risk of exposure to HIV, there is an ongoing need to carefully monitor and evaluate the involvement of young people in program development, implementation, and outcomes. Demonstrating positive outcomes associated with this practice will help make a stronger case for the greater involvement of young people in all aspects of care.

Sources of Information
Young people may accept information about HIV regardless of its source, whether it be from friends, family members, teachers, health-care providers, religious leaders, or the mass media. The health system must work with these constituents to ensure a coherent and consistent package of information for
young people about HIV and related risk behaviors. Most importantly, the health system must ensure that the information being used and disseminated by this network of sources is accurate and up-to-date. Young people value accuracy, and research indicates that they trust information given by a nonjudgmental and friendly health-care provider.\textsuperscript{20,85,86} As health services become more accessible and acceptable to young people, the role of health-care providers in providing information about HIV will increase.\textsuperscript{73}

**Mobilization of and Technical Support to Nonhealth Sectors**

It is important that the health sector interact with other sectors in the following ways:

- The health sector should enlist the help of other sectors in strengthening and facilitating health interventions targeting young people. For example, the education and media sectors can provide information to young people about the availability of health services, thus generating greater awareness of and demand for services, along with greater community support.
- The health sector can also play a role in supporting HIV/AIDS initiatives being undertaken by other sectors. For example, educational institutions and the media have an important role to play in providing young people with information, as well as developing their skills and shaping their beliefs. The health sector should ensure that the information provided through these channels is technically sound and consistent with other messages young people are receiving, and that any strategies that are being implemented are evidence-based.

**Utilization of Information to Inform Programming**

It is important that the health system collect, analyze, and disseminate data on the prevalence and impact of HIV among young people for the wider research and programmatic community. Such data are important to monitor progress on global commitments and support the development of youth-focused policies and programs, and they also serve as a platform for advocacy and for the monitoring and evaluation of program effectiveness. To this end, following a global technical consultation, a set of 16 global and national-level indicators have been developed and proposed for use in countries to provide more comprehensive information on the provision of health services for young people.\textsuperscript{88} Additional ways to provide data that will better inform programs targeting young people include the following:

- Disaggregating routinely collected data by age, sex, school attendance, and marital status. This basic requirement, an ongoing challenge in many countries, is essential for designing appropriate interventions.
- Collecting data that help programmers understand young people who are most at risk of HIV, in order to develop and monitor appropriate responses. Specific data can include the following:
  - Percentage of young people who have had sex before the age of 15
  - Percentage of young people who have had sex with a sex worker in the preceding 12 months
  - Percentage of young men who have had anal sex with a male partner in the preceding 6 months
  - Percentage of young people who report intravenous drug use during the past 12 months
  - Percentage of young women who have exchanged sex for money or gifts in the preceding 12 months
- Collecting data to help understand the linkages needed between HIV/AIDS and other related public-health problems confronting young people, such as other sexually transmitted
and despite the articulation of commitment by the international community to addressing HIV infection in youth, HIV-positive young people are often conspicuously absent from national strategic plans, policies, and guidelines. Oftentimes, the paucity of systematic research addressing HIV and youth compromises the implementation and operationalization of evidence-based programming for young people living with HIV. While advocating for increased resources for quantitative and qualitative research to guide programming, countries and organizations must not allow these gaps in knowledge to serve as an impediment to supporting a greater multisectoral response facilitating the access and utilization of HIV services by young people. In the words of a young man living with HIV in Uganda:

HIV is everyone’s problem and needs the involvement of all stakeholders including religious people, politicians, scientists, women, children, and the community. . . . What is important, however, is not how one gets infected but how one can live positively after knowing one is living with HIV and helping stop further infection. . . . I am a free person, and cannot spend a day without thinking about HIV because it is a part of me. . . . I want to be remembered for contributing to change, and advocating for equality and justice. I am hopeful that when that day comes, people can look back and reflect on the struggles and pains some people went through to help save lives of the future generation . . . I don’t want to die with the little knowledge I have. I want to share it with the rest so that it can be passed on to the future.89

ACKNOWLEDGMENTS
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FROM THE GROUND UP: ESTABLISHING A FRAMEWORK FOR SUCCESS

FROM THE GROUND UP: ESTABLISHING A FRAMEWORK FOR SUCCESS


77. Meuwissen LE, Gorter AC, Kester AD, Knottnerus JA. Can a comprehensive voucher


IN 1995, AT ONE OF THE first public forums on AIDS in Ethiopia, Mengistu Zemene, a former police officer, listened in shock to one of the speaker’s comments. The man said that if the government learns a person is infected with the virus, it should either put them in prison or kill them. “If they are left alone, they will spread the virus,” the man said, explaining his reasoning.

Zemene and three other people then gave their presentations. When they finished, Zemene turned to the man with the idea of jailing or killing those infected with the virus.

“One of us who spoke today is HIV-positive. Could you identify that person?” Zemene asked him.

written by John Donnelly
photographs by Dominic Chavez
PROFILE: MENGISTU ZEMENE

MENGISTU ZEMENE IN HIS OFFICE IN ADDIS ABABA, ETHIOPIA
The man looked at him dumbfounded.

“It is me,” Zemene said.

The man apologized, saying, “We don’t understand this virus. We don’t know what to do.”

Since then, Zemene, 42, has helped his country develop responses to AIDS prevention, care, and treatment. He has also helped the man at the forum understand that those infected with HIV can play important roles in society; the two have become friends in the process.

Zemene formed Mekdim Ethiopia, a group of people infected and affected by HIV. It started with 21 members in 1996 and has expanded to six branches around the country, with more than 5,000 members. Mekdim, which means “pioneer” in Amharic, oversees treatment and care of those living with HIV and offers support for orphans.

His impact, say observers, has been far reaching. “What people love to see about him is that he is strong and he is healthy,” said Netsanet Assaye, a radio journalist based in Addis Ababa.

She remembered a day in 2002 when Zemene graduated from college. “There was big publicity,” she said. “It was wonderful for HIV-positive people, and the rest of the country, to show that if you have the virus, you have a future.”

Zemene, a father of two, now wants to enter a master’s degree program. “The problem is,” he said, “that I’m so busy with this work. I don’t have time.”

Q: In the early 1990s, you were coinfected with HIV and TB, and you started to improve after taking the TB medication. How did you rebuild your life?

“What was most important was that I believed I could live. That helped me grow strong not only in my body but also with my mind. I approached an organization of Catholic nuns that was providing health care. It was the Medical Mission of Mary. I told them I don’t want your support. I said I wanted to work. That surprised them, but they promised me work. Two months later, I was working for them as a receptionist.”
Q: How did you make the jump into being an activist?
“I saw so many people coming in who were infected with HIV. When I saw them, they were afraid. I wanted to support these people. So I asked the nuns whether it was possible to start a support group for positives. They gave me permission. But there was still one issue—the nuns did not know my status. So I told them, and some thought I was trying to cheat them, that I couldn’t be telling the truth because I looked so healthy. They didn’t want to believe me. So I showed them my documents, my test results.”

Q: How did you start the support group?
“The nuns sent me to Uganda for training. That was very important. Uganda was far more advanced than Ethiopia in supporting AIDS patients. I went for two months—one month in a big hospital that was seeing almost only AIDS patients, and one month training for home-based care. When I returned, I had many ideas. I was ready to bring positives together.”

Q: Was it difficult in the beginning?
“No. After the first support group meeting, you should have seen their faces. They were so happy, even if they didn’t know each other. They realized they weren’t the only persons who had HIV. We went out after the meeting for tea and coffee. It was a kind of a celebration. I felt so great because I was supporting them.”

Q: How did you become publicly known as being HIV-positive?
“The numbers of clients were increasing, the support group was growing, and I decided I needed to start educating the public through conferences, workshops, and the media. I started to share my personal story.”

Q: The group has experienced some trying times. Why was that, and how did you address those issues?
“It had to do with the money coming in. From 1998 to 2000, we started getting funds from donors. Conflicts started. People wanted to do different things with the money. Some were pushing for personal interests. It was so bad we closed down for a while. We didn’t talk for six months. Then we negotiated for three months and we finally solved the conflict. One of the issues was how to include HIV-negative people—orphans, for instance—and how they could avoid any stigma. We decided to expand the group to make it for people who are positive and negative and include an element of HIV education.”

Q: What is the group’s biggest challenge ahead?
“It has to do with continuing treatment for those on antiretrovirals. While the government oversees antiretroviral treatment, this is all supported by the U.S. government and the Global Fund. To be sustainable for this program, we have to do something. If the U.S. government or the Global Fund stops their support, people will have a big problem in getting treatment. I also think Ethiopia and other countries need to start companies to make these drugs within their borders.”
“Hope” 2006, Cape Town, South Africa
By Funeka Nceke
Photo courtesy of Venice Arts ©

“I want people to see beyond my HIV status.”

About the Artist

Funeka Nceke is 28 years old and lives in the Cape Town township of Khayelitsha in a makeshift home with no electricity or running water. She lives with her two children (ages 12 and 8 months), her niece, and her niece’s boyfriend. She learned that she was HIV-positive in 2003. Funeka wants people to see that those who are HIV-positive can be “fresh and healthy” and enjoys taking photos of her house, her happy children, and TAC (Treatment Advocacy Campaign) marches.

Funeka Nceke

Photo: Giselle Macfarlane
Courtesy of Venice Arts
“I want people to see beyond my HIV status.”

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DEVELOPING PATHWAYS AND PARTNERSHIPS

• Rolling Out and Scaling Up
• Community-Based Care
• Leadership and Partnerships

EDITED BY
RICHARD G. MARLINK AND SARA J. TEITELMAN
“The Union” 2007, Maputo, Mozambique
By Aires (age 18)
Photo courtesy of Venice Arts ©

“This photo symbolizes the union between African children in the struggle against HIV and AIDS.”

About the Artist
Aires is a presenter on the Mozambican Television children's program “Roda Viva” (Live Wheel). He has been participating in children's television since 2000. “Roda Viva” has given him the opportunity to travel across Mozambique learning about the experience and realities of Mozambican children. The most memorable event he covered was the launch of the campaign “Unite for Children. Unite Against AIDS”. More than 4,000 children participated in the launch. The Mozambican head of state, his wife, ministers and other government officials attended the event and he was able to meet them afterwards.
from the ground up
BUILDING COMPREHENSIVE HIV/AIDS CARE PROGRAMS IN RESOURCE-LIMITED SETTINGS
VOLUME I:
LAYING A STRONG FOUNDATION

VOLUME II:
ESTABLISHING A FRAMEWORK FOR SUCCESS

VOLUME III:
DEVELOPING PATHWAYS AND PARTNERSHIPS
FROM THE GROUND UP:
Building Comprehensive HIV/AIDS Care Programs in Resource-Limited Settings

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Introduction to Volume III: Developing Pathways and Partnerships

The title of this third and final volume, “Building Pathways and Partnerships,” reflects an essential step in HIV/AIDS service provision. Even if we build the best programs, they are of little value without efforts to increase access to the critical services they provide. As the previous two volumes have shown, there are a multitude of considerations to take into account when building comprehensive programs, yet building these programs is only the first step.

In the first section of this volume, “Rolling Out and Scaling Up,” authors share their experiences in rolling out and scaling up proven care, treatment, and prevention strategies to achieve greater coverage and access to services. They also highlight the formidable challenges inherent in these efforts when both human and financial resources are in short supply. And while many efforts tend to focus on the formal health care sector, these authors remind us that the community is at the core of everything we do. Without effective community linkages, even the most robust programs will be weakened and the effectiveness of vital interventions greatly diminished in the absence of massive outreach efforts and “bottom-up” support.

In the “Community-Based Care” section, we will learn about some of the key strategies for engaging the community in HIV/AIDS efforts, and ways in which community members can be mobilized to strengthen and support existing services, especially in light of human resource shortages. These include the use of lay counselors and peer support groups, which play a critical role in bridging the gap between the formal health care system and the individuals that often lay just beyond its reach.

Finally, in “Leadership and Partnerships,” we will take a look at some of the key strategies for greater cross-sector collaboration. Strategies highlighted include the formation of public-private partnerships, which capitalize on existing networks and private-sector innovation, as well as greater integration with faith-based initiatives, which often play a central role in supporting the health and well-being of many communities.

It is also important to step back and take a broader look at the current policy environment in which we operate. The mechanisms of the key institutions that both influence and support our work must be understood in order for us to work more effectively together, and to look for opportunities to progress beyond the status quo and reach new heights as we strive for excellence in all that we do. While the chapters in this volume contain a snapshot of the impressive efforts taking place around the globe to expand the reach of vital HIV/AIDS services, they also remind us that as long as people are becoming newly infected and are dying from HIV, and as long as orphans are not receiving adequate care and support, our work is not yet done. There will always be a need to ensure that our policies and programs continually respond to the ever-changing social and political environments in which we work. As governments change hands and funding priorities shift, we must never cease to mobilize all resources, whether human, financial, or otherwise, at our disposal to ensure that all people everywhere benefit from the highest quality programs and services.

Mark Dybul
Ambassador Mark Dybul, M.D., served as the U.S. global AIDS coordinator until early 2009, leading the implementation of the President’s Emergency Plan for AIDS Relief (PEPFAR). In his role as global AIDS coordinator, Ambassador Dybul oversaw all U.S. government engagement in the Global Fund to Fight AIDS, Tuberculosis and Malaria and served as chair of the Global Fund Finance and Audit Committee. He also previously served as both vice chair and chair of the Joint United Nations Programme on HIV/AIDS (UNAIDS) Programme Coordinating Board. Dybul is currently a senior advisor at the Global Business Coalition on HIV/AIDS, Tuberculosis and Malaria and a distinguished scholar and co-director of Georgetown University’s O’Neill Institute for National and Global Health.
NURSE SYPROSE SETS OUT TO VISIT ONE OF HER PATIENTS AFTER FINISHING A FULL DAY'S WORK AT THE HOSPITAL.
IN THE MID-1980s, when word spread that a disease called AIDS was killing people, administrators at Chulaimbo Hospital in western Kenya panicked. They moved all patients testing HIV-positive into one room, separate from all other patients. Almost all the health workers stayed clear of that room, but not nurse Syprose Adhiambo Oduor.

“My colleagues feared these patients. They did not feel free in helping them,” Oduor remembered. “It was the fear of the virus, a fear of getting infected themselves. I tended to those patients. The others couldn’t believe the way I was handling those with HIV. But as a Christian, I felt the Lord would protect me. And even if I did die, I would die with the Lord.”
With that strong belief, Oduor set off on a path defined by the devastating arc of AIDS. The virus claimed the lives of one of her sisters and a brother. It created orphans in her family; she took in a niece and nephew. Then, in 2000, she had to weigh a very personal risk to herself: Her husband announced he was taking a second wife, which is common in Kenya. She almost decided to leave him. But, she said, through prayer and considering the cold fact that she needed her husband’s economic support to keep their children in school, she decided to remain with him. She had one condition, though: “If we were to come together, he must use a condom every time,” she said. “He agreed. So I accepted him.”

AIDS didn’t stop there with Oduor. It dominated her work as well. For more than 20 years, she has toiled as a nurse and HIV counselor at Chulaimbo Hospital. And since 2004, she has helped run a home-based care network for a tiny pittance of a salary, supervising the cases of more than 250 patients spread out across the surrounding rural communities.

For Oduor, 45, mother of three, that means she is constantly on the go. From late afternoon into evening during the week, she visits patients. On Saturday, it’s the same. Only on Sunday does she rest—unless there’s an emergency. Then she goes to help.

One Saturday afternoon, she checked in on two of her patients who were both in difficult situations. The first was a 13-year-old orphan girl named Mercy who had just given birth. Her two-month-old baby, Carolina Akoth, had a fever soon after birth but now was doing well. Still, Oduor remained concerned about both of them.

“For one thing, I’m worried that Mercy has dropped out of school. She should go back,” Oduor said, standing underneath a canopy of red and pink bougainvillea blossoms. “There’s also the problem they are having in feeding the whole extended family.

“The others couldn’t believe the way I was handling those with HIV. But as a Christian, I felt the Lord would protect me.”
Q: What do you see as the biggest challenges in the years ahead?
“We still need to get more people tested so they know their status. If they are positive, they can live positively—by that, I mean, take care of themselves, take the right medication, and don’t infect others. The threat of death will then not be so great, and we will not have as big a problem with orphans. We should also try to get people who are positive to go public with their status.”

Q: By going public, doesn’t that make HIV-positive people more vulnerable?
“If more people go public, it will become more normal. There is a huge public health benefit if they go public. The rate of infection will go down because the community will know who is infected and take the right precautions. One person can infect so many.”

Q: What will encourage people to go public?
“We need to get people to join support groups. It’s so important for people to discuss openly what has happened to them, and they can share stories that help them prepare for what will come next.”

Q: How do you find the energy for your work?
“I just like doing it. When I see a patient improve, I become very happy. I feel proud. That person is then seen in the community as someone who is doing well again. People talk about it. In the past, before we had antiretroviral drugs, people used to die in great numbers. Sometimes I would get very depressed. You felt no matter what you did, people would die. Now, the death rate has gone down. The number of support groups for HIV-positive people has gone up. That makes me very happy. This is work that I do wholeheartedly.”

They always need more food.”

Her second patient, Maurice Odielo, 38, HIV-positive and partly paralyzed in both legs, rose slowly to greet her as she entered his hut. He had tears in his eyes.

“She’s helping me a lot,” he said. “When I needed to get tested, I went to her. When I needed counseling, I went to her, too. And when I needed food, she found a program that would bring food to me.”

Odielo told her that he had a dream—that he would walk again. “Then I could find work, feed myself, and,” he said, “I could visit you in your house.”

Oduor smiled. “I hope for that, too,” she said.
ROLLING OUT AND SCALING UP
In the early 2000s, the international community was finally able to gather the necessary political will, momentum, and financial resources to begin making antiretroviral (ARV) treatment widely available in developing countries. AIDS activists, United Nations organizations, and health workers (notably Médecins Sans Frontières [MSF]) from around the globe led this dramatic shift in thinking. A cascade of events then occurred that would forever change the way that HIV was treated and managed in resource-limited settings. The XIII International AIDS Conference in Durban, South Africa, in 2000 served to raise global awareness about increasing AIDS-related mortality and the need to provide combination antiretroviral therapy (ART) to all those in need. The XIV International AIDS Conference in 2002 in Barcelona, Spain, reaffirmed the need for wealthy nations to finance the cost of HIV treatment and prevention in developing countries. Shortly after the Barcelona conference, the Global Fund to Fight AIDS, Tuberculosis and Malaria was created, along with the World Bank’s Treatment Acceleration Program and the Clinton HIV/AIDS Initiative. Rapid declines in the costs of ARV drugs soon followed, spurring a change in global attitudes toward the widespread provision of ART. In 2003, the World Health Organization (WHO) launched the “3 by 5” initiative (i.e., treat three million people by 2005). This goal was not reached, but the term “3 by 5” lived on. In 2004, the President’s Emergency Plan for AIDS Relief (PEPFAR) proposed to invest roughly $15 billion in the global AIDS effort through 2008, the largest single-focus foreign-aid initiative in U.S. history. Once in place, these programs provided unprecedented funding to help combat HIV through the widespread provision of ARVs.

Although this unparalleled international effort to combat HIV through expanded access to treatment and prevention has benefited many people in developing countries, huge challenges still remain. For instance, the true burden of disease in many countries is still not known, nor is there a clear picture of the magnitude of resources needed to halt the pandemic. Debates also continue regarding the most cost-effective approaches to treatment and prevention. Despite these and other challenges, the initiation and scale-up of programs in the most affected countries continue, producing important lessons that can be shared across a variety of settings.
Many of the most affected nations in sub-Saharan Africa and Southeast Asia also have among the lowest health expenditures in the world (less than US$10 per person per year), a high percentage of the population living in poverty (more than 50% of the population living on less than US$2 per person per day), extremely high illiteracy rates in rural areas (greater than 50%), and limited access to useful health services.\(^1\) Given the severe programmatic constraints in these countries, there are a number of practical issues to consider when scaling up HIV/AIDS care and treatment programs (see Box 1). The challenges these nations face when attempting to scale up ARV programs are far different from those experienced by countries with well-functioning primary health-care systems (see Box 2). This chapter will discuss both the practical issues and challenges inherent in scaling up ART programs in resource-limited settings.

Before 2000, the provision of ART in developing countries was deemed too impractical (or impossible) because of high costs and the lack of developed health-care infrastructure. Many considered the complexities of managing patient care and follow-up to be insurmountable given the high cost of ARV drugs and the shortage of trained health-care professionals. Another concern was that the availability of ART might fuel the pandemic as a result of poor patient adherence to therapy, thereby increasing the risk of drug-resistant viral strains. Also, some believed that ART might lead to disinhibition (also termed “risk compensation”) of people living with HIV, whereby behavioral restraints that might have existed before receiving treatment are relaxed due to the patient believing that there is now a “cure” for AIDS. Despite these concerns, it was eventually concluded that it would be morally and ethically reprehensible to deny treatment to millions of people living with HIV in low-income countries.

Several groups set out to demonstrate the feasibility of ART provision in resource-limited settings through pilot projects in several low-income countries. One notable example is the work of MSF, which sponsored many pilot ART programs around the world and effectively pushed the agenda of providing ARVs under very challenging conditions (see sidebar on page 4). The work

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**Figure 1. Estimated number of people needing antiretroviral therapy in lower-income countries as of December 2006 (WHO and the Joint United Nations Program on HIV and AIDS)**
of Partners in Health in Haiti, led by Paul Farmer from Harvard University, demonstrated that when ARVs are made available, treatment programs can succeed and achieve high rates of drug adherence through the use of *accompagnateurs*, or treatment "buddies." These treatment buddies provide directly observed therapy for ART, a technique that was originally developed to promote adherence to TB treatment.2-5 Yet these model programs were relatively small and well-funded in contrast to the larger-scale, resource-constrained national programs that would be initiated soon thereafter.

Between 2000 and 2002, activists, academics, United Nations organizations, and governments began to put a great deal of energy behind combating the AIDS pandemic on a global scale. Aiding this effort, the cost of ARVs was lowered due to activist demands focused on Western pharmaceutical manufacturers and competition from generic manufacturers, especially those in India. The emergence of successful models of care in resource-limited settings combined with lowered drug costs made it a moral imperative for policymakers to get as many eligible people into treatment as quickly as possible.

### THE NEED FOR COHERENT NATIONAL PLANNING

Aggressive expansion of ARV programs in resource-limited settings was (and is) seen as a very positive turn of events, despite the fact that it has been accompanied by what might be described as a "mad race" to enroll patients, regardless of the effect of HIV/AIDS programs on other services. Yet the sustainability of these programs is an ongoing concern. Given the generally poor state of health-care systems in many affected countries due to limited health manpower, inadequate infrastructure, risk of drug stock-outs, and dependence on outside financing, it is unlikely that national governments will be able to take over externally funded HIV/AIDS programs in the foreseeable future.6 These programs can also compromise other primary-care priorities (e.g., due to redistributions in staff time) unless special measures are taken to preserve and improve baseline primary-care programs as part of national HIV/AIDS strategies.7

Rapid program expansion can result in activities that have had only cursory planning and coordination, causing imbalances in the distribution

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**Box 1. Considerations for Scaling Up Antiretroviral Therapy**

- Making HIV testing and counseling widely available
- Choosing a manageable number of primary and secondary antiretroviral drug regimes
- Making CD4 lymphocyte measures, basic hematology, and biochemistry laboratory capacity widely available
- Implementing prevention of mother-to-child transmission in increasing phases of complexity, e.g., graduating from single-dose nevirapine when the health system can support a more complex regimen
- Decentralizing antiretroviral therapy initiation and patient management
- Creating a patient-tracking health information system
- Creating a culture of patient follow-up with “buddy systems”
- Creating community outreach and education systems to facilitate patient tracking for treatment adherence and support
- Adjusting commodity procurement and distribution systems to reduce stock-outs and accommodate new drugs and supplies
- Creating appropriate systems to diagnose children early and follow up with them in an appropriate health context
- Implementing a basic package of wraparound care and support services
- Implementing an HIV drug-resistance surveillance system
- Integrating HIV-related services into health care, particularly primary care
EARLY ACHIEVEMENTS IN EXPANDING ACCESS TO ANTIRETROVIRAL THERAPY

The early action of the Brazilian Ministry of Health and the Thai Ministry of Health, the innovative rural work of Paul Farmer and Partners in Health (PIH) in rural Haiti, and model projects worldwide by Médecins San Frontières (MSF) demonstrated that successful provision of ARVs was feasible in resource-constrained settings. These organizations were among the first to argue that individuals in developing countries should have access to antiretroviral therapy.

South African high court judge Edwin Cameron electrified an audience of HIV researchers, care providers, and activists at the XIII International AIDS Conference in Durban in 2000 with his speech criticizing the way that his government had failed to address its HIV epidemic, calling “indefensible” the viewpoint (which was prevalent at the conference) that HIV care could not be implemented in poor nations. Farmer, Cameron, and others have argued that primary prevention in the form of education about HIV and condom distribution was an insufficient response in countries most heavily affected by the epidemic; treatment had to be part of the response if the fabric of society was to be preserved. They also argued that palliative care should not be the only option for those already infected.

Early on, countries received ARVs from pioneers such as PIH and MSF that demonstrated how therapy could be provided in resource-limited settings. The PIH work in Haiti using directly observed therapy provided much needed evidence that helped pave the way for ARV availability in many other developing countries. The work of Brazil, Thailand, and MSF added to the international body of evidence in favor of more widespread availability of ARVs. Both local health authorities and national- and international-level policymakers began to adopt the view that allocating resources for ARVs was a legitimate investment. MSF started demonstration projects in seven developing countries and also used its status as a major international non-governmental organization to advocate a reduction in ARV pricing through the use of generic drugs for developing countries. Effective advocacy and evidence-based successes eventually led to a global change in attitude favoring therapy and care as a vital component in the fight against HIV/AIDS.2,3,8

of resources by location or geographical region. This rush to achieve results (e.g., an increase in the numbers of patients on ARVs) to justify substantial budget allocations has led to programmatic incoherence and fragmentation of health care in some settings.9,10 For example, in Mozambique, different ARV regimens were in use by various nongovernmental organizations (NGOs) supporting ARV treatment before the Ministry of Health established fixed national ART guidelines. Diverse and uncoordinated approaches to HIV/AIDS care within a country can result in a number of challenges. For example, patients may move from one care setting (e.g., an NGO-run facility) where they are receiving a complex ARV regimen to a different setting (e.g., a public ART clinic) where only a simpler
Regimen is available, necessitating a change in treatment and possibly jeopardizing patient health. Additionally, an NGO might run out of funds, leaving patients who have been receiving specialized, complex care in the hands of local health workers trained according to different treatment protocols. These examples illustrate how a temporary, expedient “solution” can create additional, unexpected problems due to lack of stakeholder consultation and buy-in. Conversely, not adopting an expedient solution in the face of delays in the implementation of a national policy may result in additional mortality due to lack of treatment. To avoid such problems, the ideal approach is to temper the goal of rapid program expansion with careful coordination and synergy with national policies and existing systems.

**ART PATIENT SELECTION**

A principal factor shaping the approach to ART program scale-up has been the pressure from funders and advocates to identify and enroll patients. For instance, one of the main objectives of programs supported under PEPFAR is to place a targeted number of people on treatment during each year of implementation. In theory, this is a good strategy; clear, measurable, and ambitious yet achievable goals are set in place, and targets are (hopefully) met. However, in an environment where planning and management capacity is poor and implementation capacity varies considerably outside the major urban centers, it is inevitable that the use of target numbers results in the “cherry-picking” of patients in urban areas; this technique makes it possible to place a large number of HIV-infected people on therapy quickly and comparatively easily. For example, in Mozambique, almost half of all the patients enrolled in ART programs in 2005 lived in the capital city of Maputo (unpublished data [see sidebar on page 6]). This naturally caused considerable anger among human rights groups, health officials, and patient advocates in rural provinces, who demanded to know why only those who lived in urban centers were deemed eligible to receive lifesaving treatment. Strategies to address these imbalances and disparities continue to emerge yet remain challenging due to the higher costs associated with providing services to harder-to-reach populations.

Despite the massive scale-up efforts now under way, it is expected that ART will not reach all those in need for the foreseeable future. Determining how this limited resource should be distributed within each country has become an important responsibility in the hands of national governments. Although public discussion about the rationing of ARVs has been avoided, “passive decisions” are being made about who is given access to ART; typically only those who currently know their status or are living close to a clinic are selected. Other programs accept only ARV-eligible persons who can demonstrate adherence with cotrimoxazole and/or multivitamins before initiation on ART. By only selecting patients who are likely to adhere to treatment, providers may be inadvertently selecting a greater proportion of people with higher educational levels or better socioeconomic status.
From the Ground Up: Developing Pathways and Partnerships

Antiretroviral Therapy Roll-Out in Mozambique

The influx of international funding beginning in the early 2000s enabled developing countries, such as Mozambique, to rapidly intensify their HIV/AIDS efforts. In December 2001, the Ministry of Health (MISAU) created its first normative framework, outlining its intended response to the HIV epidemic. The following year, Mozambique’s proposal to the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) was approved and the first “day hospitals” focusing on HIV care and treatment opened in the nation’s capital city, Maputo. With the help of PEPFAR resources, the government of Mozambique began ART distribution in 2004. This was a huge national milestone because before 2004, ART had been restricted to a few pilot sites run by MISAU with support from various nongovernmental organizations.

As demand for services grew along with treatment capacity, MISAU decided to substantially revise the initial care and treatment protocols that were established in 2001. As a result of these revisions, several changes took place in 2006: provincial coordinators for HIV, TB, and malaria were created; greater responsibility was given to MISAU’s Department of Medical Assistance to help alleviate the shortage of trained health personnel; and ART training was extended to include other health units in suburban and rural areas. These changes were aimed at achieving total integration of services within health units and expanding services into rural areas. The evolution of Mozambique’s HIV/AIDS protocols and regulations that began in 2001 resulted in a steady and more equitable increase in the number of patients enrolled on ART. In 2004, 15 health units, mostly in Maputo, were providing ARVs to 4,182 people. By 2006, 180 health units were providing ARVs to more than 57,000 people. Half (90) of these units were located in rural areas, resulting in the percentage of people on ARVs that were living in Maputo falling from 67% to 44%.

The national scale-up continues. Progress so far demonstrates that increasing access to ART for those in need is feasible in a resource-limited setting such as Mozambique.

When resources are scarce, there should be guidelines in place for their fair and effective long-term allocation, including a transparent rationale for priority assignment of immediate treatment. Human rights and ethical principles must be the foundation for any distribution plan to ensure that it is legitimate and fair for all those affected.14

However, the use of human rights and ethical principles is only one aspect of a sound policy for the allocation of ART. Community participation is a necessary component for the creation of any policy, so that the needs of affected communities and individuals can be understood and addressed. The participation of relevant stakeholders and their representatives in the planning process helps to create policies that all view as fair and legitimate. A fair process is one that helps citizens to understand each other’s values and preferences within the context of human rights and ethical norms. It is the use of fair process that allows the development of policies based on reason, ethical principles, and the needs of the community.14
HIV COUNSELING AND TESTING

During the latter part of the 20th century, a traditional model of HIV voluntary counseling and testing (VCT) began to be promoted as a global standard of care. Despite concerted efforts encouraging people to learn their HIV status, uptake of VCT remained low. From the perspective of a potentially HIV-infected person in sub-Saharan Africa at that time, there was little incentive to be tested given that no effective treatment was available. Since then, both treatment and VCT services have become more widely available and effective. Approaches such as couples HIV counseling and testing, aggressive social marketing or outreach, and provider-initiated opt-out and opt-in testing have all played a role in increasing uptake.15

In spite of conceptual and programmatic advances, VCT has not increased at a fast enough pace to have a significant effect on prevention. As a result, many public-health practitioners are now advocating universal, provider-initiated, opt-out testing either in select facilities (e.g., sexually transmitted infection or prevention of mother-to-child transmission clinics) or as a universal component of care in public-health facilities. The combination of routine counseling of patients with opt-out testing can be an effective strategy for increasing the uptake of services, as has been demonstrated in Botswana16 and elsewhere.

Even in situations where other HIV/AIDS-related services are not yet available, establishing access to VCT should be a priority for any national program. In addition to enhancing life choices and preventive measures available to individuals and couples, VCT enhances awareness and acceptance of HIV/AIDS in the general population and contributes to reducing denial, stigma, and discrimination. Universal access to VCT is therefore a cornerstone of all HIV programs.

DIAGNOSTIC LABORATORY CAPACITY

Laboratory capacity at the point of service should, at a minimum, include HIV diagnosis using dual rapid tests according to the WHO algorithm adopted in most developing countries.17 Other important diagnostic services include:

- TB sputum collection and smear
- Malaria smear or rapid test
- Syphilis testing with basic serology
- Pregnancy testing
- Urine sugar and protein via “dipstick”
- Gram stain and microscopy for basic sexually transmitted infection diagnosis, when possible
- Provision for adequate sample collection and referral for CD4 cell count, hematology, biochemistry, and infant early HIV diagnosis using nucleic acid amplification testing

Poor roads, lack of electricity, and tropical climates are some of the major challenges faced in lab functioning and sample collection and handling. Establishing quality control / quality assurance programs, including laboratory proficiency testing, is costly and difficult to sustain. Alternative technologies, such as dry fluid spot collection and rapid HIV tests, have resulted in tremendous improvements in the ability to implement care and treatment in low-income countries.18-20

Balancing the need for complex laboratory technologies with the need to expand access to ART services has been a highly debated topic. For instance, it has yet to be established whether viral load testing (the “gold standard” in developed countries) can be offered as part of a standard of care in developing countries. There are concerns that inadequate treatment practices and adherence, coupled with lack of viral load testing, will fuel the spread of drug-resistant viral strains.21-24

However, the currently prohibitive cost of viral load testing has made it unrealistic for use in routine patient care in developing countries. Instead,
pharmacy-based measures of adherence, such as pill counts and surveillance-based confirmation of patient self-reported adherence, are used together with CD4 cell counts to assess patient adherence.25 Conversely, the use of viral load measurements in a population-based surveillance system to track the development of drug resistance both in treatment-naïve and treatment-experienced patients is more affordable and highly advisable for monitoring the speed at which drug resistance develops over time.

HEALTH-CARE WORKFORCE
There are not enough trained health-care workers available to meet the demands of rapid HIV program expansion, and lack of human resources is seen by many experts as the single most important challenge to HIV/AIDS program scale-up. In many sub-Saharan African countries, health-worker shortages are so severe that job descriptions have been completely redefined. For instance, relatively junior health-care workers are being assigned tasks including HIV diagnosis, care, ART management, and community health education.26,27 Long-term health-care education strategies to address these shortages must be implemented alongside shorter-term strategies to address sustainability aspects of worldwide efforts to control the HIV pandemic. Examples of short-term strategies include recruiting expatriate medical staff as volunteers or paid workers,28 improving the efficiency of services through better utilization of health workers (e.g., task shifting),27 using skill substitution and deskilled processes in combination to provide complex treatment,29,30 and using cell phones, the Internet, and/or telemedicine to support service provision in remote areas. Many countries are currently implementing several of these strategies.31

COMMODITY PROCUREMENT AND DISTRIBUTION
Already overtaxed commodity procurement and distribution systems are vulnerable to collapse from the pressures of expanded service provision. Even before the era of HIV, these systems were often unreliable and/or inefficient. The HIV pandemic has served as an impetus to address these chronic problems and is leading to the development of stronger systems. For example, the volume and variety of ARV treatment regimens and dosages for adults and children have made it necessary to improve the processes used to forecast and monitor ARV stocks. The added variety of ARV medications, along with other medicines used to treat AIDS-related illnesses and the chronic nature of the disease, makes supply management considerably more complex in settings where management capacity was previously lacking. Yet despite these challenges, supply management systems are being continually improved in a variety of ways, such as through the integration of laboratory supply management systems with drug and hospital supply systems and the conversion from paper-based to computerized systems.

DATA COLLECTION
The massive expansion of HIV/AIDS care and treatment programs underscores the need for high-quality data collection methods that are standardized and timely. Once data are collected, they should be utilized in a way that leads to improved short- and long-term care outcomes for patients. Training in this area is particularly important to ensure that data are successfully collected and utilized in a way that leads to improved patient management and program monitoring. Because ART programs often began as pilot projects (typically supported by various international NGOs), early data collection and management systems varied significantly from program to program. In the current context of large-scale, donor-funded scale-up of services, massive efforts are under way to enable the creation of standardized health information systems that are capable of compiling data from multiple sources.
As a result of the lessons learned from earlier experiences with foreign aid, many low-income countries have embraced a strategy called the sector-wide approach (SWAp) to help minimize funding inefficiencies. SWAp has been advocated since the mid-1990s to facilitate a gradual shift away from highly specific donor projects to more coordinated support, sometimes through the Ministry of Finance, that helps governments achieve efficiency in fund allocations. SWAp is not a simple or quick “fix” but rather a long-term strategy focused on building local management capacity. As such, it requires the recipient to make a large investment in management to match the more integrated approach of the donor.

However, the SWAp approach stands in stark contrast to global health initiatives that target specific diseases and are implemented as vertically managed projects. Lack of coordination among external funding sources, coupled with the fact that many low-income countries receive a substantial portion of health funding through implementing partnerships with NGOs, makes the management, administration, and regulation of funding highly complicated. This area has been a significant challenge for many countries, particularly in light of the recent massive increases in HIV/AIDS funding. As many people feel that both approaches are needed to effectively deal with a health problem of the magnitude of the AIDS pandemic, efforts have focused on improving coordination of funding and partner participation in the field; an example is the creation of coordination committees at the provincial and district levels.

Health Sector Financing

Financial resource limitations are a principal barrier to scaling up any health intervention. Donor funding accounts for more than 25% of health expenditures in roughly 40 low-income countries, with more than half of those countries receiving funding for over 50% of their total health expenditures from external donors. This heavy reliance on foreign donors has serious implications for the financial sustainability of health-service programs in general and resource-intensive HIV programs in particular. Historically, problems associated with reliance on foreign aid have been numerous, including fluctuation in the degree of donor commitment over time, delays in fund disbursements, earmarks for activities that do not necessarily align with national priorities, and fragmentation of funding into many small categories and program lines, resulting in a higher local administrative burden.

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Monitoring and Evaluation

Monitoring and evaluation (M&E) is a vital component of the implementation and scale-up of any significant health-care intervention. An M&E plan must be developed to manage the implementation efficiently, to monitor and evaluate progress, to evaluate programmatic effect, and to make

One promising example is the OpenMRS, which began development in 2004 through a nonprofit, collaborative effort to facilitate the development of high-quality, open-source medical record systems in developing countries. OpenMRS is a non-proprietary platform for large, complex databases designed to collect and manage medical records. This platform is successfully addressing complex technological issues, such as compatibility with various data formats, standardization, ability to handle very large amounts of data, synchronization of data from various sources, privacy and confidentiality, preservation of data, and ease of use by primary (clinician) and secondary users. This initiative also successfully addresses sustainability by promoting local capacity building through collaboration. In addition, its open-source design eliminates dependencies on costly proprietary software and, if proven successful, would be a welcome path to improved patient management and program monitoring in developing countries.
adjustments based on successes and failures. This is termed “learning by doing,” an essential step in the scale-up of any program.

A reliable and accurate data collection system is an essential component of any M&E strategy. But data collection is only the first step. Data then need to be analyzed and disseminated to the appropriate entities for reporting and further dissemination. Dissemination may include the creation of timely progress reports that inform program planners and policymakers about any needed changes in the direction or pace of the program. Data also need to be shared with other stakeholders, such as healthcare workers, patients, and community leaders. The more informed people are about program progress and outcomes, the more chance they have to develop innovative solutions that address program challenges.

Many of the best innovations in program improvement come from those closest to the point of delivery, either the beneficiaries (i.e., patients and community members) or the healthcare workers implementing the program. These people have first-hand knowledge of what is and is not working. The quality of services is improved through a cyclical series of activities that includes (1) reviewing performance data; (2) planning, designing, and implementing a strategy for improvement; and (3) reviewing indicators to assess whether the improvement was achieved. This cycle is the basis of the M&E framework and is most effective when implemented by a team of providers intimately involved with the provision of services. Well-defined M&E systems and processes not only are important for large-scale planning and progress tracking but also are vital for improving the quality of health services and public-health interventions at the local level.

Research, in particular operations research, is also an essential component of the M&E process. Operations research has many definitions, but all include the application of scientific techniques to a decision-making process. A vital component of operations research (or implementation research) is determining cost-efficiency and selecting the best solutions from competing options. Ideally, M&E would be integrated with operations research.

THE FUTURE OF HIV/AIDS CARE PROGRAMS

It is very difficult to predict what the future of HIV/AIDS care programs will look like. Yet regardless what form various national programs will take, there are a number of key elements that seem essential: integrating health and social services, utilizing community structures to extend the reach and capacity of the health system, decentralizing services to the local level, and utilizing health, social, and economic development interventions to improve overall health and well-being.

The treatment of people living with HIV involves the management of a complex and widely varying set of interventions. The success of the HIV/AIDS program depends on the efficient implementation of an integrated set of high-quality interventions by health workers and other social and community service entities. Given the lack of resources, particularly human resources (including experienced managers), integrated program implementation is very challenging. HIV and TB program integration in Brazil has been mutually beneficial, demonstrating the potential when programs are bridged effectively.34 Successful prevention of mother-to-child transmission programs are usually fully integrated into antenatal, perinatal, and child health services. Likewise, integrating ARV programs into the overall patient care and follow-up systems is imperative.35-39

It is also necessary to plan integration of HIV/AIDS programs into the mainstream of other support activities. Referrals within the health system, as well as those outside the health sector for social services, can be difficult and ineffective in many
cases, but engaging community-based organizations or special interest groups in such linkages can be highly beneficial. Lifelong adherence to ARVs will be possible only if local investments are made to support “buddy systems” and community “wraparound” programs that address a variety of needs such as (1) health needs (nutritional education, access to clean water and sanitation, health education, and prevention and treatment of sexually transmitted infections, TB, malaria, and other infectious and parasitic diseases), (2) social services needs (referrals to social and psychological counseling services, financial support, legal counsel, and school support programs), and (3) economic development and income-generation programs.

The lack of resources argues for optimizing their use according to the needs of the setting. In a context where government institutions are, for all practical purposes, the sole service providers, it makes sense to empower and encourage localities away from central government to analyze and act on their needs with the means at their disposal rather than wait for help from the central level that is often late or unavailable. Finally, it is extremely important to promote social and economic development as a means to address the sustainability of these efforts. In low-income settings, the lack of basic necessities such as adequate nutrition, water and sanitation, education, and access to a minimum income disproportionately affects health and well-being. Without addressing these basic needs, it is unlikely that a major influx of money and public-health programs will be able to sustain long-term changes in health status in any population.
REFERENCE LIST


37. Maher D, Harries A, Getahun H. Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes;

I N MOST COUNTRIES WITH HIGH HIV prevalence, the demand for treatment with antiretroviral therapy (ART) has rapidly outstripped the capacity of traditional tertiary health-care facilities (hospitals) to provide that treatment. If national and international targets for treatment access are to be met, ART will therefore need to be delivered in a wide range of settings and at multiple levels of the health-care system, from large referral hospitals in capital cities to primary health-care clinics in rural areas. Different models of treatment delivery may result in different patient outcomes, as measured by the proportions of patients who remain in care and responsive to therapy, remain in care but fail to respond to therapy, and do not remain in care at all. Similarly, the cost per patient initiated on ART and the cost per patient retained in care and responding to therapy are likely to differ based on facility characteristics, such as setting (urban, peri-urban, rural), level (hospital, clinic, mobile clinic, general practitioner’s office), sector (public, private, nongovernmental), professional inputs (doctor and nurse time), and scale (number of patients treated). Costs may also be affected by national factors, such as standardized drug regimens and laboratory availability, and by patient characteristics, such as choice of drugs, underlying health status, and disease stage at ART initiation.

Information about how the model of treatment delivery influences patient outcomes and treatment costs is important in order for policymakers and program managers to make efficient and sustainable decisions about current resource allocation and future program expansion. It would also be useful to know how costs and outcomes affect one another. Does spending more—for example, by performing more laboratory tests or requiring more frequent clinic visits—lead to better patient outcomes? To what extent does patient condition at treatment initiation affect costs? If outcomes improve, will treatment program costs rise or fall? In this chapter, we first briefly review what is known about the costs and cost-effectiveness of treatment in resource-constrained settings. We then present a methodology for assessing costs and outcomes of treatment sites and programs using data that are routinely collected by most treatment facilities.
COST AND COST-EFFECTIVENESS OF TREATMENT PROGRAMS

Cost analysis and cost-effectiveness analysis are two commonly used approaches to understanding the economics of health-care interventions. Cost analysis focuses on how much must be spent to provide a specified service (e.g., to build a clinic) or level of service delivery (e.g., to treat a thousand patients per year). Accurate cost estimates are essential to budgeting and serve as core inputs to most other types of economic analysis.

Cost-effectiveness analysis goes a step further in asking the cost per outcome achieved. As its name suggests, cost-effectiveness analysis requires that we know both the cost and the effectiveness of an intervention. Typical units of effectiveness include patients cured, life years gained, disability-adjusted life years (DALYs) gained, or quality-adjusted life years (QALYs) gained.

Using a standard unit of cost-effectiveness, such as the cost per life year gained, allows for the comparison of interventions to address disparate conditions, as well as alternative strategies for addressing the same condition. Cost-effectiveness analysis is usually undertaken to identify the option that will produce the specified outcome (e.g., one additional quality-adjusted life year) at the lowest cost.

Although it is possible to design very elaborate cost-effectiveness models to explore the differences among multiple intervention strategies, costing and cost-effectiveness analysis can also be used for practical, on-the-ground decision making and planning. A first very useful question to ask is, How much does it cost to provide treatment for HIV/AIDS at my clinic, in my program, or in my country?

Despite nearly five years of experience with large-scale ART delivery in a number of resource-constrained countries, only a few estimates of costs have been published. Some of the most recent are summarized in Table 1. Based on the limited information available from other African countries, costs in South Africa appear to be substantially higher than elsewhere: estimates of US$145–US$207 per patient year and US$396 per patient year have been reported for Uganda and Rwanda, respectively. It is unclear whether these much lower estimates include the cost of clinic infrastructure, however. It should also be noted that most of the estimates in Table 1 are for the first year on ART; costs in the second year were found to be much lower in the one study that estimated them.

All the estimates in Table 1 are of the average cost per patient treated. A logical next step is to ask whether the costs incurred are more or less than those associated with an alternative treatment strategy, which might involve different antiretroviral (ARV) drugs, different timing of ARV initiation, or no ARVs at all. A small number of cost-effectiveness studies asking these questions have been conducted in resource-limited settings. We summarize the findings of several of them in Table 2 (page 18). Results of cost-effectiveness studies are typically presented as incremental cost-effectiveness ratios (ICERs), which simply indicate the cost per additional unit of effectiveness gained by implementing a strategy, compared to the status quo or a different strategy. The second study in Table 2, for example, reported an ICER of US$1,023 per life year gained by providing ART, compared to a no-ART strategy.

The first two studies in Table 2 compare the costs of patient care with and without ART in South Africa; the others use data from multiple sources and settings to model differences among treatment strategies.

\[\text{Cost per lifetime gained, South Africa: US$396 per patient year}^{\text{Note}}\]

\[\text{Cost per lifetime gained, Uganda: US$145 per patient year}^{\text{Note}}\]

\[\text{Cost per lifetime gained, Rwanda: US$207 per patient year}^{\text{Note}}\]

\[\text{Cost per lifetime gained, South Africa: US$396 per patient year}^{\text{Note}}\]

\[\text{Cost per lifetime gained, Uganda: US$145 per patient year}^{\text{Note}}\]

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\[\text{Cost per lifetime gained, Uganda: US$145 per patient year}^{\text{Note}}\]

\[\text{Cost per lifetime gained, Rwanda: US$207 per patient year}^{\text{Note}}\]

\[\text{Cost per lifetime gained, South Africa: US$396 per patient year}^{\text{Note}}\]

\[\text{Cost per lifetime gained, Uganda: US$145 per patient year}^{\text{Note}}\]

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\[\text{Cost per lifetime gained, Rwanda: US$207 per patient year}^{\text{Note}}\]

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\[\text{Cost per lifetime gained, Rwanda: US$207 per patient year}^{\text{Note}}\]

\[\text{Cost per lifetime gained, South Africa: US$396 per patient year}^{\text{Note}}\]
Table 1. Recent Estimates of the Costs of Providing ART in Resource-Constrained Settings

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Facility</th>
<th>Year</th>
<th>Average Cost per Patient per Year (USD)</th>
<th>Composition of Average Cost Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td>Koenig et al (2006)</td>
<td>Haiti</td>
<td>Urban clinic</td>
<td>2004</td>
<td>$1,305</td>
<td>$342 (26%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over et al (2007)</td>
<td>Thailand</td>
<td>Provincial and community hospitals</td>
<td>2004</td>
<td>$842†</td>
<td>$471 (56%)</td>
</tr>
<tr>
<td>Harling and Wood (2007)</td>
<td>South Africa</td>
<td>Urban public clinic</td>
<td>2004</td>
<td>$2,020 (1st year)†</td>
<td>$599 (30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$1,375 (2nd year)†</td>
<td>$562 (41%)</td>
</tr>
<tr>
<td>Martinson et al (2006)</td>
<td>South Africa</td>
<td>Urban NGO clinic</td>
<td>2005</td>
<td>$1,322</td>
<td>$449 (34%)</td>
</tr>
<tr>
<td>Aledort et al (2007)</td>
<td>South Africa</td>
<td>Peri-urban NGO clinic</td>
<td>2006</td>
<td>$852</td>
<td>$494 (58%)</td>
</tr>
</tbody>
</table>

†Assumed to be for first year on ART unless otherwise specified.
‡Nutritional support.
§Excludes costs for patients who died, transferred, or were lost to follow-up.
¶May be included in other categories.
¶¶Opportunistic infection) treatment.
#### First-line regimen only.
#### TB treatment.
#### Cost breakdown estimated from graph.
<table>
<thead>
<tr>
<th>Source</th>
<th>Setting</th>
<th>Comparison</th>
<th>Unit Estimated*</th>
<th>Main Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badri et al (2006)</td>
<td>South Africa</td>
<td>Two strategies for patient care: no ART (strategy 1) v. ART (strategy 2)</td>
<td>Cost per LY gained by moving from strategy 1 to strategy 2</td>
<td>Median ICER &lt; $0 (cost saving) per LY gained for patients with AIDS and $675 per LY gained for patients pre-AIDS (compared to strategy 1)</td>
<td>Data drawn from clinical trial patients and prior to large-scale provision of ART.</td>
</tr>
<tr>
<td>Cleary et al (2006)</td>
<td>South Africa</td>
<td>Two strategies for patient care: no ART (strategy 1) v. ART (strategy 2)</td>
<td>Cost per LY and QALY gained by moving from strategy 1 to strategy 2</td>
<td>ICER = $1,023 per LY gained and $1,166 per QALY gained (compared to strategy 1)</td>
<td>Data predate large-scale provision of ART.</td>
</tr>
<tr>
<td>Vijayaraghavan et al</td>
<td>South Africa</td>
<td>Two strategies for starting and initiating ART: strategy 1 (start at CD4 ≤ 200 and CD4 counts every 6 months) v. strategy 2 (start at CD4 ≤ 350 and CD4 counts and viral load tests every 3 months)</td>
<td>Cost per LY and QALY gained by following strategy 2 rather than strategy 1</td>
<td>ICER = $5,146 per LY gained and $5,314 per QALY gained (compared to strategy 1)</td>
<td>Modeled using input data from multiple sources.</td>
</tr>
<tr>
<td>Goldie et al (2006)</td>
<td>Côte d'Ivoire</td>
<td>Three strategies for patient care: no ART (strategy 1), ART without CD4 testing (strategy 2), and ART with CD4 testing (strategy 3) (All strategies included cotrimoxazole prophylaxis.)</td>
<td>Cost per LY gained by moving from strategy 1 to strategy 2 and from strategy 2 to strategy 3</td>
<td>ICER = US$590 per LY gained by moving from strategy 1 to strategy 2 and US$1,180 per LY gained by moving from strategy 2 to strategy 3</td>
<td>Modeled using input data from multiple sources. Other variations of these strategies were also analyzed.</td>
</tr>
<tr>
<td>Bishai et al (2007)</td>
<td>Resource-limited settings (general)</td>
<td>Four strategies for laboratory monitoring: no lab tests (strategy 1), total lymphocyte counts (strategy 2), CD4 counts (strategy 3), and viral loads (strategy 4)</td>
<td>Cost per QALY gained by strategies 2–4 relative to strategy 1</td>
<td>Strategy 3 was cost-effective compared to all other strategies. Median ICER = US$238 per QALY gained (compared to strategy 1)</td>
<td>Modeled using input data from multiple sources.</td>
</tr>
</tbody>
</table>

*All cost estimates include the provider costs of outpatient and inpatient medical care.

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year
strategies. In general, the studies shown in the table indicate that the provision of ART is cost-effective, in terms of both cost per life year gained and cost per QALY gained, compared to the no-treatment scenario. Depending on the assumptions made, providing ART may even be cost-saving (result in a net saving of money) due to the reduction in the cost of medical care for AIDS patients not on ART. This is more likely to be the case in settings where inpatient hospital care is widely available than in settings in which patients are more likely to die at home.

A SIMPLE METHODOLOGY FOR EVALUATING COST-EFFECTIVENESS

In all the cost-effectiveness studies shown in Table 2, the strategies compared involve policy decisions that are usually made at the national or international level, rather than at the level of the individual clinic or program. The findings thus have limited relevance for on-the-ground decisions about site management and resource allocation. For practical purposes, it is possible to learn quite a lot about the costs and cost-effectiveness of individual ART sites and programs using information that is routinely collected by most health-care facilities. In this section, we describe a methodology that we developed for estimating and comparing costs among different treatment delivery models in South Africa. The method does not involve life years gained or QALYs, as these are more relevant at the level of national policymaking and budgeting than at the level of the provider. Instead, it focuses on estimating the average cost per patient treated and per patient who remains in care and responsive to therapy 12 months after ART initiation. It can easily be modified to consider other outcomes, longer follow-up periods, and other variations.

The method relies largely on data drawn from a retrospective (historical) review of existing patient records. Patient records usually contain, at a minimum, information about clinic visits, laboratory tests performed, drugs dispensed, and diagnoses made. This information is sufficient to make a rough estimate of both outcomes and costs.

Step 1: Identification of Resources

The first step is to make a list of all the resources used by the site to treat ART patients. This list will almost certainly include variable (patient-dependent) resources such as ARV drugs, basic laboratory tests, and clinical staff. It might also include non-ARV drugs, inpatient days, and other services. It should also reflect the fixed (site-level) resources required to maintain the site itself: building, electricity, telephones, supplies, support staff, and so on. The list should be as comprehensive as possible, but it should exclude resources that do not contribute to the ART program, such as primary-care services provided by the same site.

Step 2: Sample Selection

Once a list of resources has been generated, the next step is to select a representative sample of patients who initiated ART at least one year before data collection. The sample can be drawn from the patient register, a computerized record system, pharmacy records, or whatever other source of information is available at the site. To ensure that the sample is representative, it is easiest simply to include all patients who initiated ART during a specified time period. A sample might comprise, for example, the first 100 patients who initiated ART in 2007 or, if the characteristics of the patient population are thought to vary by month or season, every nth patient who initiated ART over the course of the year. The only patients who should be excluded from the sample are those reported to have transferred to another treatment site within 12 months of initiation, as their outcomes at the new site will not be known.
Step 3: Record Review
For each patient in the sample, the information needed to estimate costs and assign outcomes must then be entered into a database. For costs, all resources used to treat the patient during the period from ART initiation to 12 months following initiation should be captured, including the following:
- Drugs dispensed (ARVs and non-ARVs, by name, brand, quantity, and date)
- Laboratory tests performed (with dates and the specific laboratory used if the site uses more than one)
- Outpatient visits (including dates and specific professionals seen if recorded, e.g., doctor, nurse, pharmacist, counselor)
- Inpatient care if recorded (facility, dates, number of days admitted, drugs dispensed, laboratory tests performed)
- Other services provided, if any, by type and date (e.g., food parcels, home visits)

For outcomes, information is needed about each patient’s condition 12 months after initiating ART. Since patients don’t always visit the clinic exactly 12 months after initiation, information generated during a window of up to 2 months on either side of the 12-month point can be used for assigning outcomes (i.e., between month 10 and month 14 after initiation). The length of this window can be changed to reflect visit schedules at particular sites. For the assignment of outcomes, the following indicators should be collected:
- Viral load result, if available (detectable or undetectable according to the site’s standard) in months 10 to 14 (the result closest to month 12 if there is more than one result in that period)
- CD4 count closest to initiation of ARVs and in months 10 to 14 if available (again, use the closest to month 12 if there is more than one)
- AIDS-defining opportunistic infections in months 10 to 14 (all)

Viral load and/or CD4 count data may not be available for any or all patients in the sample. The procedure for assigning patients to outcome categories, detailed below, takes this possibility into account. The result should be a database containing resource utilization and outcome data for each patient in the sample.

Step 4: Unit Cost Data Collection
The next step is to record a unit cost for each of the resources used to treat the patients in the sample. Unit cost estimates do not come from the patient sample but from the clinic as a whole. Unit costs of variable resources, such as drugs, lab tests, and consultations, are relatively easy to estimate. Price lists or invoices should provide accurate prices for drugs, laboratory tests, and other purchased items. Consultations can be costed by dividing clinicians’ monthly salaries by the total number of consultations per clinician per month for the clinic as a whole.

Unit costs of fixed resources are a bit harder to come by. Fixed resources include clinic infrastructure (buildings), utilities, vehicles, equipment, insurance, communications, nonclinical staff, and general supplies. There are standard methods for costing these resources,\textsuperscript{1,13-15} and various costing tools (spreadsheets) and guidelines can be downloaded from the Internet free of charge.\textsuperscript{a}

Alternatively, one can take the total annual budget for the clinic, subtract all the variable resources and the services unrelated to HIV/AIDS treatment, and divide the remaining amount by the total number of patient-months of care provided during the year. This will generate a rough but reasonably accurate estimate of the clinic’s average fixed cost per patient-month.

\textsuperscript{a}For example: http://www.who.int/choice/sitemap/en/.
Table 3. Treatment Outcome Definitions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Criteria for Assigning Outcome</th>
<th>Definitions of Criteria</th>
<th>Medical Record Data Required to Use Each Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No longer in care (NIC)</td>
<td>Died or Stopped attending initiating clinic (lost to follow-up)</td>
<td>Died or ≥3 months late for last scheduled consultation or medication pickup</td>
<td>Confirmation of death in month 0–12 or Date of last scheduled consultation or medication pickup</td>
</tr>
<tr>
<td>In care but not responding (NR)</td>
<td>AIDS-defining illness or Detectable viral load or Unacceptable CD4 change</td>
<td>WHO stage III or IV illness at most recent visit or Viral load &gt; 400 (or site standard) or CD4 increase &lt; 50</td>
<td>Clinic visit in month 10–14 (viral load and CD4 count not considered) or No WHO stage III or IV illness; viral load test in month 10–14 (CD4 count not considered) or No WHO stage III or IV illness or viral load test; CD4 count in month 10–14</td>
</tr>
<tr>
<td>In care and responding (IC)</td>
<td>Undetectable viral load or Sufficient CD4 change or No AIDS-defining illness</td>
<td>Viral load ≤ 400 (or site standard) or CD4 increase ≥ 50 or No current WHO stage III or IV illness at most recent visit</td>
<td>Viral load test in month 10–14 (CD4 count not considered) or No viral load test; CD4 count in month 10–14 or No viral load test or CD4 count; clinic visit in month 10–14</td>
</tr>
</tbody>
</table>

The result of this step should be a list that shows the unit cost of each resource identified in Step 1.

**Step 5: Estimate of Cost per Patient**

Multiplying the unit cost of each resource by the number of units used will generate a total cost for treating the patients in the sample for one year. For variable resources, this is quite easy, as the quantities used can be taken directly from the database created in Step 3. For fixed resources, a simple approach is to multiply the number of months that each patient in the sample is in care at the clinic by the average fixed cost of care per month. Note that although our study period is 12 months, it is not likely that all the patients in the sample will have remained in care for the entire period. A patient who dies or stops coming to the clinic 3 months after ART initiation, for example, should be allocated only 3 months’ worth of fixed costs, along with the medications, lab tests, and visit costs that the patient incurred in his or her 3 months of care. The total cost to treat all the patients in the sample can then be divided by the number of patients in the sample to create an average cost per patient treated. This average does not tell us anything about the outcomes achieved for the patients, but it does provide an accurate estimate of the clinic’s budgetary needs per patient initiated on ART. It is important to bear in mind, however, that this is not the average cost for a year on ART, since not
all patients in the sample remained on ART for the full year.

Step 6: Definition and Assignment of Outcomes

There is no consensus among clinicians or researchers about how much progress a patient on ART must make to be considered a treatment “success.” On one hand, since untreated AIDS leads to death, simply remaining alive and in care can be regarded as successful; on the other hand, a few patients who do remain in care do not respond well to ARVs. Further complicating matters is that patients’ medical records may vary in terms of both available information (e.g., whether or not a particular lab test was done at all) and timing of the information, which reflects what may be a highly variable schedule of clinic visits by individual patients. A year after initiating ART, for example, some patients may have two or three CD4 counts and/or viral load tests reported in their records, while others may have made several clinic visits to pick up medications but never had a laboratory test.

To overcome these challenges, three mutually exclusive outcome categories can be defined, with the goal that every patient be assigned to one of them on the basis of information routinely found in the medical record. The outcome categories and the information needed to assign patients to them are defined in Table 3 (previous page).

Figure 1. Procedure for assigning treatment outcome categories

Note that the definitions of the criteria can be adapted to the individual site. For example, some sites may regard a patient who is more than one month late for a medication pickup as lost to follow-up; others may use change in body mass index as an indicator of response. Similarly, some sites may prefer to classify a patient whose viral load is undetectable as “in care and responding” even if he or she has an AIDS-related opportunistic infection. Provided that the criteria are applied consistently to the entire sample, their definitions can be changed as desired.
should be followed for each patient in the sample, with the result being each patient assigned to a single outcome category.

Using the definitions in Table 3, the flowchart in Figure 1 (previous page) was created to ensure that a consistent approach is used to assign patients in the sample to outcome categories.

In Figure 1, the decision point is 12 months after the patient is initiated on ART. If the patient is no longer attending the clinic, the patient may have died or been lost to follow up, and he or she is classified as “no longer in care at study site” (NIC). Among those still in care, anyone who had a current AIDS-defining condition at the last clinic visit in the 12-month period is considered “in care but not responding” (NR). Viral load is then considered. Subjects whose medical record report an undetectable viral load 10 to 14 months after the starting point are classified as “in care and responding” (IC); those whose viral load is still detectable are NR. Next, if no viral load test is reported, a CD4 count in month 10 to 14 can be used, assuming that a CD4 count prior to ART initiation is also available. Patients whose CD4 count shows an increase of at least 50 cells/mm³ by the end of 12 months are defined as IC. Finally, if neither viral load nor CD4 results are reported in month 10 to 14 but the patient remains in care and does not have a current AIDS-defining condition, a default outcome of IC is assigned. The flowchart should be followed for each patient in the sample, with the result being each patient assigned to a single outcome category.

**Step 7: Estimates of Average Cost per Outcome**

Once each patient in the sample has been assigned an outcome, the average cost for each outcome category can be calculated using the formulas in Box 1.

Each of these values is simply the average cost incurred in the first 12 months after ART initiation for a patient with the specified outcome. In general, we would expect the average cost per NIC patient to be quite a lot lower than the average cost per IC or NR patient, simply because NIC patients do not remain in care for the full 12 months and thus utilize less than 12 months’ worth of medications, clinic visits, and so on. We might also expect NR patients to cost more than IC patients, because those who do not do well on first-line ARVs might be switched to more expensive second-line drugs or incur additional costs for management of toxicities, and so on. Calculating the values shown in Box 1 will confirm or refute these expectations for individual clinics.

### Box 1. Average Cost per Outcome Formulas

<table>
<thead>
<tr>
<th>Formula</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Average cost per patient initiated} ) = ( \frac{\text{Total cost for all patients in the sample}}{\text{Number of patients in the sample}} )</td>
<td></td>
</tr>
<tr>
<td>( \text{Average cost per patient in care and responding (IC)} ) = ( \frac{\text{Total cost for all patients in care and responding}}{\text{Number of patients in care and responding}} )</td>
<td></td>
</tr>
<tr>
<td>( \text{Average cost per patient in care but not responding (NR)} ) = ( \frac{\text{Total cost for all patients in care but not responding}}{\text{Number of patients in care but not responding}} )</td>
<td></td>
</tr>
<tr>
<td>( \text{Average cost per patient no longer in care at study clinic (NIC)} ) = ( \frac{\text{Total cost for all patients no longer in care}}{\text{Number of patients no longer in care}} )</td>
<td></td>
</tr>
</tbody>
</table>
Step 8: Calculation of Cost to Produce a Patient in Care and Responding

The final step in the methodology is to calculate the cost-effectiveness measure, which is the average cost to produce a patient in care and responding. The formula for this value is shown in Box 2. This value will be larger than the average cost per IC patient, because it takes into account the resources used for patients who were NIC or NR at the end of the 12-month period. It thus captures in a single measure both the resources used and the outcomes achieved by the clinic. As is evident from the formula, a lower cost to produce an IC patient can be achieved by either spending less per patient initiated or improving patient outcomes. For some sites, it might make sense to spend more per patient initiated, if patient outcomes can be improved by the same or a greater amount.

APPLICATION OF THE METHODOLOGY: A LARGE PUBLIC HOSPITAL IN SOUTH AFRICA

As part of an ongoing evaluation of the costs and outcomes of AIDS treatment in South Africa, we are applying the methodology described above to diverse ART delivery sites. In this section, we present the results for our first study site, an HIV/AIDS clinic within a public hospital in Johannesburg.

The study site is one of the largest AIDS treatment clinics in South Africa. By mid-2007, it had nearly 6,000 patients on ART and was monitoring some 12,000 patients who were not yet eligible for ART under South African guidelines. Most support for the clinic is provided by the provincial government, but renovation of the clinic building, data management, and some clinicians’ salaries are paid for by an international donor. The clinic provides the full range of clinic-based HIV/AIDS care and treatment services, with the exception of treatment for TB, which is provided elsewhere in the hospital. The clinic serves an urban population living in both formal and informal settlements within a large metropolitan area.

Patient Outcomes

We drew a sample comprising the first 100 adult patients who initiated ART at the clinic as of January 1, 2005, and who did not transfer formally to another treatment facility in the 12 months after initiation. Because the clinic was initiating so many patients on ART each month, we were able to fill our sample with patients who started ART in just the first two months of the year. Our study period was thus almost identical to the calendar year 2005.

After we entered all the data for our patient sample into a database, we found that their outcomes were as shown in Table 4.Of the 100 patients in our sample, 67 were classified as in care and responding, 7 as in care but not responding, and 26 as no longer in care. Table 4 also shows which indicators we used to assign outcomes. For example, of the 67 IC patients, 37 had undetectable viral loads, 4 had not had viral load tests done but had CD4 increases of at least 50 cells/mm³, and 26 had not had viral load tests or CD4 counts performed but had no AIDS-defining conditions and were thus classified as IC by default. Of the 26 who were no longer in care, 2 were known to have died and 24 had stopped attending the clinic for unknown reasons. It is likely that a large number of those who

<table>
<thead>
<tr>
<th>Box 2. Cost to Produce a Patient in Care and Responding Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average cost to produce a patient in care and responding = Total cost for all patients in the sample / Number of patients in care and responding</td>
</tr>
</tbody>
</table>
stopped attending were in fact unreported deaths, though some patients may have resumed treatment at other sites later on. Although 26% attrition is substantial, it is consistent with the experience of public sector treatment programs throughout sub-Saharan Africa, which have so far reported all-cause attrition rates averaging 25% after 12 months.\textsuperscript{16}

**Costs**

Most of the patients in our sample were started on the standard first-line ARV regimen indicated by the South African national guidelines. There were some variations, however, due to previous ARV exposure and clinician judgment. Although the guidelines call for laboratory tests to be performed on a predetermined schedule, there was also quite a lot of variation in lab test utilization by the patients in our sample. For example, some patients had several CD4 counts over the course of the 12-month period, while others had none after their initial test to establish treatment eligibility. The unit costs for some of the most commonly used resources at our site and the average number of units used per patient are shown in Table 5 (next page).

When we added up all the costs the site incurred in treating the 100 patients in our sample for the 12 months after they initiated ART, we found an average cost per patient initiated of US$756 (standard deviation US$308). This total consisted of US$371 for drugs (49%), US$197 for laboratory tests (26%), US$116 for outpatient clinic visits (15%), and US$72 for infrastructure and other fixed costs (10%).

### Table 4. Study Sample Treatment Outcomes at 12 Months after ART Initiation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients in sample</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>In care and responding (IC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable viral load</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Acceptable CD4 change</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No WHO stage III/IV condition</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Total in care and responding</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td><strong>In care but not responding (NR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO stage III/IV condition</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Detectable viral load</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Unacceptable CD4 change</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total in care but not responding</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><strong>No longer in care (NIC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Stopped attending site</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Total no longer in care</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>
The average cost per IC patient, US$903, is the cost per patient that our site would incur if it could keep 100% of its patients in care and responding. In our sample, however, only 67% of patients remained in care and responding. The average cost to produce a patient who remains in care and responding at 12 months is thus considerably higher. Dividing the total cost to treat all the patients in our sample by the number of IC patients gives us an average production cost of US$1,128 per IC patient. This value, our cost-effectiveness measure for this site, takes into account both the resources the site used to treat our sample of patients and the outcomes that were achieved. As can be seen from Table 6, if

<table>
<thead>
<tr>
<th>Resource</th>
<th>Unit Cost (USD)</th>
<th>Average Number of Units Used per Patient in 12-Month Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T (stavudine)</td>
<td>$3.57</td>
<td>7.8</td>
</tr>
<tr>
<td>3TC (lamivudine)</td>
<td>$6.20</td>
<td>9.3</td>
</tr>
<tr>
<td>EFV (efavirenz)</td>
<td>$27.75</td>
<td>8.1</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 count</td>
<td>$8.82</td>
<td>2.7</td>
</tr>
<tr>
<td>Viral load test</td>
<td>$44.12</td>
<td>1.4</td>
</tr>
<tr>
<td>Liver function test</td>
<td>$31.94</td>
<td>2.8</td>
</tr>
<tr>
<td>Full blood count</td>
<td>$5.96</td>
<td>2.8</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor consultation</td>
<td>$14.40</td>
<td>6.1</td>
</tr>
<tr>
<td>Nurse consultation</td>
<td>$3.88</td>
<td>6.1</td>
</tr>
<tr>
<td>Pharmacy medication pickup</td>
<td>$0.63</td>
<td>9.0</td>
</tr>
<tr>
<td>Fixed costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average monthly fixed costs</td>
<td>$6.85</td>
<td>10.5</td>
</tr>
</tbody>
</table>

**Average Cost per Outcome and Cost-Effectiveness**

Using the formulas introduced earlier in this chapter, we then estimated the average costs per outcome shown in Table 6. The average cost per patient who remained in care and was responding to therapy at the end of the 12-month period was US$903. As expected, patients who did not remain in care for the full 12 months (NIC) cost much less (only about a third as much) as those who did. It is also not surprising that somewhat more was spent on those who remained in care but did not respond (NR) than on those who did respond (IC).
our site were to retain 100% of its patients in care and responding, its total costs would rise, from an average of US$756 per patient treated to US$903 per patient initiated. Its production cost per IC patient, however, would fall, from US$1,068 to US$850. The site would thus become more cost-effective despite the increase in its absolute costs.

CONCLUSION

The methodology described in this chapter can be used by individual treatment sites and programs to generate practical information about the costs and outcomes they are achieving and to answer questions about why some patients cost more to treat than others, why some sites appear to be more efficient than others, and what the relationship is between resources used (costs) and outcomes achieved. This information can then be used to improve resource allocation both within and among treatment sites and to strengthen overall program quality. Counterintuitive findings, such as that a site may be spending too little rather than too much, or that reducing a site’s loss-to-follow-up rate may cause total costs to rise, can also help planners and funders predict future needs more accurately. Finally, by comparing results across multiple sites and settings, research of the type described here can create a better understanding of the challenges faced by national treatment programs as a whole and of the successes they are achieving.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Average Cost in USD per Patient with This Outcome (Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated (all patients)</td>
<td>$756 ($308)</td>
</tr>
<tr>
<td>In care and responding (IC)</td>
<td>$903 ($173)</td>
</tr>
<tr>
<td>In care but not responding (NR)</td>
<td>$981 ($53)</td>
</tr>
<tr>
<td>No longer in care (NIC)</td>
<td>$317 ($154)</td>
</tr>
</tbody>
</table>

a This assumes that the cost to treat the patients who previously would have died or stopped attending the clinic will be the same as the cost to treat the patients who remain in care now. This may not be the case, as NIC patients may differ from IC patients in ways that will affect their medical care needs.
REFERENCE LIST


Implementing the Continuum of Care for HIV: Lessons Learned from Tanzania

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aFamily Health International, Tanzania
bMinistry of Health and Social Welfare, Tanzania
cWorld Health Organization, Tanzania

The increasing availability of antiretroviral therapy (ART) in sub-Saharan Africa has brought with it the possibility of better health and longevity. But people living with HIV continue to require a broad array of services ranging from psychosocial and medical care to nutritional and legal support.1 As HIV infection progresses to illness and advanced-stage disease, the patient’s psychological, social, nutritional, clinical, and nursing care needs also change in nature and intensity. These needs are determined by biological factors (e.g., age, gender, and nutritional status), social factors (e.g., living environment and poverty level), and health system factors (e.g., distance to a facility and quality of services), and consequently care and support programs were developed in response to these various and changing needs. While life expectancy has improved tremendously with the provision of ART, improved care and support can further enhance a patient’s quality of life and well-being. The early experiences of those receiving long-term ART in sub-Saharan Africa show that medical, psychosocial, and nutritional needs persist during treatment and, if properly met, can help improve patient adherence to ART.2

HIV/AIDS-specific interventions and responses cannot operate in isolation; they must be integrated into a broader network of care and support programs within health facilities, communities, workplaces, and households. Now that HIV has become a chronic, manageable disease, proper treatment requires the patient’s continual engagement with various parts of the health-care and social-support system. It is therefore necessary that the provision of HIV care be comprehensive in nature and provided along a continuum across homes, communities, and care facilities.

In the late 1980s, local nongovernmental organizations (NGOs) in Uganda, Zambia, and Thailand pioneered a comprehensive approach to HIV/AIDS care and support delivered across a continuum from hospitals to communities.3,4 These early continuum-of-care (COC) initiatives were informed by lessons learned from experiences and qualitative studies pointing to the comprehensive needs of people living with HIV and by the fact that most of the care for chronic illnesses in resource-limited settings is being provided in the home.5,7

In response to these findings and the rapid expansion of home-care initiatives, global public-health
FROM THE GROUND UP: DEVELOPING PATHWAYS AND PARTNERSHIPS

institutions such as the World Health Organization (WHO), the Joint United Nations Program on HIV/AIDS (UNAIDS), and international NGOs developed norms and standards in the early 1990s for a comprehensive care approach. These were then adapted into national guidelines in several countries by national AIDS programs within ministries of health. Soon thereafter, additional norms and standards were adopted for the safe and effective use of ART in resource-limited settings that follow public-health approaches at the hospital and community level. Many health authorities at the local level, together with public and not-for-profit health facilities and community programs, are strategizing and implementing comprehensive care activities across a continuum, including the provision of and adherence to lifelong ART.

HEALTH-CARE REFORM AND DECENTRALIZATION

As early responses to the HIV pandemic were being developed in the most affected countries, ministries of health in these countries wanted to shift responsibility for planning and executing HIV care activities away from the central, national level to the district and community level. To accomplish this, a peripheral public administrative unit, called the district in anglophone Africa, cercle in francophone Africa, or thana in Southeast Asia, was created to lead the planning and implementing of HIV care activities for each respective district or community.

By holding district and local health authorities accountable for administering care activities, the governments encouraged collaboration among the relevant providers within the local medical and social sectors. This would mean, for example, that private and not-for-profit facilities, such as NGO and mission hospitals, would work together to:

- share and inform;
- develop action plans and relevant HIV care packages at both the facility and community care level;
- develop district budgets; and
- design functional mechanisms for referring patients between community care programs, home care, and facility-based clinical care.

Working in partnership is particularly important for clinical HIV care providers, as it offers opportunities to standardize essential HIV care packages with the aim of rapidly reaching more people in need while acknowledging individual patient care needs. Cost-recovery modalities are another reform put into practice throughout sub-Saharan Africa, with provisions that exempt some groups from contributing, such as TB and HIV patients, pregnant mothers, and children under five years of age. Through these modalities, patient contributions from general outpatient and inpatient care can be invested at the local level to directly improve patient care for all. However, it is too early to determine whether such health-care reform activities have improved the overall quality of care in general and HIV care in particular. With the concurrent trend toward privatization of health-care delivery, it continues to be difficult to ensure affordable access for the most economically disadvantaged individuals.

In response to concerns about affordability, observational studies began to explore the impact of HIV/AIDS at the household level. A study in Uganda found that it was unrealistic, even at a relatively early stage of the epidemic, to expect extended families to provide the full range of necessary care services to people living with HIV. It was also discovered that extended families in rural and highly affected areas were unable to provide assistance and that many were in fact unwilling to do so.

Further research revealed the following:
It is evident that the relatives and friends are valuable resources in times of need. Research has, however, questioned the notion that the extended family is a resource to be relied upon at all times, and has suggested that families may not be able to deal with AIDS as they have with other health problems . . . We must therefore question whether the traditional reliance on extended kin systems will address the needs of HIV/AIDS patients and their informal carers.15

The authors of this study concluded by asserting that blanket statements about the role of the extended family in African countries serving as a safety net need to be questioned, and assumptions that the extended family will be ready and able to assist sick members should be treated with caution. The extended family, they assert, is a “safety net with holes.”15

To a certain extent, informal care provision at the household level has been complemented by formal HBC (home-based care) programs.16 The PHC (primary health care) initiatives started in the 1970s brought with them the establishment of Village Health Committees and trained PHC volunteers. In the mid-1980s, a revival of PHC practice occurred in response to the immediate palliative care needs of people living with HIV within households.3,4 With the increased availability of ART since 2005, HBC programs have been strengthened and equipped to provide an essential, comprehensive care package that includes ART services and results in better rates of survival.17

CONTINUUM OF CARE IN PRACTICE
During the mid- to late 1990s, programmers and policymakers realized that public-sector health-care providers alone were not going to be able to manage the high levels of AIDS-related morbidity. To alleviate some of this burden, they began considering ways to shift the locus of clinical care from the health facility to the community. Initial efforts in this area were modeled after hospital-based outreach, whereby hospital staff travel directly to patients’ homes to provide care. As Osborne et al explain:

The argument for the hospital initiated home-care models was that, given the limited treatment available in hospital for many AIDS patients, it was neither in the health services’ nor the patients’ interest for them to be in hospital. Instead it was better to care for patients at home, looked after by their own families with dignity. Not surprisingly, however, these outreach programs were found to be time-consuming and expensive, especially in rural areas.18

Faith-based hospitals, NGOs, and community-based organizations (CBOs) have been particularly adept at responding to patient care needs at the household level through outreach programs. The role of government hospitals and clinics in the implementation of HBC has been largely limited to coordinating functions.19

In response to the growing recognition that a more programmatic approach to care for people living with HIV was needed to assist and coordinate the many ongoing responses, the WHO, in consultation with a wide group of experts, developed a framework for comprehensive care across a continuum, known as the Care Continuum (Figure 1, next page).20-22

The WHO continuum contains a range of comprehensive services, including counseling and testing, clinical management, nursing care, and community-based social support. The provision of care extends from the individual/home to the hospital, through various levels of care linked with discharge planning and referral networks, and back to the individual/home. The intent of this model is to promote, create, and sustain a holistic approach to care and support for people living with HIV. The framework locates the person living
with HIV at the center of a wide range of actors who are dynamically linked. The entry point to the continuum is counseling and testing for HIV. Home care is one element of this broader system of care provision, and it is an element perceived to be particularly relevant and important in resource-limited settings.

Services that meet the needs of people living with HIV and their families reflect four interrelated domains: medical services throughout all infection stages; psychosocial services, ranging from emotional support to adherence counseling to orphan support; socioeconomic support services; and human rights and legal support services. Over the years, these services have become known as comprehensive care and support (Figure 2).

The comprehensive Care Continuum framework is an important advance in the development of an agenda for HIV care from an international public-health perspective. It provides a standard that governments can follow to ensure that they enable people living with HIV to receive clinical and nonclinical care in the four domains, while illustrating the need to create linkages between these various care domains. However, viewed through the care-economy lens, and taking into account the common practice of unlinked care, a number of key areas must be addressed to make the COC fully functional.
1. **Strengthening of the prevention component within care delivery.** The recently developed intervention from the Centers for Disease Control and Prevention (CDC) and WHO calls for essential elements to be considered as part of the intervention, such as the following:
   - Psychosocial counseling and support, including disclosure, partner notification and testing, and counseling for prevention and psychosocial adherence support
   - Cotrimoxazole prophylaxis
   - Screening for TB and TB-preventive therapy
   - Prevention of fungal infections
   - Sexually transmitted and other reproductive-tract infection services
   - Malaria prevention
   - Nutritional assessment, support, and micronutrient supplements
   - Family planning
   - Water, sanitation, and hygiene

2. **Operational tools, which are essential to implement a COC.** These tools include the following:
   - Directory of services (i.e., a listing of who provides what in the district)
   - Networking (i.e., well-linked, coordinated collaboration between different comprehensive care programs or institutions in all four domains)

3. **Referral systems.** Referral relationships must be developed or strengthened within the various hospital units, such as the following:
   - Between the ART clinic and counseling and testing services, TB clinic, antenatal clinic (ANC) / prevention of mother-to-child transmission (PMTCT) clinic, and inpatient wards

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**Figure 2. Components of comprehensive HIV/AIDS care and support**

VCT = voluntary counseling and testing; PMCTC = prevention of mother-to-child transmission; OI = opportunistic infection; STI = sexually transmitted infection; PLHIV = people living with HIV

*Source: Adapted from Family Health International* [23]
• Between the hospital and the community-based services, including support services for people living with HIV
• Between district-level facilities and higher-level specialized medical services

**LINKING HOME-BASED CARE WITHIN THE CONTINUUM OF CARE IN TANZANIA**

**Development of Home-Based Care in Tanzania**
Implementation of organized HBC services by the Ministry of Health and Social Welfare (MOHSW) in Tanzania started in 1996 as pilot projects in eight districts of the Rukwa and Coast regions with support from DANIDA (Danish International Development Assistance). Findings from the pilots at the community level revealed that the services were highly appreciated and in ever increasing demand. Since then many organizations, including WHO and UNAIDS, international and local NGOs, faith-based organizations (FBOs), and community groups, have joined in to support HBC services in different parts of the country. By 2002, HBC services had been established in 28 districts, and by the end of 2006, the services had reached 70 out of 126 districts, with an estimated 50,000 patients reached. However, the pace of expansion is still slow and services have yet to reach the target set by the MOHSW of 320,000 patients in need of HBC and support for orphans and other vulnerable children (OVC).

To support program implementation and monitoring and to harmonize various trainings, the MOHSW, in collaboration with its partners, has developed a national program with manuals, course plans, supervision tools, and guidelines.

HBC service provision in Tanzania follows two approaches: (1) health-care staff trained as HBC providers deliver outreach services on a part-time basis in addition to performing other health-care duties in hospitals or clinics, or (2) trained community-based providers who are primarily volunteers working for NGOs, FBOs, or CBOs provide HBC exclusively. The latter approach is the approach most often used.

**The Importance of a Continuum of Care for Treatment**
Before the availability of ART in Tanzania, HBC focused primarily on AIDS-related chronic and terminal illness. Palliative care services focused on nursing care, psychosocial support, and home management of opportunistic infections. With the introduction of ART in the public sector in October 2004, the role of HBC has expanded to include care and support of patients on ART and directly observed therapy short course (DOTS) for TB patients. The role of HBC providers as treatment assistants and in monitoring adherence has proven to be particularly appreciated by people living with HIV; these roles widen the scope of HBC in the context of the COC for people on lifelong ART.

The new ART-related roles of HBC volunteers/providers in all Tanzanian HBC programs include the following:
• Preparing clients, family, and community members by setting expectations concerning treatment
• Addressing issues of disclosure
• Recognizing and linking patients who need referral to HIV care and treatment clinics (CTCs)
• Identifying treatment assistants within the household
• Discussing issues of safe storage of antiretroviral drugs (ARVs) at home
• Monitoring and supporting adherence to ART
• Identifying, managing, and referring side effects of ART as well as nutritional issues

Since ART is initiated at the hospital and clinic level while the majority of ART support services
are needed at or near the patient’s home, HBC services are well placed to contribute greatly to the success of the COC.

Tanzania has opted for an integrated delivery model for the provision of ART. As part of this strategy, outpatient services at all hospitals in the country will be expanded to include integrated HIV CTCs. Each CTC will include space for triage nursing, clinical and counseling services, and data management. The CTC will also be closely linked to the TB clinic and the reproductive health department. Among the CTC staff is an HBC focal person who refers informed patients to HBC services. Often staff from HBC programs and/or support groups for people living with HIV serve as go-betweens between patients and providers.

Community- and facility-based care go hand in hand and are mutually reinforcing in making

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**Figure 4. Model for the Tunajali community network for home-based care and care of orphans and other vulnerable children**

CSO = civil society organization; CMAC = community medical advisory committee; CTC = care and treatment clinic; DHMT = district health management team; DSW = department of social work; HBC = home-based care; IGAs = income-generating activities; MVCC = most vulnerable children committee; OVC = orphans and other vulnerable children; PLHIV = people living with HIV
CASE STUDY: THE TUNAJALI PROJECT

THE TUNAJALI ("WE CARE") partner program is one example of COC implementation in Tanzania. The program operates in three regions—Dodoma, Morogoro, and Iringa—where the capacity of government and faith-based hospitals and community organizations is being strengthened to provide HIV care, HIV treatment, and orphan support across a continuum (Figure 53). Health facilities and community organizations in these three regions are provided with technical, managerial, and financial assistance through the Tunajali project. The project was implemented by Family Health International (FHI) and Deloitte and supported by USAID.

The Tunajali project initiated the nationally mandated steps toward regionalization in the Iringa, Morogoro, and Dodoma regions. Currently all 33 hospitals in the three regions have the basic elements needed to run CTCs, with support from the MOHSW. Tunajali’s financial and technical assistance is helping centers reach more people, maintain quality of care, and integrate the program into the existing health-service delivery system. A major constraint that was recognized early on in the development of the CTCs was the lack of human resources. Staff were unwilling to take on additional tasks or train for new tasks in addition to their ongoing duties in the hospitals. With Tunajali’s major focus on training, supportive supervision, and effective referrals, this was a serious constraint. Few hospital staff were shifted to CTCs full-time, with the majority of CTC positions filled on a rotating basis.

Tunajali also began to pilot a strategy that involved hiring, training, and deploying retired health-care professionals at the major regional and district hospitals in the three regions to alleviate the human resource shortage (i.e., the “Retired But Not Tired” program). An assessment of the functioning of 28 retired hospital workers in four hospitals showed remarkable acceptance by staff and patients and improved efficiency in running the CTC.

In the same regions, Tunajali is assisting community HBC programs to enroll clients as early as possible into care and treatment programs and to ensure a COC.

Household support offered by various CBOs is emphasized during patient CTC visits, and referrals are made and recorded to ensure follow-up at the next visit. The impact of HBC is magnified by the provision of home care kits to help with immediate medical, hygienic, and nutritional needs. The kits include such items as bed nets, water purification tablets, micronutrients, and pain-relieving and other essential drugs. HBC volunteers are advised to accompany people living with HIV when they go for their hospital visits. This ensures consistency and bridges the gap between the hospital and other clinical services patients may need. Volunteers are asked to follow up with patients to make sure they strictly adhere to their daily treatment schedules and do not miss their clinic appointments.

Tunajali encouraged communities to go one step further by promoting the establishment of income-generating activities to help support families looking after people living...
with HIV. Animal husbandry is one popular activity that not only provides income but also helps meet the increased nutritional requirements of patients. Volunteers for these programs are supported with travel stipends, bicycles, and in-service training.

People living with HIV and community members, particularly adult males, still raise the issue of stigma as a hindrance to their access to care. Currently, HIV CTC services reach twice as many adult females as males, and less than 10% of patients enrolled are children. The Kimara project, in collaboration with Muhimbili University of Health and Allied Sciences (MUHAS) in Tanzania, has developed tools that teach people how to discuss shame, blame, and disclosure in an effective way at the community and household level. Training of national facilitators on the use of this tool is ongoing, with 106 trained so far.28 Piloting of the tool has led to a noticeable transformation among staff and volunteers toward greater openness, and they are now capable of training families and communities on how to overcome stigma and related issues. Tunajali plans to apply this tool in all regions where it operates.
long-term quality care, treatment, and support possible. This linkage is ensured by the HBC focal persons from hospitals and district health services, who meet with civil society organizations such as CBOs, support groups for people living with HIV, FBOs, and NGOs to coordinate activities. In districts where active HBC programs are adequately funded, district coordinating committees have been formed to ensure effective referrals of patients from one service to another. District directories of services have been established, and these are given to service providers, who use standardized referral forms to refer patients and their families to different types of services that they may need from time to time.

The CTCs have procedures to link patients easily with community and HBC programs, usually run by civil society organizations. Patients can be referred in a timely manner to CTCs to be assessed for clinical or treatment needs. Likewise, patients can be referred to HBC programs close to their homes so that staff and volunteers can provide follow-up, reinforce adherence, and provide other comprehensive care services such as nutritional and emotional support, and prevention education for all household members.

Regionalization of Care and Treatment Services
In 2005, the National AIDS Control Program (NACP), together with key staff of Family Health International (FHI), WHO, CDC, and the United States Agency for International Development (USAID), developed a novel approach for partners assisting the MOHSW in implementing the COC. Under this plan, formally initiated by the MOHSW in September 2005, partners were assigned specific regions of the country instead of specific hospitals. This lessened the duplication of resources and the administrative burden on care and treatment facilities, because each facility could work with just one partner rather than with multiple partners. The partners then helped regional and district authorities plan and support the scale-up of care and treatment at regional, district, and health center levels.

The goals of regionalization are to reach a greater number of patients more quickly, foster more ownership and commitment among national authorities, make it easier for patients to be referred within the region, and achieve the desired results more cost-effectively (Figure 4).29

CHALLENGES IN MAINTAINING A CONTINUUM OF CARE
In the course of implementing Tanzania’s COC approach to reach all in need—estimated to be 400,000 people in need of care, treatment, and support and over one million orphans30—critical challenges still need to be addressed. These challenges, along with key recommendations, are listed in Table 1.
<table>
<thead>
<tr>
<th>Challenge</th>
<th>Key Recommendation</th>
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<tbody>
<tr>
<td><strong>Adequate access to quality continuum-of-care services</strong></td>
<td>Rather than initially focusing only on hospitals, a district-based approach can be used, whereby all facilities are assessed and receive regular training and follow-up. Regionalization has helped this process in Tanzania and could be explored in other countries.</td>
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<tr>
<td><strong>Inadequate infrastructure</strong></td>
<td>The government and supporting partners should continue to mobilize resources to renovate health-facility infrastructure.</td>
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<td><strong>Human resource constraints</strong></td>
<td>The “Retired But Not Tired” model should be extended to all hospitals nationwide.</td>
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<td><strong>Persistent stigma and low community HIV awareness</strong></td>
<td>Activities addressing stigma should be included in care and treatment packages for people living with HIV at all service delivery points across the continuum.</td>
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<tr>
<td><strong>Lack of health insurance for people living with HIV</strong></td>
<td>Community-based health insurance schemes should be promoted and piloted to assess their feasibility in resource-limited settings.</td>
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**Table 1. Critical Challenges and Recommendations for Implementation of the Continuum-of-Care Approach**

Care and treatment services have not yet reached most rural areas. Travel to urban district hospitals is unreliable and expensive for the majority of Tanzanians. Although the regionalization process allows for division of resources to cover all facilities, effective referrals and regular follow-up need to be improved.

Obtaining adequate space for care and treatment services has become a huge challenge due to the increasing numbers of patients. Crowding and long waits are reported.

Understaffing causes major bottlenecks at most sites in Tanzania. With support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), an emergency hiring plan for 375 posts will be established, but a deficit of 10,000 vacancies remains. The pilot "Retired But Not Tired" project was successful in alleviating some of this burden.

HIV care and treatment center services reach twice as many adult females as males, and less than 10% of patients enrolled are children. Higher stigma among males, poor community knowledge about antiretroviral (ARV) effectiveness, and missed opportunities to identify exposed or infected children are believed to be some of the reasons for low uptake of care and treatment services by males and children.

Regular visits for treatment and all necessary referrals within the continuum incur travel expenses and often payments to clinics and hospitals. As the great majority of people living with HIV do not have health insurance, all these are out-of-pocket costs.
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<th>Challenge</th>
<th>Key Recommendation</th>
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<tr>
<td>Irregular and inadequate supply lines to the various services within the</td>
<td>Continued pressure is needed to increase the share of gross domestic product (GDP) allocated to the health sector and sustain donor commitments.</td>
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<td>continuum Large numbers of patients enrolled at care and treatment</td>
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<td>centers and in home-based care programs generate increasing demand</td>
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<td>for home-care kits and supplies, laboratory reagents, drugs for</td>
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<td>preventive therapies, and other items. Supplies are largely reliant on</td>
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<td>external donor funding from the Global Fund, the President’s Emergency</td>
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<td>Plan for AIDS Relief (PEPFAR), or other organizations.</td>
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<td>Low involvement of council and regional health management teams</td>
<td>Health reforms and decentralization should be supported with clear guidance on roles and responsibilities in areas such as networking, coordination</td>
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<tr>
<td>Field observations revealed that key council and regional health</td>
<td>of various stakeholders, supportive supervision, and monitoring.</td>
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<td>management team members are not fully involved in planning, budgeting,</td>
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<td>and monitoring HIV care and treatment activities in their areas.</td>
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<td>Low priority given to community home-based care by donors and national</td>
<td>Better and more widespread documentation of the contribution of home-based care service-delivery programs in improving quality of life, strengthening</td>
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<tr>
<td>government Most funds are earmarked for antiretroviral therapy (ART)</td>
<td>the effectiveness of care and treatment programs, and reviving primary health care is needed to support greater resource mobilization.</td>
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<td>services and management of opportunistic infections, with very few</td>
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<td>donors supporting the scale-up of community home-based care services.</td>
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<td>Consequently, the coverage of home-based care services lags far</td>
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<td>behind that of facility-based care and treatment in several regions.</td>
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<tr>
<td>Poor integration of care, treatment, and support programs with preventive</td>
<td>The international public health community, including major donors and stakeholders, needs to agree on global guiding principles regarding the essential</td>
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<td>services A good continuum-of-care program should be fully integrated</td>
<td>complementary and mutually reinforcing relationship between prevention and care.</td>
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<td>with preventive services Yet care, treatment, and support interventions</td>
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<td>are not being integrated with preventive services, leading to many</td>
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<td>missed opportunities.</td>
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HERE ARE MORE THAN 40 MILLION people living with HIV infection globally, 24.7 million of whom live in sub-Saharan Africa. Increasingly, women are disproportionately affected by HIV; 60% of HIV-positive adults in Africa are female, and the vast majority are women of childbearing age. Young women ages 15 to 24 are four times more likely to be HIV-infected than men of similar age; these are the years during which many women become mothers and begin to raise families.

Children and families are strongly affected by issues that affect women. The vast majority of the more than two million children living with HIV were infected through mother-to-child transmission. The specific vulnerabilities of women to acquiring HIV infection, coupled with inadequate access to family planning and HIV prevention and treatment services, have resulted in an unabated worldwide pediatric HIV pandemic. Children living with HIV are at high risk for morbidity and mortality early in infection, with almost half dying by the age of two if their disease is not properly managed. Those who survive face the potential loss of infected parents, along with intermittent ill health and overwhelming stigma. In short, the effect of HIV on families, with women as the lynchpin, has been devastating.

Recognizing the disproportionate vulnerability of women to HIV infection as well as to poverty, stigma, and discrimination, the MTCT-Plus Initiative at the International Center for AIDS Care and Treatment Programs (ICAP), Columbia University Mailman School of Public Health, was established to address the needs of HIV-positive women, children, and families in low-resource, high-HIV-prevalence settings. In this chapter, we share the genesis and principles of the MTCT-Plus Initiative and, using a case study of the MTCT-Plus Initiative site at the Makerere University–Johns Hopkins University (MU-JHU) clinic at Mulago Hospital in Kampala, Uganda, illustrate the successes and challenges of establishing family-focused HIV care programs.

HISTORICAL BACKGROUND

In the year 2000, there were few programs in sub-Saharan Africa to meet the needs of HIV-positive adults, let alone children and their families. Several explanations have been advanced for this lack of attention. The costs of antiretroviral therapy (ART) and associated care were considered prohibitive. Health-care infrastructure was viewed as too weak to support the comprehensive, continuous care services required to maintain large numbers of
individuals in care over long periods of time. There were concerns that individuals in developing countries would not be able to meet the rigorous demands of twice-daily treatments, frequent medical visits, and a lifetime commitment to therapy. There were no models for treating women and children in large numbers. Finally, no group had explicitly attempted to treat individuals as part of a family unit.

Historically, the first HIV care programs implemented in Africa targeted prevention of mother-to-child transmission (PMTCT). The results of HIVNET study 012 demonstrated that when a single dose of the antiretroviral (ARV) drug nevirapine was given to a mother at delivery and to her baby shortly after birth, the risk of transmission could be reduced by 42%. These results, coupled with the availability of rapid HIV tests, propelled the establishment of PMTCT programs within existing antenatal and maternity services. Importantly from a programmatic perspective, PMTCT services were consistent with the prevailing “episodic” health-care model; diagnosis and treatment could be accomplished within a single health visit and required little additional healthcare infrastructure. However, while women were given the opportunity to make use of a potentially lifesaving measure for their infants, few programs offered ongoing care and treatment beyond delivery for the woman or her baby.

**BIRTH OF THE MTCT-PLUS INITIATIVE**

In 2000, Allan Rosenfield, dean of the Mailman School of Public Health at Columbia University and an obstetrician/gynecologist, gave a talk at the 13th International AIDS Conference in 2000 in Durban, South Africa, entitled “Where is the M in MTCT?” In this talk, he called upon conference attendees to consider the mothers in the context of PMTCT—for the women’s own health, for the health of their babies, to ensure that children did not become orphans, and to preserve the integrity of the family. This address coincided with an effort by the Rockefeller Foundation to define its future efforts in relation to the AIDS pandemic. These themes coalesced into an initiative to provide care and treatment to individuals living with HIV infection, in direct contrast to existing programs, which primarily focused on prevention activities. With expanded financial support from multiple philanthropic foundations, the MTCT-Plus Initiative was launched with an ambitious plan to provide pregnant women, their babies, and their partners and household members with access to HIV care and treatment.

This initiative was one of the first multinational efforts that made HIV care and treatment a reality in resource-limited settings. The initiative predated the development of most national ART scale-up strategies, but experience accrued within the initiative and enabled partners and programs to positively impact the design and implementation of their national ART programs. The MTCT-Plus Initiative was also the first program in resource-limited settings to use PMTCT as an entry point for service delivery. In this model, pregnant women diagnosed with HIV through local PMTCT programs could enroll in the initiative’s comprehensive HIV care and treatment services. Once enrolled, all women were encouraged to enroll their HIV-exposed infants as well as partners or spouses, older children, and other household or family members living with HIV infection (Figure 1).

The services offered under the initiative were designed to be comprehensive, with a focus on keeping each member of the family healthy and engaged in long-term care. This approach addressed the different needs of HIV-positive family members, which are likely to change over time with the progression of HIV disease and improvements in health after initiating ART. In addition to ART for those who were eligible, a variety of HIV-related
and primary health-care services were provided, including opportunistic infection prophylaxis for Pneumocystis jirovecii pneumonia (PCP), bacterial infection, and cryptococcal disease; TB screening, treatment, and isoniazid preventive therapy; multivitamins and nutritional evaluation and support; access to family planning; and clinical and immunologic monitoring. Psychological support and adherence counseling were considered critical components of MTCT-Plus, and work with peers was actively nurtured. All services, including ART, were provided free of charge to participants. Costs associated with hospitalizations were generally not covered by the program, and at different times during the course of the initiative several sites charged participating adults a nominal fee that was subject to waiver in the case of financial hardship.

Pediatric care was emphasized as an essential component of family-focused services. All HIV-exposed infants were enrolled and followed until HIV infection could be definitively diagnosed or excluded. This emphasis on pediatric care included providing support to help sites access virologic tests that can provide early diagnosis of HIV infection during the first months of life. An algorithm of care for HIV-exposed and infected infants was established, and all children were subject to regular assessments of growth, developmental status, and CD4 lymphocyte counts while receiving opportunistic infection prophylaxis and ART, if eligible.

To accommodate the diverse and expanded workload associated with providing comprehensive care, multidisciplinary teams (MDTs) were hired at each site. These teams included some combination of counselors, nutritionists, social workers, peer supporters/educators, outreach workers, nurses, medical officers, and physicians. The teams were charged with meeting regularly to discuss patients and families, with everyone actively contributing to the care of the patients. The initiative also supported infrastructure development, including the purchase of CD4 count machines and other equipment, structural renovations, the development of ARV procurement and data collection systems, and improvement of local administrative and financial expertise. Extensive and ongoing training was conducted on-site to ensure high-quality HIV services and promote the mutual growth and development of the MDTs. Each site was also able to offer services to members of the healthcare teams and their families who required HIV care and ART. Together, these supports have promoted
and developed strong clinical MDTs that are now caring for women, children, and families and are increasingly able to support other local clinicians to give family-focused HIV care and treatment.

The sites for the MTCT-Plus Initiative were chosen through a competitive process. A request for applications was sent out by Columbia University in 2002. Grants were awarded to sites in Cameroon, Côte d’Ivoire, Rwanda, Zambia, Uganda, Mozambique, Kenya, Thailand, and South Africa (Table 1). Each site was asked to enroll at least 750 HIV-positive adults and children and to provide a package of multidisciplinary, family-focused care and treatment services based on a protocol developed by the initiative’s leadership group. Exposed infants as well as older children in the family or household living with HIV infection were routinely enrolled, but the proportions of adults and children were not specified. Ongoing close collaboration with local, often longstanding partners was key in the early stages of site development. Many sites awarded MTCT-Plus grants were providing PMTCT services or involved in PMTCT and HIV research and worked closely with their established partners to implement MTCT-Plus services. Other sites were part of early government programs to develop HIV services. Of note, many sites were initiating ART for the first time. There was limited experience and guidance available on how to support these kinds of large-scale HIV care and treatment programs in multiple RLCs and little experience in providing comprehensive, multi-disciplinary continuity services to pregnant and postpartum women and their families. Over time, each site has written its own unique blueprint toward self-sufficiency, but all passed through similar phases of program initiation, growth and development, and maturation. The MTCT-Plus site at the MU-JHU clinic discussed in this chapter illustrates this process.

IMPLEMENTATION OF THE MTCT-PLUS INITIATIVE AT MULAGO HOSPITAL, KAMPALA, UGANDA

Program Initiation
The MU-JHU site began by bringing together an MDT to learn and practice this new model of care. The team was selected on the basis of previous experience in the PMTCT program, commitment to provision of long-term HIV care, and desire to work within an MDT. The MDT consisted of a physician who was to coordinate the team, a nurse, a counselor, a pharmacist, a pediatrician, an outreach worker (health visitor), and a data clerk. Significant input was also obtained from other institutional staff who were not part of the core team. A PMTCT counselor coordinator and two nurses, one from the antenatal clinic (ANC) and another from the postnatal clinic, were later invited into the team to strengthen the relationship between the PMTCT clinics and the MTCT-Plus program.

The MDT had many activities to perform prior to initiating services, including developing standard operating procedures (SOPs), establishing linkages within the institution and community, determining enrollment criteria, customizing MTCT-Plus protocols, and training staff. The team embarked on weekly meetings to develop SOPs and identify key programmatic areas. The team met with health-care providers in key units such as the emergency, medical, pediatric, ANC, and maternity, units to sensitize medical personnel within Mulago Hospital about the program and to facilitate communication between personnel within various hospital departments.

The MDT set site-specific, nonclinical eligibility criteria for enrollment in the program. These criteria were necessary due to the limited number of women who could be enrolled in the MTCT-Plus Initiative from the large number of HIV-positive women attending antenatal care, as well as the need to provide long-term follow-up of enrolled women.
All women who met the nonclinical eligibility criteria were enrolled through the ANC. Eligible women were assisted in disclosing their HIV status to their partners and were then requested to bring all family members in for HIV testing and enrollment. In addition, HIV-positive women who had attended the PMTCT program, who had delivered within the last 18 months, and who had received follow-up care in the postnatal/child health clinic were also offered enrollment. Forty-seven orphaned HIV-positive children whose mothers had participated in HIVNET 012 and other research studies at the MU-JHU site were also enrolled in the program, as MTCT-Plus represented the only

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Table 1. Location of MTCT-Plus Initiative Sites

<table>
<thead>
<tr>
<th>MTCT-Plus Initiative Site</th>
<th>Location</th>
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<tbody>
<tr>
<td>FSU (Formation Sanitaire Urbaine) deYoupougon-Attie and Abobo Clinics</td>
<td>Abijian, Côte d’Ivoire</td>
</tr>
<tr>
<td>Nyanza Provincial General Hospital Clinic</td>
<td>Kisumu, Kenya</td>
</tr>
<tr>
<td>Moi University College of Health Sciences</td>
<td>Eldoret, Kenya</td>
</tr>
<tr>
<td>Beira and Chimoio Day Hospitals</td>
<td>Beira, Mozambique</td>
</tr>
<tr>
<td>Treatment and Research AIDS Center</td>
<td>Kigali, Rwanda</td>
</tr>
<tr>
<td>Perinatal HIV Research Unit, University of the Witswatersrand</td>
<td>Soweto, South Africa</td>
</tr>
<tr>
<td>Langa Health Clinic</td>
<td>Cape Town, South Africa</td>
</tr>
<tr>
<td>Cato Manor Clinic, University of Natal</td>
<td>Durban, South Africa</td>
</tr>
<tr>
<td>Mulago Hospital Clinic</td>
<td>Kampala, Uganda</td>
</tr>
<tr>
<td>St. Francis Hospital Clinic</td>
<td>Kampala, Uganda</td>
</tr>
<tr>
<td>Mtendere Health Clinic and Chelstone Clinic</td>
<td>Lusaka, Zambia</td>
</tr>
<tr>
<td>Camerooon Baptist Health Convention Board Clinics</td>
<td>Northwest Province, Cameroon</td>
</tr>
<tr>
<td>Thai Red Cross Clinic</td>
<td>Bangkok, Thailand</td>
</tr>
</tbody>
</table>

and ensure the involvement of the entire family. The criteria were: residence within a 20 km radius, partner disclosure, adherence to PMTCT care, willingness to be visited at home, and a stable living situation (defined as residence in a stable home in the vicinity of Mulago and planning to stay in Kampala for a long period).

Enrollment was also extended to co-wives and their children in the case of polygamous families. (Notably, few other MTCT-Plus sites included partner disclosure as a requirement for enrollment, and the disclosure criterion at MU-JHU was later changed from sharing HIV status with a partner to sharing with any other adult.)
As the team members became more experienced and recognized the lost opportunities to enroll prior to delivery, they developed a fast-track process to expedite enrollment and ART initiation for pregnant women with advanced disease. All women received a home visit from an outreach worker to map their residence and identify social barriers (e.g., drug and alcohol abuse), cultural norms, and beliefs likely to affect their care. A psychosocial evaluation was performed using the opportunity available at that time to provide ART to children living with HIV infection.

Due to the large number of women seeking HIV care and the limited program capacity, the enrollment process was initially staggered, with only three new families enrolled daily. In this way, the team was able to enroll new participants while providing intensive patient education, counseling, and high-quality care. The staggered nature of enrollment and the lengthy disclosure process led to a number of women being enrolled postpartum. As the team members became more experienced and recognized the lost opportunities to enroll prior to delivery, they developed a fast-track process to expedite enrollment and ART initiation for pregnant women with advanced disease.

All women received a home visit from an outreach worker to map their residence and identify social barriers (e.g., drug and alcohol abuse), cultural norms, and beliefs likely to affect their care. A psychosocial evaluation was performed using

![Figure 2. Adult clinical monitoring schedule](image-url)
site-specific standardized psychosocial evaluation forms. At enrollment, the patients’ HIV disease was clinically staged using World Health Organization (WHO) criteria, and laboratory tests were performed, including CD4 counts. On subsequent visits, the patients were separated into those eligible for ART and those ineligible. Those who did not meet the criteria for ART initiation were counseled, educated, and given appointments in three to six months, depending on their CD4 counts and WHO clinical stages. ART-eligible participants continued counseling sessions until the team was satisfied that they were ready to initiate ART (Figures 2 and 3).

**Program Growth and Development**

Primary HIV care, with attention to both medical and psychosocial needs, was the main focus of medical care and staff activity. Services provided included, but were not limited to, ART; cotrimoxazole prophylaxis; multivitamin supplementation; opportunistic infection prophylaxis; treatment of latent TB infection (LTBI); and screening, diagnosis, and referral for TB. These services, coupled with intensive patient education and family support, resulted in minimal patient loss to follow-up and an ART adherence rate of 99% (MTCT-Plus monthly statistics, unpublished data). Over 95% of patients remained on their first-line ART regimens at three years after ART initiation (MTCT-Plus monthly statistics, unpublished data). Pediatric care was colocated with adult services and included follow-up of HIV-exposed infants, early infant diagnosis, growth and developmental monitoring, ART for eligible children, and a battery of supportive care services similar to those received by the parents. As of this writing, almost 100% of children eligible for ART at the site are currently receiving treatment. The most common reason eligible children do not initiate ART is that the mothers or caretakers are not ready to initiate ART for themselves.
Three phases of training, with increasingly advanced subject matter, were organized and implemented by MTCT-Plus staff and U.S.-based HIV experts. Over time, the notion of “advanced” in this setting came to include both medical management of complicated cases and emerging complex areas such as pediatric disclosure and adherence, management of discordant couples, and personal and community care management. This increasing emphasis on the holistic support of the family by the MDT became integral to supporting increasingly advanced medical practice and expertise. Similarly, MDT weekly meetings evolved to include both logistical and case-based issues, with a particular emphasis on challenging medical and psychosocial situations.

During this period of program development, particular attention was paid to the growth of peer activities. The Pfizer Foundation awarded a grant to the MTCT-Plus Initiative to expand or develop peer educator programs in the countries where it was operating. This enabled the initiative to provide additional financial support to the MU-JHU site to expand ongoing support groups and develop a peer educator program. People living with HIV were identified, trained, and supported to provide a linkage between providers and clients and to offer psychosocial support to other clients with regard to a variety of issues. These peer educators began to play a particularly critical role in bridging the gap between providers and service recipients in the ANC and were increasingly viewed as key members of the MDT. Over time, the group expanded its activities to include income generation, home gardening and food support, and a children’s and teens’ support group. Furthermore, the MDT increasingly recognized that family-focused programming touched on complex gender roles within families, where men often held decision-making power. The peer educators therefore focused particular attention on increasing male involvement in the program.

Program Maturation

As the MU-JHU program matured, the MDT became more proficient at addressing the complex medical and psychosocial needs of the participants. More than 950 women, infants, and family members are currently enrolled in the program, including 380 pregnant and postpartum women and 180 of their male partners; 290 adults and 127 children are receiving ART. To date, only 25 adults and two children have been reported as lost to follow-up.

Over time, the MDT recognized that the staff also needed attention and nurturing, due to the increasing burdens caused by the rapid growth of the program and the ongoing need to respond to medical and psychosocial situations. Staff retreats were offered to support team building and ease provider burnout. During these retreats, team members interacted freely with each other through games and competitions, jokes and entertainment. They also took time to reflect on their achievements and challenges. In addition, didactic and skill-building educational sessions were regularly organized for the MDT staff. After some time, these sessions were extended to other hospital staff.

Since its inception, the MTCT-Plus program has been recognized as an exemplary model of holistic HIV care. The program has become a clinical mentorship site for health providers from across Africa, in collaboration with the Infectious Disease Institute of Makerere University and the Baylor College of Medicine Children’s Foundation, Uganda. MTCT-Plus staff provide consultation and training for HIV care for pregnant and postpartum women in Mulago Hospital, the national referral hospital in Uganda, and many MTCT-Plus protocols and algorithms for care have been adapted and adopted by other local programs. Similarly, the peer support program has evolved to include a wide range of activities and has been emulated throughout clinics on the hospital campus. The peer educators have been called upon to train and help establish similar groups across the
country. Countless visitors from across the continent have come to the site to learn from this initiative.

In July 2006, in collaboration with ICAP staff, a pilot workshop was held to assess the feasibility of formalizing the mentorship role of the MU-JHU MTCT-Plus MDT. Themes of the workshop included explicitly understanding the role of the mentor in the context of the MTCT-Plus model of care. The importance of disseminating this model was discussed as an approach to building the capacity of families and communities; other topics included HIV care and treatment teams, programs, and infrastructures. The workshop ended with a commitment to address the need to promote this model throughout Africa. Funding was then obtained from the Stephen Lewis Foundation to enable the MU-JHU MTCT-Plus MDT to mentor and conduct workshops for HIV care and treatment teams from across Africa.

LESSONS LEARNED FROM THE MTCT-PLUS INITIATIVE

The MTCT-Plus Initiative has grown and matured since its inception. Close communication with individual sites, the monitoring of outcomes, and exchange with partners and leaders in the field led to changes in protocols and approaches over the duration of the initiative. One key change in the program was the revision of its relationship with PMTCT services. When the MTCT-Plus initiative was first developed, it was expected that women would receive PMTCT services and subsequently enroll in the MTCT-Plus Initiative. MTCT-Plus did not directly support PMTCT activities, as they were preexisting at the sites. With time, however, it was recognized that engaging women during pregnancy rather than immediately postpartum offered significant advantages. Rapid enrollment, screening, and initiation of ART for eligible women during pregnancy could offer health benefits to the mother and further reduce the risk of transmission to the infant by rapidly lowering maternal viral load during pregnancy.14 The initiative then shifted focus and began encouraging and supporting sites to engage women during pregnancy and initiate treatment for those who were eligible. Furthermore, the initiative extended support to sites interested in providing more complex PMTCT regimens for women with less advanced disease. In this way, the relationship between prevention and treatment interventions was further solidified.

As exemplified in the MU-JHU program, the initiative changed to address the complex gender issues impacting women in many societies.15 While the initiative focused on the needs of women as the cornerstones of their families, male partners often held decision-making authority and made all key decisions affecting the women and their children. Implementation of family-focused care required sites to explore and consider societal and cultural issues not traditionally addressed within health-care systems. Over time, methods were developed to support women in disclosing their HIV status to their partners and to encourage men to learn their HIV status and engage in family-focused services.

It was also recognized that the MTCT-Plus model of care was not a perfect fit for every site. In some settings, larger government-run treatment programs did not support a multidisciplinary, family-focused approach to care and treatment, and pregnant women were rarely prioritized. At some sites, the large demand for ART among the many individuals with advanced HIV disease took precedence over efforts to engage and retain healthier HIV-positive individuals in care services. In some instances, initiative protocols were altered to be more consistent with local policies, while two sites opted to transition their programs into the national ART treatment programs. Over time, each MTCT-Plus site has had to consider the most effective ways to integrate program services into new, larger national initiatives to roll out ART. This speaks to
the remarkable opportunities now afforded by the global scale-up of HIV care and treatment services.

The MTCT-Plus Initiative has been successful on many fronts. First and foremost, there are families that are healthy and well today because of the initiative. As of September 30, 2007, there were 14,058 individuals enrolled in the MTCT-Plus Initiative: 6,870 women, 1,437 men, and 5,751 children. The majority of participants, 8,538, are women who were identified in PMTCT programs, and more than 3,000 started care during pregnancy.

More than three-quarters of these women have enrolled at least one family member, most often their newborn babies. Of more than 5,200 HIV-exposed infants in active follow-up, 2,784 infants have been determined to be uninfected. More than 3,000 adults and 500 children have initiated ART. Long-term follow-up has been excellent, with more than 85% of those who started ART returning regularly for appointments, as of June 2007. Similar to the experience in well-resourced settings, response to ART has been robust, with adults achieving an average increase in CD4 lymphocyte counts of 187 cells/mm³ and children seeing an average CD4 increase of 7.2% after 12 months of treatment.14,17

The teams of HIV care providers, from peer supporters to physicians, not only provide excellent HIV care but are now teachers of others coming into the field. Their years of treatment experience now support the next generation of HIV care providers. The MTCT-Plus Initiative has provided a framework of care, from protocols and manuals to ARV and commodity procurement systems, that did not previously exist. In many settings, this framework informed and was often the springboard to broader HIV care and treatment efforts.

The MTCT-Plus Initiative has also informed the global dialogue about HIV care and treatment in several important ways. The initiative brought local leaders and decision makers into contact with a family-focused model of HIV care and demonstrated that it could and does work. Treatment of pregnant women and infants and children has now been performed successfully through an MDT approach. Those leaders, in turn, are in dialogue with national policymakers and have become the strongest advocates for a family-focused HIV care model. In select countries, such as Kenya, Cameroon, and Rwanda, the protocols and treatment framework of the initiative were the starting point for many aspects of national HIV/AIDS treatment policies.

Many lessons have been learned from the MTCT-Plus Initiative. In the past, PMTCT programs were viewed as entities unto themselves. Through the MTCT-Plus Initiative, they have become gateways to HIV treatment for the entire family. MTCT-Plus has reframed the relationship women have with PMTCT programs, as well as the relationship between prevention programs, especially PMTCT, and care and treatment services. In particular, MTCT-Plus has demonstrated that by bringing HIV care and treatment services to PMTCT programs, more pediatric infections can be averted.14 And finally, MTCT-Plus has demonstrated that HIV care extends beyond diagnosis, CD4 lymphocyte testing, and ART to the vast social and psychological needs of HIV-positive individuals and their families and communities.

ACKNOWLEDGMENTS
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REFERENCE LIST


In 1996, combination antiretroviral therapy (ART) became available for the routine treatment of patients living with HIV in the industrialized world, transforming what had been a fairly rapidly progressing, fatal disease into one that was chronic and manageable. Despite the availability of improved treatment in high-income countries, sub-Saharan Africa, with the greatest burden of HIV/AIDS, was largely left behind. Until 1999, it was commonly believed that ART could not be delivered on any scale in this region. The drugs were considered to be too expensive, too complicated, and too toxic to deliver and to monitor; the infrastructure was thought to be too poor; and African patients were viewed as being unable to adhere to lifelong therapy. The 13th World AIDS Conference, held in Durban, South Africa, in 2000, brought about a radical change in thinking almost overnight. Activists, advocates, health economists, and world opinion leaders gave inspiring speeches, and participants left the meeting believing that it might just be possible to scale up ART in developing countries, and particularly in sub-Saharan Africa.

Bold steps were taken in the international arena. In 2003, the World Health Organization (WHO) and the Joint United Nations Program on HIV/AIDS (UNAIDS) launched the “3 by 5” initiative, with an ambitious goal of having three million people on ART in developing countries by the end of 2005. Fortunately, this call to arms was associated with a huge injection of funding for HIV/AIDS prevention and treatment through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM); the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR); and the World Bank. In all areas of the world, and particularly in the hardest-hit regions of sub-Saharan Africa, gallant efforts were made to provide ART to needy populations. By December 2005, WHO and UNAIDS estimated that more than 1.3 million people from low- and middle-income countries had been placed on treatment, with 810,000 of them in sub-Saharan Africa.

This chapter follows the scale-up of ART in Malawi, a poor, landlocked country in sub-Saharan Africa, from the first germs of an idea to program planning and implementation. It describes the results of ART scale-up to the end of 2006, the reasons why the country was able to achieve a good degree of success, and the challenges that still confront stakeholders.
BACKGROUND

Malawi is a very poor country with a population of between 11 and 12 million people and a per capita gross domestic product (GDP) of less than US$200 per year. The HIV epidemic in the country is dire. Approximately 930,000 people are thought to be HIV-infected, with another 100,000 new infections annually. Every year, 90,000 people die of AIDS, and at any one time it is estimated that 170,000 are in immediate need of ART. In January 2004, before the national scale-up of ART, there were nine health facilities in the public sector delivering ART to about 3,000 patients. ART delivery was unstructured, very few health workers had been formally trained in this activity, and there were no national systems of monitoring or reporting. In short, there was “ART anarchy.”

FROM IDEAS TO IMPLEMENTATION

Following the 13th World AIDS Conference, some key steps were taken that enabled the country to prepare for the national ART scale-up slated to begin in February 2004 (see Table 1). Right from the start, it was recognized that ART delivery using a “medicalized” model would not work, and that the key to rapid and massive scale-up was to keep the principles and practices of ART delivery as simple as possible. In this regard, many of the principles of DOTS (directly observed therapy short course—the system used to successfully deliver anti-TB treatment to people in

<table>
<thead>
<tr>
<th>Key Step</th>
<th>Outcome</th>
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<tbody>
<tr>
<td><strong>December 2000:</strong> National Vice-Presidential Chaired Conference on Treatment of HIV/AIDS</td>
<td>The first ideas about the use of a DOTS TB model for delivering ART to patients were discussed.</td>
</tr>
<tr>
<td><strong>June 2001:</strong> Paper published by Malawi National AIDS Commission and National TB Programme on how to deliver ART using the TB DOTS model</td>
<td>The concept of using DOTS to deliver ART was formulated and put to paper and peer review in the <em>Lancet</em> publication of “Preventing antiretroviral anarchy in sub-Saharan Africa.”</td>
</tr>
<tr>
<td><strong>July 2002:</strong> Malawi submitted (and received approval of) its proposal for Round 1 of the GFATM, in which ART provision to HIV-infected eligible patients was a core component</td>
<td>The first definitive plan for delivering ART was incorporated into a national submission to the GFATM. The national plan was approved in the amount of US$190 million over five years; this was deemed a large amount of money, and this was one of the reasons why no PEPFAR funds were allocated to ART scale-up.</td>
</tr>
<tr>
<td><strong>October 2003:</strong> Publication of the first edition of national guidelines for the use of antiretroviral therapy in Malawi</td>
<td>The guidelines provided definitive advice about how to stage HIV-infected patients; how to start and follow up patients on treatment; how to manage side effects; and how to register, record, and report on cases and treatment outcomes.</td>
</tr>
<tr>
<td><strong>February 2004:</strong> Approval of first two-year scale-up plan for ART in Malawi</td>
<td>The plan provided clear objectives, activities, and timelines for scale-up as well as details about the 60 sites selected for Round 1.</td>
</tr>
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</table>

DOTS = directly observed therapy short course; ART = antiretroviral therapy; GFATM = Global Fund to Fight AIDS, Tuberculosis and Malaria; PEPFAR = U.S. President’s Emergency Plan for AIDS Relief
some of the poorest countries of the world) were borrowed and adapted to ART delivery (see Table 2). A standardized system was put in place, so that wherever one traveled in the country and wherever one accessed ART, from central hospital to health center, the same system of finding cases; initiating treatment; and registering, recording, and reporting cases and outcomes was followed. Above all, the country made an important policy decision that ART in the public sector was to be free for all patients.

**DEVELOPING AND MONITORING ART**

The important steps in delivering and monitoring ART are outlined briefly here.

**Eligibility for ART**
In order to be eligible for ART, adults and children must be HIV-seropositive, patients or guardians must understand the implications of ART, and patients must be in WHO clinical stage III or IV or have a CD4 lymphocyte count below the threshold value for severe immunodeficiency. Most ART clinics do not have a machine for measuring CD4 lymphocyte counts, and the emphasis is therefore on clinical staging. Once deemed eligible for ART, patients go through a process of group counseling, individual counseling, and then initiation of treatment (see Figure 1).

**Standardized ART**
Malawi focused on the use of one generic, fixed-dose combination treatment containing stavudine, lamivudine, and nevirapine. Two alternative first-line regimens (for cases of serious ART drug side effects) and one second-line regimen (for cases of ART drug failure) were placed in central and major district hospitals.

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**Table 2. Principles Borrowed from TB Control Programs for Delivering ART**

<table>
<thead>
<tr>
<th>TB Control Program</th>
<th>ART Delivery Program</th>
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<tbody>
<tr>
<td>Standardized diagnosis and case finding based on:</td>
<td>Standardized diagnosis and case finding based on:</td>
</tr>
<tr>
<td>• Smear microscopy</td>
<td>• Positive HIV test result</td>
</tr>
<tr>
<td>• Different categories of TB (smear-positive, smear-</td>
<td>• Understanding implications of ART</td>
</tr>
<tr>
<td>negative, and extrapulmonary)</td>
<td>• WHO stage III or IV, or low CD4 count</td>
</tr>
<tr>
<td>Standardized treatment based on:</td>
<td>Standardized treatment based on:</td>
</tr>
<tr>
<td>• Treatment regimen for new TB</td>
<td>• First-line regimen for new cases</td>
</tr>
<tr>
<td>• Retreatment regimen for relapse TB</td>
<td>• Alternative regimen for side effects</td>
</tr>
<tr>
<td>Standardized recording and reporting based on:</td>
<td>• Second-line regimen for failure</td>
</tr>
<tr>
<td>• TB patient treatment cards</td>
<td>Standardized recording and reporting based on:</td>
</tr>
<tr>
<td>• TB patient registers</td>
<td>• ART patient treatment master cards</td>
</tr>
<tr>
<td>• TB patient identity cards</td>
<td>• ART patient registers</td>
</tr>
<tr>
<td>• TB cohort analysis forms</td>
<td>• ART patient identity cards</td>
</tr>
<tr>
<td>Standardized system of procurement based on:</td>
<td>• ART cohort analysis forms</td>
</tr>
<tr>
<td>• Forecasting of new patients on treatment</td>
<td>Standardized system of procurement based on:</td>
</tr>
<tr>
<td>• Taking into account old drug stocks</td>
<td>• Forecasting of new patients on treatment</td>
</tr>
<tr>
<td>Management by paramedical officers</td>
<td>• Forecasting established patients on ART</td>
</tr>
<tr>
<td>Free drugs for patients</td>
<td>• Taking into account old drug stocks</td>
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<tr>
<td></td>
<td>Management by paramedical officers</td>
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<td>Free drugs for patients</td>
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hospitals over the first two years, and a referral system was set up so that any patient in need could access appropriate therapy (see Table 3 for Malawi’s ART regimens). As sites have become more experienced in the use of ART, more of them have been directly given alternative first-line therapy. Patients are started on treatment, seen two weeks later, and then followed up every four weeks for life. Monitoring for well-being, side effects, and drug adherence is all performed clinically, and in most sites there is little in the way of laboratory investigations.

Registration, Recording, and Reporting at ART Sites
Much like patients in TB programs, all ART patients are given a unique ART registration number, which is their key identification in the monitoring tools. Each facility is assigned a unique three-letter code, and each new ART patient in that facility is assigned a number preceded by the facility code. The numbers increase sequentially as new patients are recruited into therapy. This means that at any point in time, a facility can be contacted and the last number in the ART register (see below) equates to the total number of patients started on therapy at that facility.

At ART sites, the two most important tracking tools are the ART patient treatment master card (see Figure 2) and the ART patient register.

Both of these contain the case-finding details of the patients (i.e., ART number, name, address, age, sex, occupation, and reason for ART) and their monthly treatment outcomes (see Table 4).

The management of patients who transfer from one facility to another deserves special mention. The transfer out and the date of that particular patient’s transfer are recorded in the master card and in the register. The patient is given a copy of his or her master card and takes this to the new facility, where he or she is given a new code and number related to the new facility and is now recorded as “alive and on ART.” This means that at the national level transfer-out patients are recorded twice, in one facility as a “transfer out” and in another as “alive and on ART.” This is recognized in the national aggregate reporting, where transfer-out patients essentially mean patients double counted.
At the end of every quarter, the ART clinic team is expected to cross-check the records, specifically to check that treatment outcomes in the master card have been accurately recorded in the register, and perform cohort analysis of cases and end-of-quarter outcomes with events censored at the end of that particular quarter. There are two types of cohort analysis: (1) a quarterly analysis of new patients started on ART in the latest three-month period and (2) a cumulative analysis of all patients ever started on ART.

Supervision and Monitoring of ART

Every three months the HIV Unit of the Ministry of Health and its partners conduct supervisory and monitoring visits to all ART sites in the country. The purpose of these visits is to ensure that guidelines and standards are being adhered to, to collect data for national reporting, to provide encouragement and support (and sometimes admonishment if performance is poor), and to obtain information on drug stock levels to help with drug procurement. Each quarter, facilities are awarded certificates of excellence if the register and master cards are completed according to national guidelines and if the cohort analyses have been done and are correct, as judged by the supervising team.

### SCALING UP ART AT THE NATIONAL LEVEL

#### Preparing Staff and Sites for ART Delivery

The process for readying staff and sites for ART delivery is outlined in Figure 3. Facilities are briefed about ART scale-up and asked to apply to be ART delivery sites. Considering the shortage of doctors in the country, it was recognized that paramedical officers (i.e., clinical officers and medical assistants) and nurses would make up the frontline force responsible for ART delivery at site level. These clinicians and nurses must undergo a formal ART training package consisting of classroom training for five days, an end-of-course examination for competence, and a two-week attachment at an experienced ART site. The HIV unit of the Ministry of Health then carries out a formal inspection of the ART facility for accreditation purposes using a standard structured questionnaire. Once sites have been accredited, the public is informed through announcements in the two main national newspapers. ART drugs, ordered some months before in good faith that the site would pass its assessment, are distributed, and ART delivery can commence.
PATIENT MASTER RECORD CARD FOR ARV [front]: Unique ARV Number _____________ Year __________

Name __________________________ Age _______ Sex __________ Initial Wt (Kg) _______ Initial Ht(cm) ______ Transfer-In (Y/N) ______

Address (physical / PO Box) __________________________

Name of identifiable guardian __________________________ Date and place of positive HIV test __________________________

Date of starting 1st line ARV regimen ___________ Reason for ARV: ___________ PTB ______ EPTB ______ KS ______ PMTCT ______

Date of starting alternative 1st line ARV regimen (specify) ___________ Date of starting 2nd line ARV regimen (specify) ___________

<table>
<thead>
<tr>
<th>Month</th>
<th>Date</th>
<th>Wt Kg</th>
<th>Ht cm</th>
<th>Outcome status</th>
<th>Of those alive</th>
<th>Ambulatory</th>
<th>Work/school</th>
<th>Side effects</th>
<th>No. Pills in Bottle</th>
<th>ARV Given</th>
<th>CPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan</td>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>D</td>
<td>DF</td>
<td>Stop</td>
<td>TO</td>
<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
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<tr>
<td>Feb</td>
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<td>A</td>
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<td>Apr</td>
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<td>D</td>
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<td>Stop</td>
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<td>Start</td>
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<td>Switch</td>
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<tr>
<td>May</td>
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<td>A</td>
<td>D</td>
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<td>Stop</td>
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<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
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<tr>
<td>Jun</td>
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<td>A</td>
<td>D</td>
<td>DF</td>
<td>Stop</td>
<td>TO</td>
<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
</tr>
<tr>
<td>Jul</td>
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<td></td>
<td></td>
<td>A</td>
<td>D</td>
<td>DF</td>
<td>Stop</td>
<td>TO</td>
<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
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<tr>
<td>Aug</td>
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<td></td>
<td></td>
<td>A</td>
<td>D</td>
<td>DF</td>
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<td>TO</td>
<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
</tr>
<tr>
<td>Sep</td>
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<td>A</td>
<td>D</td>
<td>DF</td>
<td>Stop</td>
<td>TO</td>
<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
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<tr>
<td>Oct</td>
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<td>A</td>
<td>D</td>
<td>DF</td>
<td>Stop</td>
<td>TO</td>
<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
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<tr>
<td>Nov</td>
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<td>A</td>
<td>D</td>
<td>DF</td>
<td>Stop</td>
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<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
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<tr>
<td>Dec</td>
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<td>A</td>
<td>D</td>
<td>DF</td>
<td>Stop</td>
<td>TO</td>
<td>Start</td>
<td>Sbs</td>
<td>Switch</td>
</tr>
</tbody>
</table>

Specify reason for ARV therapy (Stage III, Stage IV, CD4 < 200, PTB, EPTB, Transfer-in)

**Outcome status:**
- A = alive
- D = dead
- DF = defaulted and not seen for 3 months
- Stop = stopped medication
- TO = transferred out to another unit

**Of those alive:**
- Start = alive and on first line regimen
- Sbs = alive and substituted to alternative first line regimen
- Switch = alive and switched to a second line regimen because of failure of first line regimen

**Ambulatory:**
- Amb = able to walk to or at treatment unit and walks at home unaided
- Bed = most of time in bed at home

**Work/school:**
- Yes = engaged in previous work / employment or at school
- No = not engaged in previous work / employment or not at school

**Side effects:**
- If Yes, specify – YES-PN= peripheral neuropathy
- YES-HP= hepatitis
- YES-SK= skin rash

**No. Pills in bottle:**
- If patient comes at 4 weeks count number of pills in bottle (8 pills or less = 95% adherent)

**ARV given / not given:**
- Ticks whether ARV therapy given in the appropriate column

| P = patient | G = Guardian |

**CPT = cotrimoxazole preventive therapy**

Figure 2a. Antiretroviral patient treatment master card (front)
### PATIENT MASTER RECORD CARD FOR ARV  [back]: Clinical Record Form

Indicate in the columns below what disease(s) the patients has by placing a ring around the bullet point next to the disease or clinical problem.

<table>
<thead>
<tr>
<th>WHO Clinical Stage I</th>
<th>WHO Clinical Stage II</th>
<th>WHO Clinical Stage III</th>
<th>WHO Clinical Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Asymptomatic</td>
<td>- Unintentional weight loss &lt; 10% of body weight in the absence of concurrent illness</td>
<td>- Oral candidiasis</td>
<td>- HIV wasting syndrome (weight loss ✧ 10% of body weight and either chronic fever or diarrhoea in the absence of concurrent illness)</td>
</tr>
<tr>
<td>- Persistent Generalised lymphadenopathy</td>
<td>- Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)</td>
<td>- Oral hairy leukoplaikia with other systemic features</td>
<td>- Pneumocystis carinii pneumonia</td>
</tr>
<tr>
<td></td>
<td>- Herpes zoster within the last 5 years</td>
<td>- Vulvo-vaginal candidiasis with other systemic features</td>
<td>- Toxoplasmosis of the brain</td>
</tr>
<tr>
<td></td>
<td>- Recurrent upper respiratory tract infections (ie, bacterial sinusitis)</td>
<td>- Unintentional weight loss &gt; 10% of body weight in the absence of concurrent illness</td>
<td>- Cryptosporidiosis with diarrhoea &gt; 1 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Chronic diarrhoea &gt; 1 month</td>
<td>- Isosporiasis with diarrhoea &gt; 1 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prolonged fever (intermittent or constant) &gt; 1 month</td>
<td>- Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Active Pulmonary Tuberculosis (PTB)</td>
<td>- Cytomegalovirus of an organ other than liver, spleen or lymph node</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- PTB within the past year</td>
<td>- Herpes simplex infection, mucocutaneous for &gt; 1 month or visceral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Severe bacterial infections (eg pneumonia, pyomyositis)</td>
<td>- Progressive multifocal leucoencephalopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Any disseminated endemic mycosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Candidiasis of oesophagus, trachea and bronchus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Atypical mycobacteriosis, disseminated or lungs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Non-typhoidal salmonella septicemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Extrapulmonary tuberculosis (EPTB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Kaposi’s sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- HIV encephalopathy</td>
</tr>
</tbody>
</table>

Figure 2b. Antiretroviral patient treatment master card (back)
Involvement of the Private Sector

Within six months of preparing for ART scale-up in the public sector, private-sector facilities were brought on board as willing participants. They agreed to follow the national systems, undertake a modified weekend ART training course with an examination of competence, and prepare for accreditation in the same way as facilities in the public sector. Private facilities receive drugs free of charge, but charge patients for the drugs at a subsidized rate (US$3.50 per course of treatment per month) and are allowed to keep part of this money to cover dispensing costs.

The quarterly supervision of all sites ensures that standards are maintained. If sites fall below the required standard, they can lose their accreditation status and, through a letter from the Secretary for Health, lose their status as ART sites. In practice, sites have been warned for poor performance but no site has yet lost its status.

**ART Drug Procurement**

Malawi has developed its own rather unique system of drug procurement (see Table 5), with drugs delivered directly to ART sites by the procurement agent every six months.

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**Table 4. Standardized ART Outcomes**

<table>
<thead>
<tr>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive and on ART</td>
</tr>
<tr>
<td>Dead</td>
</tr>
<tr>
<td>Defaulted</td>
</tr>
<tr>
<td>Stopped</td>
</tr>
<tr>
<td>Transferred out</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcomes for those alive and on ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of regimen</td>
</tr>
<tr>
<td>First line (abbreviated as “start”)</td>
</tr>
<tr>
<td>Alternative first line (abbreviated as “substituted”)</td>
</tr>
<tr>
<td>Second line (abbreviated as “switch”)</td>
</tr>
<tr>
<td>Ambulatory</td>
</tr>
<tr>
<td>At work/school</td>
</tr>
<tr>
<td>Side effects</td>
</tr>
<tr>
<td>Drug adherence</td>
</tr>
</tbody>
</table>
By December 31, 2006, the number of patients started on ART was 81,821 in the public sector and 3,347 in the private sector. Some of the characteristics of patients in the public and private sectors are shown in Table 6, and treatment outcomes are shown in Table 7. As previously mentioned, patients are grouped into quarterly cohorts, which allows, through the routine system, time-bound treatment outcome analysis. For example, all patients registered in a cohort between April and June 2006 (Q2, 2006) can have their outcomes assessed on December 31, 2006, and this constitutes a 6-month outcome analysis. It is recognized that this in effect means an analysis of patient outcomes at 6 to 9 months after starting ART. Patients registered 12 months previously, between October and December 2005 (Q4, 2005), can also have their outcomes assessed on December 31,
responsibility for national scale-up, and a desire by all implementing partners to work together with the Ministry of Health and use the national standardized systems; (2) a focus on scaling up using one first-line, fixed-dose combination regimen, which was made possible by the fact that Malawi’s sole funding source for ART was the GFATM; (3) clear national ART guidelines, in which an emphasis is also placed on the system of registration, monitoring, and recording of results10,11; (4) an intensive training schedule, focused particularly on clinical officers and nurses learning the ART guidelines and undertaking practical attachments at experienced ART sites; (5) a structured system of accrediting ART sites before they are permitted to deliver treatment to patients; (6) quarterly supervision and monitoring of all ART delivery sites by the HIV unit of the Ministry of Health and its partners8; and (7) no stock-outs of antiretroviral (ARV) drugs due to the use of a parallel procurement and distribution system.

CHALLENGES

Current challenges

Children, pregnant women, and patients with TB were, and still are, relatively underserved. Until 2005, only 5% of patients being started on ART 2006, and this constitutes a 12-month outcome analysis. Treatment outcome analysis of different cohorts from sites around the country at 6 months, 12 months, and 18 months showed that 72%, 64%, and 62% of patients, respectively, were alive and still on ART at their initial treatment site.

Achievements

The government health sector in Malawi has shown that by using a simple, structured approach to ART delivery, treatment can be delivered to large numbers of patients fairly quickly with good 12-month outcomes. A community-based study in Blantyre, Malawi, before the advent of ART, found the 12-month incidence of death in HIV-infected patients with stage IV and stage III disease to be 88% and 62%, respectively.9 These findings demonstrate that ART has substantially improved survival rates, at least at this early stage of development. A few facilities in the country are supported by non-governmental organizations, such as Médecins Sans Frontières and Dignitas International, but in the majority of facilities, the local health-care personnel are the sole providers of ART services.

A number of factors have been responsible for this achievement, the most important of which are (1) a clear lead taken by the Ministry of Health in assuming responsibility for national scale-up, and a desire by all implementing partners to work together with the Ministry of Health and use the national standardized systems; (2) a focus on scaling up using one first-line, fixed-dose combination regimen, which was made possible by the fact that Malawi’s sole funding source for ART was the GFATM; (3) clear national ART guidelines, in which an emphasis is also placed on the system of registration, monitoring, and recording of results10,11; (4) an intensive training schedule, focused particularly on clinical officers and nurses learning the ART guidelines and undertaking practical attachments at experienced ART sites; (5) a structured system of accrediting ART sites before they are permitted to deliver treatment to patients; (6) quarterly supervision and monitoring of all ART delivery sites by the HIV Unit of the Ministry of Health and its partners; and (7) no stock-outs of antiretroviral (ARV) drugs due to the use of a parallel procurement and distribution system.

Table 5. Key Principles for Procurement of ARVs

<table>
<thead>
<tr>
<th>Principle</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Push system and ceilings for first-line ART drugs</td>
<td>Facilities are graded as low burden (25 new patients per month), medium burden (50 new patients per month), and high burden (150 new patients per month), which makes six-monthly calculations for new patients relatively easy.</td>
</tr>
<tr>
<td>Forecasting first-line ART drug requirements for each facility</td>
<td>For new patients, forecasting is based on push system. For established patients, forecasting is based on numbers alive on ART and drug stock levels obtained from quarterly supervision and monitoring.</td>
</tr>
<tr>
<td>Prepacked kit system with starter packs and continuation packs</td>
<td>Starter packs provide 75 new patients with two weeks’ initial treatment of half-dose nevirapine, and continuation packs provide 75 patients with full-dose therapy for three months.</td>
</tr>
</tbody>
</table>
tools have been modified so that master cards can serve the interests of both adults and children in one uniform format. The standardized ART training modules have been updated to reflect the new ART guidelines, and more emphasis has been placed on pediatric ART. Clinicians and nurses in ART facilities in 2006 all received a two-day refresher training on the new guidelines, with a focus on pediatric ART. The benefits of this new approach are already being seen, and between October and December 2006, 9% of patients started on ART were children (personal communication, HIV unit, Malawi Ministry of Health, March 2007).

very few HIV-positive pregnant mothers are referred for consideration of ART. Many of these mothers are asymptomatic, and eligibility for ART depends on increased availability of CD4 testing. Potential solutions include increasing national capacity to measure CD4 lymphocyte counts, providing easier ways of performing the test, and making CD4 testing directed at HIV-positive pregnant women an explicit national priority.

Additionally, the proportion of TB patients placed on ART is small. With a national HIV-seroprevalence rate of 70% among TB patients, were children, and according to a small subanalysis, only very few were under one year of age. This finding was similar to reports from other African countries. In Malawi, children should account for an estimated 10% to 15% of patients on ART. The small number of children on treatment reflects the difficulties initially faced by clinicians in diagnosing and managing HIV in infants, and in treating children with split-tablet doses. The newly revised WHO pediatric ART guidelines, released in early 2006, assisted substantially in addressing some of these difficulties. In Malawi, these guidelines were used as a basis for revising the national ART guidelines in April 2006.

Table 6. Characteristics of Patients Started on ART in Malawi up to December 31, 2006

<table>
<thead>
<tr>
<th></th>
<th>Public Sector</th>
<th>Private Sector</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number started on ART</td>
<td>81,821</td>
<td>3,347</td>
<td>85,168</td>
</tr>
<tr>
<td>Number (%) males</td>
<td>31,659 (39)</td>
<td>1,712 (51)</td>
<td>33,371 (39)</td>
</tr>
<tr>
<td>Number (%) females</td>
<td>50,162 (61)</td>
<td>1,635 (49)</td>
<td>51,797 (61)</td>
</tr>
<tr>
<td>Number (%) adults</td>
<td>76,058 (93)</td>
<td>3,201 (96)</td>
<td>79,259 (93)</td>
</tr>
<tr>
<td>Number (%) children (under 15 years)</td>
<td>5,763 (7)</td>
<td>146 (4)</td>
<td>5,909 (7)</td>
</tr>
<tr>
<td>Number (%) on ART due to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO clinical stage III</td>
<td>53,030 (65)</td>
<td>1,447 (43)</td>
<td>54,477 (64)</td>
</tr>
<tr>
<td>WHO clinical stage IV</td>
<td>18,958 (23)</td>
<td>757 (23)</td>
<td>19,715 (23)</td>
</tr>
<tr>
<td>WHO stage I and II with low CD4</td>
<td>9,833 (12)</td>
<td>1,143 (34)</td>
<td>10,976 (13)</td>
</tr>
<tr>
<td>Number (%) on ART due to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active or previous TB</td>
<td>13,308 (16)</td>
<td>280 (8)</td>
<td>13,588 (16)</td>
</tr>
<tr>
<td>Referral from PMTCT clinic</td>
<td>885 (1)</td>
<td>0 (0)</td>
<td>885 (1)</td>
</tr>
</tbody>
</table>

were children, and according to a small subanalysis, only very few were under one year of age. This finding was similar to reports from other African countries. In Malawi, children should account for an estimated 10% to 15% of patients on ART. The small number of children on treatment reflects the difficulties initially faced by clinicians in diagnosing and managing HIV in infants, and in treating children with split-tablet doses. The newly revised WHO pediatric ART guidelines, released in early 2006, assisted substantially in addressing some of these difficulties. In Malawi, these guidelines were used as a basis for revising the national ART guidelines in April 2006.

Now the national guidelines include much better descriptions of clinical diagnosis, staging, and management of HIV in children, and include a simple chart listing the criteria that can be used to start infants on ART without the need for viral load testing. Pharmacokinetic studies conducted in Malawi showed that children were being underdosed with nevirapine when half to quarter tablets of Triomune-40 were used. The revised ART guidelines now specify split tablets of Triomune-30, which should be preferable because of the higher dose of nevirapine relative to stavudine. Monitoring tools have been modified so that master cards can serve the interests of both adults and children in one uniform format. The standardized ART training modules have been updated to reflect the new ART guidelines, and more emphasis has been placed on pediatric ART. Clinicians and nurses in ART facilities in 2006 all received a two-day refresher training on the new guidelines, with a focus on pediatric ART. The benefits of this new approach are already being seen, and between October and December 2006, 9% of patients started on ART were children (personal communication, HIV unit, Malawi Ministry of Health, March 2007).

Very few HIV-positive pregnant mothers are referred for consideration of ART. Many of these mothers are asymptomatic, and eligibility for ART depends on increased availability of CD4 testing. Potential solutions include increasing national capacity to measure CD4 lymphocyte counts, providing easier ways of performing the test, and making CD4 testing directed at HIV-positive pregnant women an explicit national priority.
Outcomes feature high rates of early death and loss to follow-up. With regard to treatment outcomes, there have been, and continue to be, two main problems. The first is the high rate of early deaths among patients starting ART. Mortality of those on ART, and early mortality in particular, is reported to be much higher in low-income countries as compared to high-income countries. In South Africa, where similar findings were reported, early mortality appears to be related to patients presenting with an advanced clinical stage of HIV disease, wasting syndrome, TB, acute bacterial infections, malignancy, and

| Table 7. Treatment Outcomes of Patients Started on ART in Malawi up to December 31, 2006 |
|---------------------------------|----------|----------|----------|
|                                 | Public Sector | Private Sector | Total    |
| Number started on ART           | 81,821     | 3,347     | 85,168   |
| Number (%) alive and on ART     | 57,356 (70)| 2,624 (78)| 59,980 (71)|
| Number (%) dead                 | 9,327 (11)| 222 (7)   | 9,549 (11)|
| Number (%) lost to follow-up    | 7,753 (10)| 132 (4)   | 7,885 (10)|
| Number (%) stopped treatment    | 365 (0)    | 7 (0)     | 372 (0)   |
| Number (%) transferred out      | 7,020 (9)  | 362 (11)  | 7,382 (8) |
| Of those alive and on ART:      |           |           |          |
| Number (%) on first-line regimen| 55,518 (97)| 2,480 (95)| 57,998 (97)|
| Number (%) on alternative regimen| 1,690 (3) | 127 (5)   | 1,817 (3) |
| Number (%) on second-line regimen| 148 (0)   | 17 (<1)   | 165 (0)   |
| Of those alive and on ART:      |           |           |          |
| Number with ambulatory status known | 51,440   | 2,624     | 54,064   |
| Number (%) ambulatory           | 50,551 (98)| 2,618 (99)| 53,169 (98)|
| Number with work status known   | 51,440     | 2,624     | 54,064   |
| Number (%) able to work         | 49,490 (96)| 2,593 (99)| 52,083 (96)|
| Number with side effects known  | 46,969     | 23        | 46,992   |
| Number (%) with side effects    | 2,132 (5)  | 1 (4)     | 2,133 (5) |
| Number for whom pill counts were performed | 38,426 | 193       | 38,619   |
| Number (%) with 95% adherence   | 35,667 (93)| 192 (99) | 35,859 (93)|
| Number dying with date/time recorded | 9,327 | 0         | 9,327    |
| Number (%) dying in first month | 3,207 (34)| 3,207 (34)|          |
| Number (%) dying in second month| 2,069 (22)| 2,069 (22)|          |
| Number (%) dying in third month | 1,100 (12)| 1,100 (12)|          |
| Number (%) dying after third month| 2,951 (32)| 2,951 (32)|          |

and 27,000 new TB patients being diagnosed and treated every year in the country, approximately 19,000 TB patients annually should be eligible to receive ART. However, placing TB patients on ART can be difficult for a variety of reasons, including difficulties with getting such patients tested for HIV due to stock-outs of HIV testing kits, HIV testing counselors being “temporarily out,” staff forgetting to refer patients, patients declining to be tested, and patients with a known result not being asked about previous testing history. Other reasons include concerns over drug interactions between rifampicin and non-nucleoside reverse transcriptase inhibitors and the fact that in Malawi, ART is delivered largely from hospital clinics while anti-TB treatment is largely decentralized to health centers.
behavior and the estimated risk of HIV transmission have declined as ART has been introduced into communities.18

Future Challenges
Malawi has developed a five-year scale-up plan to place 250,000 patients on ART by the end of 2010, as part of the national response to the call for “universal access” to HIV/AIDS prevention, care, and treatment.21 This will be a daunting challenge, and the country will succeed only if certain issues can be resolved. First, there is a need to tackle the dire human resource shortage that pervades sub-Saharan Africa.22 One way to address this problem is through task shifting, so that lower levels of health-care workers can initiate and manage the follow-up of patients receiving ART.23 Second, ongoing financial support, either from established players, such as GFATM, or new players, such as UNITAID and the Clinton Foundation, is an absolute necessity. Third, there will be a need in the next few years to invest in and secure alternative first-line drug regimens to replace those currently in use, as HIV drug resistance and long-term side effects, particularly of stavudine, become more critical. Fourth, undertaking regular supervision and reliable drug procurement for the increasing case burden will be essential if drug supplies are to remain uninterrupted and standards are to be maintained. Finally, HIV prevention methods and the prevention of mother-to-child transmission (PMTCT) program must be similarly scaled up, or caseloads in adults and children will continue to increase indefinitely.
REFERENCE LIST


IMPLEMENTATION OF A NATIONAL pediatric antiretroviral therapy (ART) program in a resource-limited setting presents a number of specific challenges. These include lack of sensitivity to children's health issues on the part of care providers, huge and still increasing populations of HIV-positive children in need of care,1-4 economies unable to bear the cost of the HIV burden, and insufficient and unprepared health personnel.

It is estimated that 780,000 children are in need of ART worldwide, yet only 115,500 children had access to these drugs by the end of 2006.5 This represents a coverage rate of roughly 15%, which is approximately a 50% increase compared with 2005 figures. However, ART coverage for children still lags far behind the total estimated ART coverage of 28% for adults (24%-34%) in low- and middle-income countries.5,6 Children are under-represented among recipients of ART in almost every setting worldwide where treatment programs have been established, with sub-Saharan Africa having the lowest treatment coverage for children of any region.7

Struggling economies are one of the main obstacles to implementing effective pediatric ART delivery. That might explain, partly, the scarcity of human resources, health infrastructure, diagnostic tools, and drugs, as well as poor education that present major obstacles to the scale-up of national programs.4,8-10 Additionally, sensitivity to and awareness of children's health needs is generally lower than for the adult population. As a result, health problems of children often go unaddressed or underserved.1,7,11-15

The population of children infected with HIV is significant and continues to increase. Of the 2.1 million children from 0 to 14 years of age living with HIV worldwide in 2007, almost 90% of them were in sub-Saharan Africa. In addition, according to 2007 Joint United Nations Program on HIV/AIDS estimates, the number of new HIV infections in children under 15 years of age is 420,000, with 290,000 HIV-related deaths annually among children.16

Cultural perceptions and the way in which people cope with chronic disease, even when asymptomatic, need to be understood and appropriately addressed. In the Mozambican setting, asymptomatic patients are generally presumed to be healthy. Therefore, running a nationwide treatment program for a disease in children that goes largely undetected presents a number of challenges. Such
a program had never been attempted before in Mozambique with any other chronic disease.

Overcoming these difficulties requires an enormous effort by several stakeholders involved in HIV pediatric health care. Mozambique had an estimated 32,000 children in need of treatment in 2007, with roughly 6,000 children enrolled in ART since 2004. In this chapter, we will describe strategies used in Mozambique to implement national care and treatment programs for children living with HIV, with a focus on lessons that may be applicable to other resource-limited settings.

**FACING THE CHALLENGES: IMPLEMENTING PEDIATRIC ART**

Successful implementation of pediatric ART programs in resource-limited settings can be aided by following a few key steps at the outset of program initiation (Box 1). As these steps imply, the strength of any national health program is largely dependent upon the right leadership, identification of stakeholders, creation of new sensitivities toward pediatric HIV infection, rationalizing and upgrading of available resources, and evaluation and continuous upgrading of HIV care services.

**Identification and Nomination of Leaders**

Appropriate leadership is fundamental to get the process of pediatric ART on the right course. Therefore, it is essential to find leaders at the outset who are known for their strong commitment to the program, and whose character, dedication, perseverance, and activities regarding pediatric HIV are well acknowledged among peers and stakeholders.

**Identification of Stakeholders**

The implementation of pediatric ART involves different players within the Ministry of Health (MOH), as well as nongovernmental organizations (NGOs) and other program partners. As such, stakeholders should be identified and their role discussed and clearly assigned from the very inception of the planning process. In Mozambique, organizations such as Columbia University, Médecins Sans Frontières, Clinton Foundation, Comunità di Sant’Egidio, Elizabeth Glaser Pediatric Foundation, Health Alliance International, and others have played a major role in supporting the Ministry of Health with rolling out the pediatric ART program.

**Advocacy and Education about Pediatric HIV and ART**

Due to discrimination and/or poor sensitivity to children’s issues, and pediatric HIV in particular, there is a need for strong advocacy to create a favorable perception of pediatric ART. Ranking stakeholders’ participation in the provision of health services allows lobbyists to know where most of their energy should be spent. For instance, the Mozambican MOH, the primary provider of health care services, was the main focus of lobbying activities in the Mozambique program. On the other hand, educational activities can help to prepare and sensitize all sorts of participants and recipients of ART, as well as their families and communities. For instance, messages were included in

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**Box 1. Steps to Implementation of Pediatric ART in Mozambique**

1. Identification and nomination of leaders
2. Identification of stakeholders
3. Advocacy and education on pediatric ART implementation
4. Integration of ART programs in the national health system
5. Establishment of simple, accessible pediatric ART guidelines for all health professionals
6. Training and controlling the quality of health professionals involved in pediatric ART
7. Guaranteeing the supply of needed laboratory reagents and pediatric drugs
8. Establishing efficient access and referral systems
9. Continuous evaluation and improvement
the education package for health providers and the general population aimed at adjusting people’s conventional thinking about what constitutes disease in the context of HIV/AIDS. Education should target health-care professionals already on duty as well as those that will soon be joining the workforce. Thus, institutions training health personnel must be included in the sensitization process.

Integration of the Pediatric ART Program in the National Health System
Integration is meant to allow counseling, screening, early detection, and treatment of HIV-infected children using the already available health infrastructure while addressing the specific need for pediatric HIV care within the national health system. This calls for the provision of updated information, instructions, and clear guidelines on pediatric HIV screening, counseling, and diagnosis for all health-care providers that may be the first point of contact for ART-eligible children.

Training of health-care personnel, such as medical doctors, medical officers, nurses, laboratory technicians, psychologists, and pharmacists already practicing in the national health system is essential. Special attention should be paid to the nurses, given that they will screen the majority of the patients. Moreover, training should be extended to health education institutions, such as schools of medicine, nursing, and laboratory technology, through adjustment of current programs or by offering packages containing specific materials. Finally, no trainee should be allowed to deal with any area of pediatric HIV/AIDS unless he or she passes the requisite exams.

Guarantee the Supply of Needed Laboratory Reagents and Pediatric Drugs
Updating or upgrading of existing laboratory services within the national health system is essential to ensure a standardized level of quality across the pediatric ART program. Therefore, program planners must: identify the type of tests to be performed and their assignment to different levels of health care, evaluate the capacity of existing laboratory facilities and human resources to perform the specific tasks related to pediatric ART, make proper adjustments in the laboratory facilities as required, acquire any additional laboratory equipment as needed, and train laboratory technicians. Following these steps will lead to readiness to deliver pediatric ART.

The laboratory tests must be in conformity with the level of services that are being offered. In Mozambique, economic constraints limited the number of tests that could be performed, potentially slowing the expansion of pediatric ART. Therefore, CD4 count and DNA polymerase chain reaction tests were elected as the first priority due to their importance and frequent use.

At the same time, reagent and drug delivery schedules should be reassessed in light of greater anticipated demand to prevent eventual shortages. In Mozambique, a parallel system of antiretroviral (ARV) drug delivery was initially set up within the national health system to prevent drug stock-outs. Now that the drug delivery system has been upgraded, a new, more efficient process is in place, eliminating the need for a parallel system. In addition, pharmacy personnel need to be trained on ART protocols and recordkeeping procedures specific to ART drugs to minimize theft and misuse.

The lack of pediatric formulations did not prevent us from establishing pediatric ART. To overcome this challenge, instructions were issued by the MOH establishing the amount of adult pills to be administrated as a function of children’s weight and were made available to pediatric ART program officials. Later on, as pediatric formulations became available, these guidelines were no longer needed.
The first pediatric ARV formulations were provided as both liquid medicines and pills, each containing a single dose of medicine. This resulted in treatment regimens that consisted of simultaneous administration of several medicines, requiring parents or caretakers to administer several drugs at the same time. After the advent of pediatric fixed-dose combinations, this process was greatly simplified. While variations of children’s weight necessitates continuous dose adjustments, this has been made easier through the use of weight-band dosing.

**Establish Efficient Access and Referral Systems**

Pediatric ART patients are mainly recruited from the national health system sanitary network. In Mozambique, the level of established health-care facilities varies from primary to quaternary, reflecting not only the increasing degree of complexity of health infrastructure and diagnostic tools but also the differentiation in quantity and quality of professional training among health-care providers. In the beginning of 2008, the Mozambican health network was made up of 1,210 primary health-care centers (PHCCs), 32 secondary health-care hospitals, 11 tertiary health-care hospitals and 3 large quaternary health-care hospitals (in Maputo, Beira, and Nampula). This sanitary network is spread out across 11 provinces to serve a population of 20.5 million. Services provided through this system are available to all children and are completely free, including the consultation, all tests, and treatment. Similarly, services provided through the national ART program are free-of-charge.

Most of the patients accessing the national health system attend a PHCC. Thus, the PHCCs are where most of the screening of suspected HIV-infected children takes place. At this level, the nurses are most commonly involved in providing care. Nurses are trained to identify and refer children suspected of being HIV-infected for testing, and to provide appropriate counseling. In addition, the nurses deliver a package of care designed for suspected HIV-infected children at this level of care that consists of nutritional assessment and supplementation (vitamin A included), distribution of cotrimoxazole, and treatment/immunizations for intestinal parasites and other endemic infections.

In order to maximize the enrollment of children into pediatric ART, further screening and surveillance must be done at sites that routinely assist sick children or potentially HIV-infected parents (Box 2). In fact, it is still considered common sense among the majority of the population to seek medical attention only when clear signs or symptoms of illness are apparent. Therefore, identification of HIV-infected children across a range of pediatric services is both practical and necessary.

Secondary and tertiary health-care services are available in rural district and regional hospitals. Health-care professionals assigned to these facilities include medical doctors and medical officers, as well as other levels of health-care providers. Generally, patients access these health services when referred from PHCCs. Secondary and tertiary health-care hospitals are the main deliverers of pediatric ART. In addition, they offer assessment of psychomotor development, treatment of more complicated opportunistic infections, and psychosocial care. Inpatient services are also available.

The highest level of health care for children affected by HIV/AIDS is offered at specialty Centers of Excellence (COEs). These centers are staffed by

<table>
<thead>
<tr>
<th>Box 2. Additional Points of Enrollment for ART-Eligible Children</th>
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<tbody>
<tr>
<td><strong>Pediatric services providers</strong></td>
</tr>
<tr>
<td>Prevention of mother-to-child transmission programs</td>
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<tr>
<td>Tuberculosis treatment and prevention units</td>
</tr>
<tr>
<td>Voluntary counseling and testing centers</td>
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</tbody>
</table>

pediatricians whose focus is pediatric HIV/AIDS. Patients attending the COE are referred from secondary and tertiary health-care facilities. In addition, COEs are used as a base for training, supervision, and coordination of pediatric HIV care.

**Continuous Evaluation and Improvement**

The monitoring system for pediatric ART in Mozambique utilizes tools that evaluate the quantity and quality of care. Every month, the MOH collects data at ART administration sites on the number of new children on treatment, patient deaths, loss to follow-up, and transfers. Pediatricians with expertise in pediatric ART are in charge of quality assessment (see Box 3 for quality indicators). Additional data is collected regarding health infrastructure and on-site training of health professionals in support of program implementation.

Quality assessment is based on a file review of at least 30% of the pediatric patient cases. The cases are then compared with the standard of care (SOC), and sites are then classified according to percentage of cases that meet or exceed the SOC as follows: good (> 95%), acceptable (80%–94%), or poor (< 80%). Within this system, different sites are compared with one another, and each individual site is assessed for improvements over time. This system also allows the assessment team to meet the site staff and be objective in suggesting what changes or improvements need to be made. The assessments are made during the supervisory visits by MOH staff; sometimes teams are a mix of MOH staff and nongovernmental organization staff; implementation of suggestions made during the visits is assessed during the next visit.

Quality assessment of ART can routinely be performed using basic parameters, such as the number and percent of patient deaths, loss to follow-up, and changes in CD4 counts. Longitudinal assessments are required to obtain a better picture of the overall quality of care. Such assessments should be performed only after the pediatric SOC is defined. In Mozambique, we perform site visits to assess SOC, which helps us to ascertain whether quality is being achieved. This is a more effective strategy than the review of reporting data alone. We are also initiating a random assessment of the pediatric sites according to the size of the site during which SOC will be evaluated, together with a random measurement of ART patient viral loads.

**Box 3. Quality Indicators for Supervision of Pediatric ART at the Site Level (Mozambique, 2007)**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Target</th>
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<tbody>
<tr>
<td>% completed entry forms</td>
<td></td>
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<tr>
<td>% children with registered age, weight, height</td>
<td></td>
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<tr>
<td>% children with nutritional classification</td>
<td></td>
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<tr>
<td>% children with psychomotor assessment</td>
<td></td>
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<tr>
<td>% children with WHO clinical staging</td>
<td></td>
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<tr>
<td>% children that received cotrimoxazole</td>
<td></td>
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<tr>
<td>% children with CD4 before ART</td>
<td></td>
</tr>
<tr>
<td>% eligible children that started ART</td>
<td></td>
</tr>
<tr>
<td>% children with correct ART dosages</td>
<td></td>
</tr>
<tr>
<td>% children with regular clinical and laboratory tests</td>
<td></td>
</tr>
<tr>
<td>% children with assessment of toxicity</td>
<td></td>
</tr>
</tbody>
</table>

**RESULTS: GAINS OF PEDIATRIC ART PREPARATION AND IMPLEMENTATION**

As a result of the preparation and implementation process of pediatric ART, some gains were made as far as trained, professional health-care staff, expansion of pediatric ART, increased number of children benefiting from ART (Figures 1 and 2), and establishment of patient monitoring (Figure 3).

Generally, in all the sites there is a good implementation of the treatment guidelines, and almost all eligible children that are followed in the visited sites do receive ART. But on the other hand, there are still some difficulties concerning the adjustment of ART dosages as well as...
Figure 1. Growth of pediatric ART in relation to adult ART (Mozambique, 2005 to 2007)
Source: Ministry of Health, Mozambique, 2007

Figure 2. Pediatric ART enrollment and percentage of total ART enrollees that are children (Mozambique, 2005 to 2007)
Source: Ministry of Health, Mozambique, 2007

FROM THE GROUND UP: DEVELOPING PATHWAYS AND PARTNERSHIPS
the importance of children’s health issues. In addition, in Mozambique more than 50% of the population is under 15 years old. Although HIV prevalence among children is less than among adults, children are highly vulnerable to the health effects of HIV infection. Therefore, plans for using adult ART programs as an avenue for the recruitment of eligible children may be a reasonable approach, in the future, for enrolling more children into ART.

Current figures of children benefiting from ART reveal that children throughout the country have not benefited equally from this program. This may be a consequence of different timing of the start of the program in different regions, as well as unequal allocation of resources. Also, health care staff involved in pediatric ART implementation might exhibit variable levels of commitment toward the program. Therefore, continuous analysis and discussion of achievements from different areas will be an important activity for all teams so that the reasons for these differences can be discovered and addressed.

**THE FUTURE OF PEDIATRIC ART**

Mozambique, one of the poorest countries in the world and equally one of the most affected with HIV, has so far succeeded in implementing a national pediatric ART program. This can be taken as an encouraging sign for those countries experiencing similar conditions. However, the implementation of pediatric ART is far from being perfect, and a lot more work has to be done to improve the current outcomes.

Available results on children versus adults benefiting from ART show a huge, yet slowly diminishing, gap between the numbers of eligible children and adults receiving treatment (Figure 2). As was affirmed earlier, advocacy for children’s ART is very much needed to overcome the uneven perception of clinical staging and treatment of opportunistic infections. There are differences between sites, essentially according to the workload and available staff at each site.

Figure 3. Selected pediatric ART quality indicators in tertiary hospital sites in Mozambique, 2007

*Source: Ministry of Health, Mozambique, 2007*

*No data reported by Mavalane on opportunistic infections or WHO staging*


8. Irish Aid. Irish Aid and the Clinton Foundation HIV/AIDS Initiative in Mozambique. Irish Aid, Department of Foreign Affairs. 2006.


To date, most pediatric HIV treatment programs have been concentrated in tertiary health facilities situated in African cities. Consequently, there is a high workload for the staff of these centers and limited access to care for the majority of African children who reside in rural settings.1,2 Challenges in scaling up programs for the prevention of mother-to-child transmission (PMTCT) of HIV and high rates of loss to follow-up for infants in PMTCT programs further underline the need for more attention to pediatric HIV care in rural settings. Evaluations of African programs for pediatric antiretroviral treatment (ART) have demonstrated that a clear reduction in hospital admissions, HIV-related morbidity, and mortality is possible through timely initiation of ART.3-6

While there is increased interest in decentralizing pediatric HIV treatment programs, little is known about the model within which such decentralization could happen most efficiently. The aim of this chapter is to describe which tasks could effectively be performed at primary and secondary health-care centers and to briefly summarize the rationale behind these tasks (as described elsewhere).7

DEFINITION OF TERMS
While we will mainly discuss governmental healthcare systems, there may be significant local differences in the resources and organization of these systems. In order to increase the practicability of the ideas presented in this chapter, three simplified health-care levels based on resources and skills, rather than a taxonomy based on the structure of governmental health-care systems, will be used as a guide:

A. The health-care level traditionally led by a less trained nurse or nurse’s aide. These individuals’ tasks consist mainly of taking medical histories, anthropometry, health education (including providing information about preventive measures), basic counseling, and referring problems to higher levels of health care.

B. The health-care level traditionally led by a clinical officer / medical assistant or a nurse who has received more advanced pediatric and HIV training. These individuals’ tasks consist mainly of taking medical histories, anthropometry, immunizations, basic clinical examinations, performing or organizing simple laboratory tests, more advanced counseling, health education (including providing
information about preventive measures), dealing with common illnesses, and identifying and referring more complicated cases to a medical doctor.

C. **The health-care level traditionally led by a general practitioner.** These individuals’ tasks consist mainly of supervising the work performed at levels A and B, taking medical histories, clinical examinations, performing additional investigations, surgery, initiation and supervision of treatment, health education (including providing information about preventive measures), and referring complicated cases to the referral hospital.

The first difficulty with this simplified model lies in defining the levels of health care. Training may help improve one or more aspects of pediatric HIV care (e.g., Integrated Management of Childhood Illness [IMCI], HIV counseling and testing, PMTCT, and care for opportunistic infections [OIs]). Since most health-care workers will not have completed all courses, they may be categorized as level A for some aspects of care and as level B for other aspects of care. And despite adequate training of personnel, other variables such as a lack of facilities may limit the type of services that can be provided at the center and consequently influence the categorization of the health-care level.

The second difficulty is that coordinated care within a district is dependent on the level of communication and leadership in that district. While nurses’ aides and less educated nurses can play a very important role in the HIV treatment paradigm, they may fulfill this role only after having been educated and sensitized to do so. Ideally, this education would take place during district health meetings and site visits from the district health team. Geographical constraints may limit contact with peripheral clinics, however.

Third, national protocols—which remain the primary guide for HIV care—may vary greatly between countries. Routine infant diagnostic tests may be an option in some settings, while even referrals for infant diagnostic testing may be impossible in other countries.

Finally, each model is inevitably based on certain assumptions about how and by whom each aspect of care is best provided. For example, in this simplified model the medical doctor initiates pediatric ART and active case finding is promoted. In some settings, the collaboration between doctors and trained nurses may be different. Thus, health-care workers will still need to adapt the information presented in this chapter to their own setting, facilities, resources, and national guidelines. The advantage of this taxonomy is that health-care workers employed in private practices or understaffed and heavily under-resourced health-care centers can also find a valuable place in the HIV-treatment paradigm.

Currently, the most common strategy to decentralize HIV/AIDS care is to shift tasks to a lower level of health care only when they can no longer be performed by overburdened staff. In many areas, the tertiary hospital was the only place where a program for pediatric HIV/AIDS care was provided; health-care planners began discussing rolling the program out to the secondary level only when the high workload at the tertiary level forced them to do so.

In this chapter, another line of reasoning will be followed. In our taxonomy, in line with the patient flow for general consultations and the call for improved access to pediatric HIV/AIDS care, health-care workers of a given level will perform all tasks of HIV care that are similar to other health-care tasks normally performed by workers of that level. Only tasks that require more skills or resources than can be offered at this level
will be shifted to a higher health-care level. Even though all health-care workers can perform level A tasks, the health-care workers of levels B and C will instead supervise these tasks and focus on their own level-specific tasks. Once a problem is attended to, down referral should take place.

While other chapters of this book address the ART preparedness of staff and health-care systems, this chapter will focus on the ART preparedness of the child and his or her caregiver(s). In the field, it is not always clear what should be done to prepare the child and the caregivers as well as possible for the initiation of ART. However, the success rate of pediatric ART is greatly determined by a thorough preparation of the child and his or her family or group of caregivers. The tasks involved in preparing the child and the caregivers for the initiation of ART can be broken down into the following three parts:

- Addressing issues relating to HIV diagnosis and disclosure to identify children who need counseling and HIV care (including ART)
- Following up on disease progression to determine the optimal timing for the initiation of prophylactic measures and ART
- Performing critical non-ART interventions to optimize the general condition of the child in order to postpone disease progression for as long as possible and reduce the risk of side effects from ART

Once ART has been commenced, many of these tasks will need to receive continuous attention. Ongoing discussions about disclosure and the collaboration between the child’s caregivers will remain necessary to optimize adherence to treatment and clinic appointments and address further counseling needs (as a result of the child’s increasing maturity or changed living conditions); follow-up of disease progression will remain necessary to identify the need to adapt or change the treatment in a timely manner; and critical non-ART interventions will remain necessary to optimize the general condition of the child and, in doing so, to help maintain a low viral load.

As we discuss the interventions leading up to and including ART, the three-level framework will be used to guide the division of tasks among the different types of health-care workers.

**DESCRIPTION OF INTERVENTIONS**

**HIV Diagnosis and Disclosure**

Before a child can begin ART, it is important to investigate how the HIV diagnosis was made. The diagnosis based on a clinical case definition or the result of laboratory tests? What are the names and the results of the various tests that were performed on the child and/or the mother? What was the age of the child when these tests were performed? How many weeks had the child been weaned when these tests were performed? Did the mother and the child ingest any antiretrovirals before or shortly after the delivery, and if so, what medication did they ingest and for how long, or how many doses did they receive? To whom was the serostatus of the child (and the mother) disclosed, and, especially for older children, what type of disclosure was used (partial or full)? It will be important to have a clear picture of the number of caregivers involved in the care of the child and an understanding of how they collaborate. This helps set the indication for HIV care and provides baseline information for adherence counseling.

An example of the division of the tasks for diagnosis and disclosure according to health-care levels is provided in Table 1.
**Follow-Up of HIV Disease Progression**

In order to identify the level of HIV progression that would indicate in a timely manner the commencement of ART, the HIV infection must be diagnosed as early as possible and the condition of the child reassessed regularly. During the follow-up period, invaluable information concerning adherence to clinic appointments and medication can be collected, and the clinician can be alerted about necessary interventions to prevent nonadherence to ART at a later point in time. Once ART has been commenced, the same interventions should take place to document catch-up (suggesting immunologic and virologic response) as well as to detect treatment failure and to alert health-care workers to possible undiagnosed interfering illnesses.

Information about disease progression can be obtained through the following means:

- **Laboratory tests:** Tests for viral loads, CD4 counts, CD4 percentages, and alternative markers such as total lymphocyte counts can provide critical data.

- **Routine anthropometry:** HIV-associated growth retardation can start before birth.\(^9\) Birth weight, as well as weight-for-age and height-for-age growth curves, is significantly different for HIV-infected and HIV-exposed, uninfected children.\(^10\) The mean head circumference is more often below the third percentile (40% of HIV-infected children, compared to 22% in uninfected children).\(^11\) Severe HIV-related malnutrition indicates a category C (Centers for Disease Control and Prevention [CDC]) or IV (World Health Organization [WHO]) disease stage and, consequently, justifies initiation of ART.\(^8\) In a Spanish cohort,
ART was associated with significant increases in $z$ scores for weight and height, but in Ivory Coast, a significant improvement in only weight for age was found 18 months after the initiation of ART. Catch-up growth can be demonstrated even five years after the initiation of ART. Virologic nonresponders were found to have significantly lower $z$ scores for weight and height. Progressive growth retardation despite ART may indicate treatment failure. However, the response to ART may be masked by non-HIV-related malnutrition or undiagnosed opportunistic infections. Weight for age is the best indicator of disease progression and survival and can easily be monitored at all levels of health care.

- **Routine neurodevelopmental assessments:** Delay of or failure to meet developmental milestones (motor, cognitive, and language) can be the first presenting symptom of HIV infection in children. Rapid developmental screening lists can be used to help identify such delay. Neurological examinations are abnormal in up to 40% of HIV-infected children, as compared to less than 5% of HIV-uninfected children. By the age of 12 months, 30% of HIV-infected Ugandan children in one study had motor abnormalities and 26% had cognitive abnormalities. Delay in (expressive) language development often precedes other neurologic abnormalities. HIV encephalopathy, failure to meet developmental milestones or loss of developmental milestones, and neurologic disease may indicate a category C (CDC) or 4 (WHO) disease stage, justifying initiation of ART. Progressive developmental delay and neurologic symptoms despite ART may indicate treatment failure. But non-HIV-related malnutrition, poverty, and opportunistic infections may cause similar problems.

### Table 2. Division of Tasks for Follow-Up of Disease Progression by Health-Care Level

<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
</tr>
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<tbody>
<tr>
<td>Checks the general physical condition of the child and refers the symptomatic child (according to IMCI guidelines)</td>
<td>Checks the child’s neurodevelopment with a larger number of questions from a rapid developmental screening checklist and refers the child in case of developmental delay or loss of developmental skills</td>
<td>Performs a general clinical examination, assesses growth retardation, and performs a neurodevelopmental assessment</td>
</tr>
<tr>
<td>Performs routine anthropometry (weight, height, head circumference) and refers the child to a higher level in case of growth retardation (according to IMCI guidelines)</td>
<td>Possibly determines the clinical stage (WHO/CDC)</td>
<td>Determines or supervises determination of the clinical stage (WHO/CDC)</td>
</tr>
<tr>
<td>Checks the child’s neurodevelopment with a limited number of questions from a rapid developmental screening checklist and refers the child in case of developmental delay or loss of developmental skills</td>
<td>Summarizes information in case of referral to level C or A</td>
<td>Orders general laboratory tests and, if possible, CD4 count, CD4%, and viral load tests</td>
</tr>
<tr>
<td>Summarizes information in case of referral to level B or C</td>
<td></td>
<td>Treats possible interfering illnesses and may refer a complicated case to a tertiary hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Summarizes information in case of down referral or referral to tertiary health-care level</td>
</tr>
</tbody>
</table>

- **Routine neurodevelopmental assessments:** Delay of or failure to meet developmental milestones (motor, cognitive, and language) can be the first presenting symptom of HIV infection in children. Rapid developmental screening lists can be used to help identify such delay. Neurological examinations are abnormal in up to 40% of HIV-infected children, as compared to less than 5% of HIV-uninfected children. By the age of 12 months, 30% of HIV-infected Ugandan children in one study had motor abnormalities and 26% had cognitive abnormalities. Delay in (expressive) language development often precedes other neurologic abnormalities. HIV encephalopathy, failure to meet developmental milestones or loss of developmental milestones, and neurologic disease may indicate a category C (CDC) or 4 (WHO) disease stage, justifying initiation of ART. Progressive developmental delay and neurologic symptoms despite ART may indicate treatment failure. But non-HIV-related malnutrition, poverty, and opportunistic infections may cause similar problems.
FROM THE GROUND UP: DEVELOPING PATHWAYS AND PARTNERSHIPS

From the ground up, developing pathways and partnerships is crucial in addressing the needs of HIV-infected pregnant women and their infants. The provision of cotrimoxazole prophylaxis, regardless of pregnancy stage, is recommended due to its benefits for maternal health and malaria prevention and treatment. Cotrimoxazole prophylaxis in women with CD4 counts below 200 has been shown to result in indirect benefits for neonatal health, such as reductions in chorioamnionitis, prematurity, and neonatal mortality.24,25

- **Prevention and treatment of opportunistic infections.** Pneumonia caused by *Pneumocystis jirovecii* has a peak incidence between three and six months and a case-fatality rate of 40% to 87%, and can be greatly influenced by commencing cotrimoxazole prophylaxis at the age of four to six weeks (or during the first healthcare encounter, e.g., for immunizations).25 About 80% of children in close contact with a TB patient will become infected with TB. Up to 40% of them will develop active TB, which causes a higher mortality in HIV-infected children.26,27 TB is 10 times more common in HIV-infected pregnant women and is responsible for 15% of maternal mortality and a doubling of the TB incidence in neonates and infants.28 Maternal TB could be identified through routinely enquiring about TB symptoms during consultations for PMTCT.

- **Prophylactic use of an antibiotic.** Daily cotrimoxazole may reduce the overall mortality by 43% (independent of baseline age group and CD4 count).29 Cotrimoxazole is highly effective against *Pneumocystis jirovecii* and *Toxoplasma gondii* but also offers some protection against bacteria (such as *Streptococcus pneumoniae*, *Salmonella*, and *Nocardia*), malaria, and other parasites (including *Isospora belli*).30,31

- **Micronutrient supplements.** Supplements, such as regular vitamin A (which may reduce all-cause mortality by 63%, diarrhea-related...
mortality by 92%, and overall morbidity by 31%), can be useful. Zinc supplementation may help by increasing weight gain and reducing the need for clinic visits for watery diarrhea. A multivitamin is useful since HIV-infected children have increased needs for vitamins and minerals, especially in the case of malnutrition.

- **Individualized breastfeeding counseling.** Counseling can help identify breast problems, breastfeeding problems, and feasible strategies to reduce HIV transmission. Mixed feeding before three months of age is associated with a risk of HIV transmission that is nearly double the risk associated with exclusive breastfeeding, while breastfeeding after six months of age is associated with a more than doubling of the risk of HIV transmission. However, the potential benefits of reduced HIV exposure through the avoidance of breast milk after six months of age are usually masked by adverse outcomes and increased infant mortality as a result of incorrect replacement feeding.

- **Nutritional counseling.** In the early stages of HIV infection, counseling should emphasize increased intake of proteins and energy (e.g., by mixing eggs, oil, or milk powder with the meal). In the more advanced stages, counseling should aim at enhanced absorption and digestion (e.g., using pawpaw, lemon, and sour milk). Nutritional interventions may be able to restore intestinal absorption and CD4 counts. Counseling alone may result in increased and improved food intake, but if caregivers are unable to prepare calorie-dense meals, nutritional supplements (such as fortified porridge) may be helpful.

- **Emotional support, pain relief, and palliative care.** These forms of support can also help reduce hospital admissions, morbidity, and mortality. In American HIV-infected children, pain reporting was found to be independently associated with mortality within the next three years. It is hypothesized that pain may be a unique manifestation of HIV.

- **Increased attention to the 16 key family practices of IMCI.** IMCI practices (such as providing safe potable water) and the promotion of other simple but invaluable interventions can help optimize the care for the child.

An example of the division of tasks for non-ART interventions according to health-care level is provided in Table 3.

### Antiretroviral Therapy

The division of tasks for ART intervention may be subject to the greatest debate, as it needs to find a balance between quality of care, access to care, sustainability, and destigmatization. Obviously, it is also affected by the HIV prevalence in the area, the available resources and staff at the various healthcare levels, national protocols, administrative and other requirements from funding agencies, and the availability of pediatric ART. The model may also need to change over time as a result of more advocacy, changes in the availability of pediatric ART, increased training and experience with pediatric ART, changes in national protocols and requirements from funding agencies, or staff turnover at the various levels of health care.

An example of the division of tasks for ART interventions according to health-care level is given in Table 4.

### COMMON CHALLENGES OF PEDIATRIC HIV TREATMENT IN RURAL SETTINGS

While it would be impossible to provide a list of all obstacles to the provision of pediatric HIV treatment in rural settings, the following points will address some of the common challenges:

- **Changes in the child’s group of caregivers.** Cultural differences in family dynamics, death among kin, labor-related migration, illness of
<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checks EPI immunization status and organizes/refers for immunizations</td>
<td>Gives EPI immunizations</td>
<td>May order additional immunizations if possible</td>
</tr>
<tr>
<td>Performs basic and supportive nutritional and breastfeeding counseling</td>
<td>Performs more advanced and supportive nutritional and breastfeeding</td>
<td>Deals with breast (feeding) problems</td>
</tr>
<tr>
<td>and identifies and refers problems</td>
<td>counseling, and identifies and refers breast (feeding) problems</td>
<td>Treats malnutrition and vitamin deficiency</td>
</tr>
<tr>
<td>Checks whether vitamin A was given six-monthly, provides vitamin A,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and records this on the growth card</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribes multivitamin syrup to all HIV-exposed children or (in case</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of limited resources) to malnourished children only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly provides nutritional supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provides and records prophylaxis against parasitic infections, and</td>
<td>Refers for stool tests or blood smears for malaria</td>
<td>Treats malaria and endemic infections and their complications</td>
</tr>
<tr>
<td>provides counseling on the prevention of such infections and the use</td>
<td>Provides treatment for malaria and other endemic infections and refers</td>
<td></td>
</tr>
<tr>
<td>of safe water</td>
<td>complicated cases to level C</td>
<td></td>
</tr>
<tr>
<td>Provides and records malaria prophylaxis during pregnancy and promotes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the use of bed nets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiates or refers for PCP prophylaxis</td>
<td>Orders sputum investigation and performs Mantoux/Tine test</td>
<td>Orders additional investigations for the diagnosis and treatment of</td>
</tr>
<tr>
<td>Supervises adherence to cotrimoxazole and clinic appointments, and</td>
<td>Treats some OIs and refers to level C for the treatment of other OIs</td>
<td>OIs, such as chest X-rays, lumbar punctions, biopsies, etc.</td>
</tr>
<tr>
<td>possibly organizes home visits for defaulters</td>
<td></td>
<td>Treats side effects</td>
</tr>
<tr>
<td>Refers in case of possible side effects</td>
<td></td>
<td>Deals with interference between different treatments and may refer to</td>
</tr>
<tr>
<td>Screens for TB in the family (through asking questions) and supervises</td>
<td></td>
<td>tertiary hospital in case of complications</td>
</tr>
<tr>
<td>adherence with TB treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checks the child’s mouth routinely for candida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refers in case of clinical symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discusses the general emotional state of the child (and the child’s</td>
<td>Counsels the child and his or her caregivers for emotional and social</td>
<td>Organizes specific counseling and/or medication in case of severe</td>
</tr>
<tr>
<td>school performance)</td>
<td>problems</td>
<td>emotional problems</td>
</tr>
<tr>
<td>Asks whether the child has pain and checks whether the pain relief is</td>
<td>Provides and adapts the pain medication</td>
<td>Adapts the pain medication</td>
</tr>
<tr>
<td>sufficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discusses the general emotional state of the caregivers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discusses the general emotional state of the caregivers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tries to link with programs for orphans and other vulnerable children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>according to the needs of the family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promotes the 16 key family practices (IMCI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summarizes information in case of referral to level B or C</td>
<td>Summarizes information in case of referral to level C or A</td>
<td>Summarizes information in case of down referral or referral to tertiary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>health-care level</td>
</tr>
</tbody>
</table>
and other medication), health-care workers should routinely check who is (still) involved in the care of the child, how these caregivers collaborate, and whether disclosure and adherence counseling has taken place for these people. It may be necessary to invite several caregivers over time or provide adherence counseling for several caregivers at the same time.

- **Transport problems.** In order to adapt the dosages (for cotrimoxazole, ART, or other medication) to the needs of the growing child, usually only a one-month supply is given out at any one time. Families may struggle to find the resources for public transport, caregivers may be too sick to accompany the child, or public transport may only be erratically available. In such cases it may be necessary to provide a greater supply or organize treatment such that medications can be collected alternately from a
Since the majority of children are seen by health-care workers of level A and B, who may not have the opportunity to ask advice from a health-care worker of level C and lack knowledge and/or confidence to perform such calculations, broad weight categories for each ARV have been determined and are accompanied by visual aids. This greatly simplifies the provision of pediatric ART but does not eliminate the need for regular adaptations of the dosages.44,45

CONCLUSION

The provision of pediatric HIV care in rural resource-limited settings is significantly more challenging than the provision of adult HIV care. However, even in the absence of ART, much more can be done than is currently being achieved. Several inexpensive and simple interventions have the potential to greatly improve the health of thousands of HIV-infected children. While these interventions can be performed by health-care workers who have received little training, they have not yet been universally implemented. Each level of the health-care system can fulfill its own distinct, invaluable role within the HIV treatment paradigm. We would also like to stress the need for a continuum of care, rather than dichotomizing pediatric HIV/AIDS care into providing either cotrimoxazole or ART.

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Disclaimer: The opinions expressed in this chapter are those of the authors and do not necessarily represent those of their organizations.


About half of the 5,000 to 7,000 HIV infections that occur every day are among young people aged 15 to 24 years, and about 30% of the 39.5 million people living with HIV globally fall into this age group. Initially perceived during much of the 1980s as predominantly affecting gay men, and then as a disease of the West, especially among rich older men, the face of HIV has now shifted to that of a young, poor African, particularly a young, poor African woman. The increasing rate of new infections among youth in resource-limited settings calls for innovative programs that address the special needs of young people, and young women in particular. One such model is youth-friendly service provision.

Youth-friendly health services are broad-based health and related services provided to young people to meet their individual needs in a manner and an environment that attract and sustain their interest in utilizing such services. Youth-friendly services—stand-alone, mobile, or within the context of a health facility—are needed if young people are to be adequately provided with reproductive health care. Offering reproductive health services for young people requires specially trained providers in youth-friendly service provision, privacy and confidentiality, convenient locations and hours of operation, affordability, and availability of services at all times.

**MODELS OF YOUTH-FRIENDLY HEALTH SERVICES**

Youth-friendly services can be offered alongside other primary health-care services in existing health facilities. They can also be offered in stand-alone or youth-only facilities, as well as in mobile or community settings. A pilot study in Jinja, Uganda, to evaluate the impact of adolescent-friendly health services, found that significantly more adolescents utilized routine reproductive health services (antenatal care, family planning, maternity care, management of sexually transmitted infections [STIs], and laboratory services) in the pilot facilities than in the control facilities. In addition, knowledge of adolescent health problems and family planning methods increased, as did the perception of STIs and HIV as problems for adolescents. The main constraint to service uptake was erratic supply of drugs and contraceptives. Elsewhere, adolescents in Kenya and Zimbabwe valued confidentiality, short waiting times, low costs, and friendly staff more than they valued...
youth-only services or young staff. The researchers concluded that most existing clinical services, even in resource-limited settings, are in a position to improve their level of youth-friendliness. Similar findings have been reported in Wakiso, Uganda; Kenya and Zambia; and Bulawayo, Zimbabwe.

Other important considerations to improve access to reproductive health services by youth include effective promotion campaigns designed with input from young people and community acceptance of reproductive health services for youth. Engaging parents and community leaders in programs to improve uptake of services by young people will address this concern and consequently reduce the shame, stigma, and embarrassment that some youth associate with being seen at health facilities. This chapter will describe how Tuungane Youth Project in western Kenya has successfully addressed these needs and remains one of the few successful youth-friendly service providers in Kenya.

BACKGROUND OF THE TUUNGANE YOUTH PROJECT
Tuungane Youth Project is a youth-friendly HIV intervention program being implemented by Impact Research and Development Organization, a local nonprofit organization based in Kisumu city, western Kenya. The project, whose name is a Kiswahili word for “let’s join hands,” was initiated in October 2004 to bring together youth, parents, teachers, and religious leaders in the fight against HIV/AIDS among young people residing in the slum settlements of Kisumu city and the fishing communities in Suba district. It employs two models—stand-alone (youth-only) and community-based (mobile) sexual and reproductive health service provision. Funding was obtained from the President’s Emergency Plan for AIDS Relief (PEPFAR) and administered through the Centers for Disease Control and Prevention (CDC). The project targets young people 10 to 29 years of age. Initially, it was funded to promote behavior change (abstinence and being faithful) among young people through training on life planning skills; peer counseling and education; health talks; referrals for treatment of STIs and voluntary counseling and testing (VCT); distribution of information, education, and communication (IEC) materials; and provision of recreational activities to reduce idleness and divert attention from potentially risky activities and environments.

Even though Tuungane was better than most programs at addressing youth-specific HIV prevention needs, we soon recognized that the program was grossly deficient in meeting many youth reproductive health needs. For example, those referred for VCT and STI services were reluctant to go to government health facilities, since those facilities were seen as not being youth-friendly. We soon realized that unless we expanded our services beyond the promotion of abstinence and being faithful, we would be meeting the needs of a very small proportion of the youth. Consequently, we expanded the program to address a variety of reproductive health needs of young people. In the following section, we describe how Tuungane Youth Project has succeeded in providing comprehensive reproductive health services.

INTERVENTION DESCRIPTION
Promotion of Behavior Change (Abstinence and Being Faithful)
The rate of HIV acquisition is lower in early adolescence than at any other stage in life. The challenge lies in keeping adolescents from becoming infected. The initial goal of the Tuungane Youth Project was to empower young people to practice positive social norms, particularly abstinence and mutual faithfulness for those in sexual relationships. The project continues to carry out activities
and provide services that are customized to promote both primary and secondary abstinence and faithfulness, reach youth with age-appropriate sexual health information, and build supportive family and community environments. This involves training young people on life planning skills from early adolescence in order to equip them with fundamental knowledge on sexuality and reproductive health, as well as the decision-making and negotiation skills necessary to manage relationships and social pressures. Tuungane has adopted two life planning skills curricula, one targeting 13- to 17-year-olds, known as Life Planning Skills for Young People in Kenya,\(^\text{18}\) and another covering youth between 15 and 24 years old, known as the Abstinence and Risk Avoidance for Youth Program.\(^\text{19}\) To circumvent the often prohibitive cost associated with engaging consultant trainers, and also to reach a large number of youth faster, we employed a strategy of training youth as trainers of trainers (ToTs). These ToTs are equipped to train other youth in their neighborhoods. With nine teams of ToTs currently active, we conduct regular training workshops and reach an average of 350 youth every month with various sexual and reproductive health education and skill-building activities.

**VCT and STI Services**

For HIV prevention efforts to register gains in addressing the pandemic among young people, VCT and prompt treatment of STIs should be made readily available and accessible to youth who are sexually active. VCT is recognized as an effective, pivotal strategy in HIV prevention and care.\(^\text{20-22}\) It is an entry point to treatment, care, and continuing counseling on risk reduction for HIV transmission. Those who test negative benefit from knowing their status and from modifying their behaviors in order to maintain their negative status.

STIs, particularly those that cause ulceration, increase one’s susceptibility to HIV infection.\(^\text{23-25}\) In addition, the same behaviors that put individuals at risk for STIs also put them at risk for HIV. In recognizing the dual benefit of VCT and STI treatment, Tuungane offers these two services free of charge at three centrally located youth-friendly clinics as well as mobile sites. Mobile services are particularly attractive to young people, as they make services readily available in their neighborhoods. For instance, we reach over 1,000 youth every month with VCT services, over 60% of whom are reached during the mobile outreaches.

**HIV Treatment and Care Services, Including Prevention of Mother-to-Child Transmission**

HIV-positive young people need multidisciplinary case management and care that integrates primary and reproductive health care with HIV-specific care, psychosocial support, and secondary prevention. Treatment of opportunistic infections and increased access to antiretroviral treatment are necessary if morbidity and death rates from HIV/AIDS among youth are to decline. Through a collaborative partnership and coordinated services with Family AIDS Care and Education Services (FACES), a PEPFAR-funded treatment and care program in Kisumu,\(^\text{26}\) Tuungane Youth Project now provides age-appropriate “one-stop-shop” comprehensive health care for HIV-positive youth up to 24 years of age. Youth are enrolled at 21 years of age or younger, and by the time they reach 24 years they are transitioned into treatment and care facilities for adults.

At the outset, we realized that two-thirds of young women enrolled in our treatment and care program had children of their own, some of whom were also HIV-infected. Rather than refer the children for care elsewhere, we expanded our program to include pediatric treatment and care services for
the children of our clients. Because adolescents and young women are at the early stage of their reproductive years, they are likely to have children in the future, regardless of their HIV-positive status. There are few data on how HIV-positive women make decisions regarding whether or not to have children, but anecdotal evidence shows that with the advent of antiretroviral therapy (ART), an increasing number of women are making conscious decisions to have children in the hope that they will be born without the virus. For women who choose to become pregnant, Tuungane Youth Project provides prevention of mother-to-child transmission (PMTCT) services, and for those who prefer not to become pregnant, we are partnering with Family Health Options of Kenya to provide family planning services, as described below.

**Family Planning Services**

Voluntary contraceptive services to help women prevent unwanted pregnancies are now accepted as an integral component of PMTCT programs, and contraceptive services in and of themselves should be recognized as significantly contributing to HIV prevention efforts. Women who are HIV-infected remain vulnerable to unintended pregnancies, which contribute to the high incidence of mother-to-child transmission of HIV. Fear of disclosing their HIV status to partners and an inability to negotiate safe sex make adolescent and young women at risk of having unwanted and/or unplanned pregnancies. Offering family planning services to young women who are sexually active provides an important new channel for combating HIV/AIDS among this vulnerable but underserved population. These services create an opportunity to counsel sexually active young women about a whole range of sexual risks, including unintended pregnancy and exposure to HIV and other STIs. Preventing unplanned pregnancies could further reduce the number of children born with HIV. In recognition of the importance of family planning in the HIV prevention arsenal, Tuungane Youth Project has integrated family planning services into its ART program for young HIV-positive women.

**Psychosocial Support for HIV-Positive Youth**

HIV-positive youth need space to talk about issues that affect them, such as disclosing their status to family, friends, and partners, as well as to share with peers how to cope with physical, social, and emotional challenges. Tuungane Youth Project has initiated a support group for HIV-positive youth aged 13 to 21 years, with a current membership of about 300. The group conducts regular meetings that involve discussions of risk behaviors for HIV transmission and coinfection with STIs and/or other strains of HIV. The meetings are facilitated by trained and experienced peer support facilitators and counselors who are themselves on ART. Meetings take place monthly at a central location and weekly in smaller groups (called cell groups) in the members’ respective neighborhoods. The cell group leaders have been trained in peer counseling and education, community mobilization, and home-based care. In addition to facilitating group meetings and providing peer education and counseling, the leaders carry out home visits to colleagues to monitor adherence to medication and clinic appointments. Furthermore, the leaders carry out community sensitization and education in schools, at religious institutions, and at social events to address issues relating to stigma and discrimination, and to promote VCT among young people. The key VCT message is that knowing one’s HIV status early is a gateway to a long and productive life, especially now that donor organizations are partnering with the government to support free care and treatment services in most public health facilities in the country.
Care Services for Rape Survivors

Many girls and young women, especially those living in slum settlements, experience rape and forced sex or are otherwise tricked or coerced into having sex. For example, 20% of all girls interviewed in Kisumu, Kenya, and Ndola, Zambia, said their first sexual encounter involved physical force. Violent or forced sex can increase the risk of transmitting or acquiring HIV because forced vaginal penetration commonly causes abrasions and cuts that allow the virus to cross the vaginal wall more easily. Tuungane Youth Project has built into its program a postexposure prophylaxis (PEP) service for survivors of rape. The project also provides community education and sensitization about facts relating to rape and its prevention, with the aim of reducing sexual violence in the targeted neighborhoods.

Alcohol and Substance Abuse Initiative

In Kenya, the recent Demographic and Health Survey found that prevalence of HIV among female alcohol drinkers was two times higher than among nondrinkers, and another recent survey showed that in a sample of 10- to 24-year-olds, 60% of nonstudents and 9% of students had used alcohol within the previous month. The interface between alcohol and other drug use and high-risk sexual behaviors is increasingly becoming a challenging reality in the fight against HIV/AIDS in Kenya. The impact of drugs and alcohol is largely due to their effects on rational thinking, sound decision making, and safe sex negotiations. Researchers have found that the abuse of alcohol and other psychoactive substances by young people correlates with high-risk sexual practices such as early sexual initiation, unprotected sexual intercourse, multiple sex partners, prolonged and traumatic sex, and premarital sex, as well as casual and transactional sex.

Reaching out to youth who are abusing alcohol and other psychoactive substances with information, counseling, education, and addiction treatment services aimed at changing these behaviors is one approach to preventing the spread of HIV among this group of young people. The Tuungane Youth Project has expanded to target this population of high-risk youth by establishing a modest, nonresidential drop-in transition center to provide tertiary HIV-prevention services to young people aged 10–29 years. The center provides rehabilitation services, including psychosocial counseling and primary outpatient treatment of conditions arising from addiction. VCT and STI treatment are also provided. In addition, the center makes referrals to government health facilities for further specialized management, if needed. The center is also open to receive youth discharged from hospitals for ongoing counseling with the goal of reintegrating them back into their families and communities. Recruitment to the center takes place through peer referrals and community sensitization, as well as through the Alcohol Use Disorders Identification Test (AUDIT) screening tool administered during VCT and STI services.

Involvement of Parents, Religious Leaders, and Teachers

Youth are strongly influenced by the people and institutions with which they are affiliated, such as their families, schools, and religious institutions. When implementing HIV prevention programs, it is important to reach out to young people's immediate and extended families, teachers, and religious leaders with behavior-change information. Adults and young people need to work together to address issues such as sexuality, sexual health education, sexual violence and abuse, gender norms, and traditional practices.

Tuungane Youth Project makes an effort to involve the adult population in many of its program activities. The project facilitates various dialogue sessions between youth and their parents,
At the root, board was an uphill task. Over time and with input from girls in the targeted communities, we learned lessons that helped us refocus our activities. For example, we learned that many girls were already teen mothers; that girls felt intimidated by the large number of boys attending our services; that to keep them indoors, girls were assigned many heavy domestic chores by parents or guardians; that girls were less likely than boys to have spare cash to pay for local transport to our center; and that girls easily got bored with routine activities and sometimes found hanging out with friends preferable to participating in Tuungane’s program activities.

To address the variety of needs and interests among young women and girls, the Tuungane youth Project has instituted several measures to attract and retain their participation. Every week, we have designated girls-only days at our centers, where all service providers are female. on these days, girls are allowed to come with their babies or any siblings left in their custody. Volunteer baby minders are engaged to allow the girls to have the whole day to themselves without the distraction of the children. Fare for bicycle taxis is provided to those not living within walking distance of the centers. Girls from each neighborhood take turns organizing activities, and consult with others to ensure that planned activities are responsive to the needs across different communities. Activities include sexual and reproductive health talks and roundtable discussions; musical gymnastics; indoor and outdoor games; aerobics; and demonstration lessons on baking cakes, cooking, hairdressing, and making sanitary pads. Because of these efforts, Tuungane Youth Project has begun registering large numbers of girls for its services and activities.

Religious leaders, and teachers, in order to provide a forum where adults and youth can engage in open dialogue on sexual health issues related to youth sexuality and HIV. Among these sessions are those that bring together youth and parents (not necessarily relatives of one another) to discuss issues that routinely get in the way of effective parent–child communication and suggest ways that these difficulties can be overcome. The project also trains parents, teachers, and religious leaders on communication skills to equip them to tackle issues related to youth sexuality and reproductive health.

Recruitment of parents, teachers, and religious leaders is performed by members of the 47 youth groups affiliated with the project, using door-to-door mobilization strategies as well as visits to religious institutions, schools, and colleges. The training materials used to date have not been derived from a formal curriculum. Starting in 2008, we are implementing an evidence-based curriculum—known as the Families Matter! program—which has been adapted and evaluated for use in Kenya. The long-term objective of such training is to improve positive parenting and effective communication between parents or primary caregivers and 9- to 13-year-old children about sexuality and sexual risk reduction for HIV infection.

Attraction and Retention of Out-of-School Adolescent Girls

The prevalence of HIV among adolescent girls in Kisumu is more than three times that among boys of the same age. Many organizations targeting young people with reproductive health services and activities face the challenge of attracting and retaining girls in their programs. Indeed, when the Tuungane program commenced, getting girls on
LESSONS LEARNED

Following are some of the key lessons we have learned in the course of implementing this program:

- Program implementers must be responsive to the needs of young people (as they are perceived and presented by the young people themselves). To keep the activities relevant to young people’s changing needs, views on client satisfaction should be collected periodically through suggestion boxes, informal group discussions, exit interviews, and other methods.
- If possible, programs should provide comprehensive sexual and reproductive health services under one roof because referrals can lead to high dropout rates. However, because youth must be referred for some services elsewhere, functional partnerships must be developed to ensure follow-through.
- Programs should train staff on youth-friendly service provision and provide services in an informal and fun environment.
- When possible, static sites should be complemented with mobile services to bring services closer to the consumers.
- Programs should build the capacity of young people at the grassroots level by training them as peer educators, counselors, and mobilizers. If funds are limited, program leaders can engage them as volunteers and provide motivation in the form of recognition days, training certificates, and other nonmonetary benefits.
- Youth should not be targeted in isolation; programs must work with or enlist the support of parents, teachers, religious leaders, and other adults.

CONCLUSION

While the Tuungane Youth Project described here represents a successful model for stand-alone and mobile health outreach strategies targeting youth, a pilot program in Uganda\textsuperscript{9,36,37} found that most existing clinical services are also in a position to improve their level of youth-friendliness. There is therefore an urgent need to improve the uptake of reproductive health services among young people, regardless of the setting in which those services are delivered. We can make great strides toward improving the uptake of these essential services as long as the basic components of youth-friendly service provision are put in place and regularly reviewed. In this way, we can ensure that programs serving young people are effectively responding to the numerous, diverse needs of this highly vulnerable population.

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In the KwaZulu-Natal (KZN) province of South Africa, more than 100,000 people are receiving antiretroviral therapy (ART), 10,000 of whom are children (as of September 2007). While this number represents one of the largest pediatric ART programs in the world, the majority of treatment-eligible, HIV-infected children in the province still do not have access to ART. The scaling up of the pediatric ART program is providing valuable lessons regarding the need for advocacy, training, and simplification of medical practices. While significant progress has been made, the sustainability of the program remains tenuous due to a number of factors, including the largely ineffective prevention of mother-to-child transmission (PMTCT) program.

Of all the nine South African provinces, KZN is the most severely affected by HIV. Antenatal seroprevalence rates and vertical transmission rates in KZN are high: the antenatal seroprevalence rate in the province was 39.1% as of 2006. High seroprevalence continues to fuel significant HIV-related morbidity and mortality in infants and children, reversing previously improving trends in child health. The majority (88%) of the population in KZN rely on the public health-care system for their health-care needs (see Figures 1 and 2). This system is currently being transformed into a district-based health system (see Figure 3), with a clear mandate to improve primary health care. However, severe shortages of skilled staff and failure to attract new staff and retain existing medical, nursing, and allied professionals are hampering the success of this transformation. Introduction of new programs, such as the PMTCT program (introduced in 2001), the Integrated Management of Childhood Illness (IMCI), kangaroo mother care, and the Expanded Program on Immunization (EPI), and escalation of these programs to scale, has been difficult. It was in this context that a province-wide, comprehensive HIV/AIDS care and treatment program was introduced in 2004.

Challenges Associated with a Poorly Functioning PMTCT Program

The PMTCT program consists of four major activities. Each of these activities will be discussed in relation to the challenges they pose for the provision of timely pediatric HIV care and treatment.
Voluntary Counseling and Testing
Most pregnant women in KZN attend antenatal facilities provided by the public health system. Opt-out testing is not currently being offered despite its proven acceptability and improved uptake. Initial group pretest counseling on HIV risks and the need for testing is given to all attendees at most antenatal clinics. This is done either in an open room, a verandah, or a designated counseling area. The number of women who accept testing after receiving counseling remains suboptimal in the context of the extremely high antenatal HIV seroprevalence. The shortage of lay counselors and health-care workers who are trained and equipped to provide counseling causes delays in the provision of individual pretest and posttest counseling. These delays lead to the failure to introduce timely ART for eligible pregnant mothers. As a result, the number of pregnant women receiving ART remains low despite the presence of ART programs at most hospitals in the province.

Use of Single-Dose Nevirapine by the Mother at the Commencement of Labor
KZN continues to follow national guidelines that recommend only single-dose nevirapine be administered as part of PMTCT. Full coverage of all HIV-positive mothers and their babies by the PMTCT program remains elusive. For those mothers who do test positive for HIV and accept the offer of PMTCT, further barriers exist. These barriers are mainly related to the current poor quality of antenatal care, fueled by shortages of trained and experienced midwives in the public sector. Failure to ensure adequate communication regarding individual patients in need of PMTCT interventions.

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*aOpt-out testing: all patients are tested routinely for HIV, unless the patient does not provide consent.

*bIntroduction of dual therapy for PMTCT, which includes the addition of AZT from 28 weeks of pregnancy, is scheduled for introduction in 2008.
within and between institutions results in further loss of mothers from the PMTCT program. For these reasons, neither all mothers that test positive nor their babies receive nevirapine.\(^{18}\)

### Counseling on Safe-Feeding Options

Many HIV-positive mothers in KZN live in an environment that does not satisfy World Health Organization (WHO) criteria for safe infant feeding using infant formula. The evidence is now clear that exclusive breastfeeding in such settings is the safest option.\(^{20-23}\)

The decision on which feeding method to use for the HIV-exposed baby is made by the mother, irrespective of her educational background or health status. Counselors are used to help the mother choose the safest and most appropriate option. However, poor training and lack of support for counselors regarding infant feeding has led to an overall poor quality of counseling. An evaluation of safe-feeding counseling revealed poor usage, compliance, and relevance of WHO guidelines.\(^{24}\)

### Follow-Up of Mother and Babies

The most pronounced deficiency in the PMTCT program is the poor follow-up of mother and baby pairs after delivery. HIV-exposed infants in KZN receive the standard immunizations given to all children. Immunization begins at birth and requires the first visit six weeks thereafter. Evaluation of all infants (both HIV-exposed and unexposed) at this six-week visit revealed a 7% HIV seroprevalence among all infants.\(^{25}\) Failure to link this visit with follow-up for HIV-exposed infants results in lost opportunities to test infants with available HIV

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**Figure 2. Pediatric programs at various stratified levels within the district health-care system in KwaZulu-Natal**

Source: Child Healthcare Problem Identification Programme.\(^{13}\)

<table>
<thead>
<tr>
<th>Regional Hospital</th>
<th>Neonatal resuscitation Kangaroo mother care PMTCT plus</th>
<th>Hospital IMCI (screen and treat infections) Comprehensive HIV/AIDS care and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>District</td>
<td>Neonatal resuscitation Kangaroo mother care PMTCT plus</td>
<td></td>
</tr>
<tr>
<td>Primary Health Clinic</td>
<td>VCT Termination of pregnancy (TOP)</td>
<td>PMTCT plus</td>
</tr>
<tr>
<td>Home/Community</td>
<td>• Adolescent and prepregnancy nutrition • Education • Prevention of HIV and sexually transmitted diseases</td>
<td>• Healthy home behaviors: reducing workload, danger sign recognition, emergency preparedness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prepregnancy</th>
<th>Pregnancy</th>
<th>Birth</th>
<th>Postnatal</th>
<th>Childhood</th>
</tr>
</thead>
</table>

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Due to the rapid deterioration of infants who are HIV-infected and the failure to identify and manage these infants at an early stage of disease progression, infant mortality rates are rising.\textsuperscript{7-9,26} This group of infants younger than one year of age, and particularly those younger than six months, accounts for the largest proportion of under-five child mortality in South Africa.\textsuperscript{26,27} Introduction of ART in infants younger than one year of age, and especially in symptomatic infants younger than six
months, should help decrease morbidity and mortality in this group. Integration of infant follow-up with antiretroviral treatment programs is essential.

In its current state, the poorly functioning PMTCT program continues to fuel the burden of HIV infection in children in KZN. It is in this context that a pediatric treatment program was introduced in 2004.

PEDIATRIC ART ROLL-OUT IN KZN: FROM IMPLEMENTATION TO PRESENT DAY

In June 2004, six months after the initiation of the adult ART roll-out, KZN began the process of providing ART to children at 55 accredited hospital-based sites. Drug regimens, protocols, and inclusion criteria were all based on national guidelines. Children had to go through a rigorous social and clinical screening as well as laboratory identification before being initiated on ART. Emphasis was placed on patient education prior to initiation, with voluntary counseling and testing (VCT) serving as the gateway for enrollment into the program.

New physical structures were erected at hospital sites that had inadequate facilities, marking the beginning of infrastructure development. The drug supply chain was expanded and laboratory capacity significantly improved for HIV testing and monitoring. New information systems were also planned and developed to meet the specific needs of the ART program.

Between July 2004 and July 2005, there was a generally poor uptake of children into the ART program. Sites demonstrating relatively good uptake of children were found to have three distinguishing characteristics:

1. Strong advocates for the care of children
2. Staff trained in pediatric-related care
3. Established patterns of care for HIV-positive children prior to the introduction of antiretroviral drugs (ARVs), resulting in streamlining of processes to identify, screen, and manage HIV-positive children.

Despite good uptake at the select sites displaying these characteristics, it was discovered that children were not being prioritized at most sites across the province. A perceived lack of pediatric experience and resultant apprehension in treating children, as well as poor integration with existing children’s services, were the major reasons found for low uptake. It was also discovered that monitoring and evaluation systems were not user-friendly for clinics experiencing human resource shortages. As a result, site-specific monitoring and evaluation systems began to be developed.

Once the poor uptake of children into ART programs was discovered at the end of the first year, three clear strategies were adopted to scale up pediatric ART. These strategies targeted shortcomings in the areas of advocacy, training, and simplification of processes. With the help of these targeted strategies, the province successfully increased the proportion of children receiving ART from less than 5% in November 2004 to more than 10% in early 2006. However, the large differences observed in the proportion of children on treatment between health districts was of concern (see Table 1).

Challenges in the following areas were found to be hampering the successful roll-out of the provincewide ART program:

1. Identification of HIV-infected children
2. Confirmation of diagnosis (laboratory testing)
3. Assessment of eligibility for starting ART
4. Preparation of children for treatment, treatment delivery, and follow-up (due to lack of integration at institutional level and within the district)
5. Sustainability of program (due to lack of community acceptance and support)
Laboratory diagnosis of children younger than 15 months remained a problem at the outset of the program due to the persistence of maternal antibodies in these patients; the available HIV Enzyme-Linked ImmunoSorbent Assay (ELISA) test was therefore not accurate. For this reason, a pilot program was implemented in the province from October to December 2004 to evaluate the use of HIV DNA PCR using dried blood spots (DBS) instead of whole blood. The results using the Roche Amplicor version 1.5 HIV DNA test showed excellent correlation. The use of DBS for HIV DNA PCR has allowed less skilled staff to collect blood samples and has eliminated the need to quickly transport whole blood samples to centralized laboratories. As a result of the success of the pilot program, the use of DBS for HIV DNA PCR was expanded to other districts.

### OVERCOMING CHALLENGES

#### Identification of Patients for Entry into the Pediatric ART Program

The new WHO and Joint United Nations Program on HIV/AIDS (UNAIDS) guidance on HIV counseling and testing for high-prevalence settings recommends that all patients, irrespective of clinical findings, be offered HIV testing. Screening of all patients for HIV as opposed to targeted testing is also suggested in infant follow-up studies. The use of VCT as the primary entry point for pediatric ART has proven to be a major bottleneck slowing entry into the program. This is due to the lack of enough trained counselors to match the need. These challenges and interventions are summarized in Table 2.

#### Laboratory Testing

Laboratory diagnosis of children younger than 15 months remained a problem at the outset of the program due to the persistence of maternal antibodies in these patients; the available HIV Enzyme-Linked ImmunoSorbent Assay (ELISA) test was therefore not accurate. For this reason, a pilot program was implemented in the province from October to December 2004 to evaluate the use of HIV DNA PCR using dried blood spots (DBS) instead of whole blood. The results using the Roche Amplicor version 1.5 HIV DNA test showed excellent correlation. The use of DBS for HIV DNA PCR has allowed less skilled staff to collect blood samples and has eliminated the need to quickly transport whole blood samples to centralized laboratories. As a result of the success of the pilot program, the use of DBS for HIV DNA PCR was expanded to other districts.
(CD4% < 20% if younger than 15 months and CD4% < 15% if older than 15 months) are eligible for initiation on ART. These criteria perpetuate the problem of most children starting treatment when they are severely immunocompromised. Change of eligibility criteria for ART in alignment with current WHO guidelines has been advocated for and tabled for national and provincial implementation. This decision is being awaited.

Infants younger than six months of age are currently not eligible for ART through the state-run pilot, the average number of HIV DNA PCR tests done using DBS in the province increased from 300 per month in 2005 to approximately 3,000 per month in 2007. See Table 3 for a summary of challenges and interventions.

**Assessing Eligibility Criteria for ART**

According to current inclusion criteria, only children who are HIV clinical stage 3 or 4 (according to modified WHO HIV clinical staging) or only children with moderate to severe immunosuppression

### Table 2. Challenges to Patient Identification and Related Responses from the Pediatric ART Program, KwaZulu-Natal

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Advocacy</th>
<th>Training</th>
<th>Simplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification documents and/or birth registration certificates required for entry into program. This proved to be difficult for children from poor, rural families.</td>
<td>At provincial level, pediatricians lobbied to have this requirement waved for children.</td>
<td>All staff trained not to exclude children from treatment if they do not have these documents.</td>
<td>All unnecessary requirements removed for children to enter treatment programs.</td>
</tr>
<tr>
<td>Poor clinical uptake of symptomatic children at all levels. Mortality audits indicated poor formalized screening of pediatric patients for signs of HIV infection.</td>
<td>Strong emphasis placed on clinical screening of every patient at every opportunity.</td>
<td>IMCI (Integrated Management of Childhood Illness) introduced in all primary health-care clinics. All staff trained in World Health Organization (WHO) staging.</td>
<td>Standardized clerking sheets and staging sheets developed and used to improve the staging of all children using the WHO classification system.</td>
</tr>
<tr>
<td>Voluntary counseling and testing acted as a bottleneck for gaining access to universal testing.</td>
<td>Continued pressure to switch to opt-out testing, due to evidence showing that it increases uptake of HIV testing. Provider-initiated counseling is now being introduced.</td>
<td>All levels of staff trained in pre- and posttest HIV counseling.</td>
<td>Group pretest counseling now being offered.</td>
</tr>
</tbody>
</table>

*In provider-initiated counseling, health workers are tasked with offering HIV testing at all points of contact, irrespective of risk profile.*
As a result of this saturation, specialized ART clinics were created that functioned as separate entities within centralized hospitals. HIV-infected pediatric patients were seen for growth monitoring and preventative services, such as immunization, at one clinic, received curative services for opportunistic infections or non-HIV-related childhood infections at another clinic, and then obtained ARVs at the specialized ART clinic. This model led to excessive waiting times and duplication of services for most patients accessing ART. Integration of all childhood care, including health promotion and preventative and curative programs with ARV dispensing, is now envisaged.

Concentrating services at centralized institutions also prevented scale-up of specialized clinics for patients with complicated and/or difficult-to-treat conditions. Major ART clinics based at tertiary and regional hospitals could not prioritize complicated cases as they were too busy treating less complicated cases. This resulted in the wasteful use of scarce specialists.

Use of primary health-care facilities as an entry point for screening, treatment, and follow-up was program. Rapid deterioration of HIV-infected infants before six months of age and success in decreasing mortality when this group is started on ART warrant an urgent review of this policy. Challenges and interventions are presented in Table 4.

**Preparation, Treatment, and Follow-up of Patients**

ARV roll-out began at 55 accredited district and regional hospitals that were believed to have the required capacity to initiate the program. As these vertical, institution-based programs were introduced, it soon became evident that hospital-based treatment sites alone could not shoulder the high burden of disease. These sites were soon saturated, leading to a drop in the initiation of new patients and a failure to transfer the skills required for further scale-up. This ongoing saturation has resulted in decreased access to care and treatment programs. Pediatric mortality data from KZN confirms this, with 60% of inpatient deaths due to HIV-related opportunistic infections; most of these deaths occurred among patients who failed to access ART.

As a result of this saturation, specialized ART clinics were created that functioned as separate entities within centralized hospitals. HIV-infected pediatric patients were seen for growth monitoring and preventative services, such as immunization, at one clinic, received curative services for opportunistic infections or non-HIV-related childhood infections at another clinic, and then obtained ARVs at the specialized ART clinic. This model led to excessive waiting times and duplication of services for most patients accessing ART. Integration of all childhood care, including health promotion and preventative and curative programs with ARV dispensing, is now envisaged.

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Use of primary health-care facilities as an entry point for screening, treatment, and follow-up was
has delayed the commencement of ART for many patients.

Integration of services within institutions, such as linking PMTCT follow-up and pediatric ART, is crucial. Reviews of mortality data from South Africa, and for KZN in particular, indicate that infants born to HIV-infected mothers form the largest group among infants dying in health facilities.26,27 Recent data indicating the rapid clinical deterioration of HIV-exposed infants by six months, as well as significant decreases in mortality with early onset of ART before six months, warrants the integration of PMTCT follow-up with pediatric ART provision.35,36

**Societal Barriers Impacting the Scale-up of Pediatric ART**

Pediatric HIV is a family disease and as such requires that entire families be screened and treated for HIV infection. Most of the biological mothers and fathers of HIV-infected children who died in the province's largest hospitals in 2006 did not indicate knowledge of their own HIV status.27 For this reason, there is a need for clear directives to ensure that biological parents are screened and if eligible, initiated on ART at the same time as their children.
<table>
<thead>
<tr>
<th>Barrier</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treating and managing infants and children of differing weights and ages perceived as difficult.</td>
<td>Sites with pediatric advocates led the way for the treatment of children. Encouragement and support of pediatric staff to serve as advocates for initiating children on ART.</td>
</tr>
<tr>
<td></td>
<td>Innovative, province-wide pediatric mentoring project (CHIVA / KZN support initiative) started in 2005. Nursing, medical, and support staff from HIV treatment sites in the UK visited, trained, and supported sites in KZN on an ongoing basis.</td>
</tr>
<tr>
<td></td>
<td>Development of easy-to-use pediatric care manuals and weight band-based treatment charts helped to simplify treatment for children.</td>
</tr>
<tr>
<td>Lack of integration at the institutional level. In most institutions in the province, 60%–80% of pediatric inpatients are HIV-positive and are still in need of antiretroviral therapy (ART).</td>
<td>Continued advocacy in children’s wards and outpatient clinics for provision of ART to both mothers and babies proved to be a major help in scale-up. Sites where such advocacy occurred showed dramatic increases in children on ART.</td>
</tr>
<tr>
<td></td>
<td>Hospital-based training of all staff is required to ensure children are not neglected in accessing care.</td>
</tr>
<tr>
<td></td>
<td>Creation of family clinics where one-stop care can be provided. Conversion of existing outpatient clinics to include ART provision remains difficult.</td>
</tr>
<tr>
<td>Failure to integrate services at the district level, including the use of primary care facilities in conjunction with hospitals.</td>
<td>Having a pediatric treatment advocate attend all district meetings and develop a norm for using all facilities to screen and treat for HIV made a huge difference in two districts: Umgungundlovu (District 22) and Umkanyakude-Mseleni subdistrict. The most critical aspect in the Mseleni subdistrict is the effective district-level management of the process (personal communication, V. Friedlund, Mseleni Hospital medical manager).</td>
</tr>
<tr>
<td></td>
<td>Providing ongoing training for additional nurses and counselors at primary health-care clinics in Umgungundlovu improved district care and integration. Nurses were trained to play a central role in this process.</td>
</tr>
<tr>
<td></td>
<td>Use of clear guidelines and protocols at primary health-care clinics were developed in the EGPAF DC22 up/down referral project. This led to an increase in screening and improved care of patients down referred from hospitals.</td>
</tr>
</tbody>
</table>

*The Elizabeth Glaser Pediatric AIDS Foundation up/down referral project started in District 22 (uMgungundlovu) provides nurses and counselors to primary care clinics.*
Table 6. Overcoming Challenges at the Community Level to Ensure Sustainability

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to screen and treat biological parents when children are identified as HIV-positive or initiated on antiretroviral therapy (ART).</td>
<td><strong>Advocacy</strong></td>
</tr>
<tr>
<td></td>
<td>Strong advocacy to ensure that mothers and fathers are tested and offered treatment when a child starts ART.</td>
</tr>
<tr>
<td>Integrating traditional medicine practice with ART.</td>
<td>Traditional medicine practitioners must be given a platform for exhibiting their role and responsibilities in HIV/AIDS control and prevention.</td>
</tr>
<tr>
<td>Introducing the need for disclosure to children.</td>
<td>Trained pediatric staff must continue to advocate for the rights of the child, including the need for disclosure.</td>
</tr>
</tbody>
</table>

More widespread community involvement with health issues and health institutions is needed in order for the necessary changes in health practice to take place. For instance, most health institutions are now using community health workers to conduct health-promotion activities at the community level, including HIV prevention. Integration of institution-based clinics with community-based health-promotion programs and community health workers remains an effective tool to ensure the sustainability of ART programs. Rural sites have been more successful than urban sites in this regard.39

Traditional medicine remains popular among the population of KZN, most of whom are Zulu.39,40 Traditional belief systems often go hand-in-hand with the use of traditional medicine and can be the key to understanding and addressing issues of HIV stigma.39,41,42 Various interventions have begun to improve upon the knowledge and understanding of HIV derived from traditional belief systems and practices. In the future, a better understanding of HIV and ART among the general population could contribute to greater uptake of care, treatment, and prevention services.

National and provincial leadership is needed to dispel mistaken beliefs about HIV/AIDS and to ensure a clear, concise message emphasizing PMTCT as the mainstay of pediatric prevention, as well as the benefits of ART.

Table 6 summarizes these challenges and interventions.
CONCLUSION
There is still much room for improvement in the scale-up of pediatric ART programs in KZN, a high-prevalence, resource-limited setting. The sustainability of the pediatric ART program also remains tenuous in the face of a poorly performing PMTCT program. Poor leadership at the political and local community level continues to hamper efforts to mobilize community members and drive the demand for improved access to life-saving medicines. Lack of adequate human resources and failure to adopt evidence-based, internationally compliant policies hampers efforts to integrate pediatric HIV care and treatment into routine child health programs.

Despite these challenges, KZN has managed to develop one of the world’s largest pediatric ART programs across a diverse and resource-poor area. This achievement is largely due to the development of innovative tools and processes to assist in the safe provision of pediatric ART. Efforts will continue to focus on advocacy for the detection and treatment of HIV-positive pregnant women and their children. Training of staff in pediatric care and simplification of pediatric care processes will also continue to assist in significant scale-up of treatment programs.

REFERENCE LIST


HEALTH CARE IN RESOURCE-LIMITED settings has traditionally been focused on the management of acute illness rather than the chronic management of asymptomatic conditions. This focus on acute, episodic care has contributed to compartmentalization of care delivery by individuals specialized in the management of particular conditions. The multifaceted nature of pediatric HIV-related illnesses requires a team approach to address not only medical complications but also nutrition, neurodevelopmental disabilities, behavioral and psychiatric problems, and social problems. Therefore, optimal care of children living with HIV ideally requires the integration of specialist care into generalist and multidisciplinary care.

Typically there have been two models for ambulatory chronic care in both high- and low-resource settings. Patient-centered, well-child care, which usually focuses on immunization, is the most widely utilized model of this type. In many regions, there is relatively high coverage of this type, especially for very young children. It is rare for otherwise healthy older children who might have a subclinical chronic disease requiring lifelong management to remain engaged in this model once their primary immunization series is complete. A second model for ambulatory chronic care is characterized by a family-centered approach. Although this model provides a variety of services all in one place and is therefore possibly more convenient for patients, optimal care of this type requires a well-established referral network between obstetricians, internists, pediatricians, and specialists, as well as more comprehensive training of care providers than typically exists in many resource-limited settings. This chapter will discuss barriers and possible approaches to the integration of pediatric HIV care within these two different models of chronic ambulatory pediatric care.

CHALLENGES IN INTEGRATING PEDIATRIC HIV CARE INTO ROUTINE CHILD HEALTH CARE

Structural and Organizational Barriers
One significant problem—particularly for management of HIV-infected infants, who have extremely high mortality rates—is that routine infant care is
often part of the maternal and child health (MCH) system. In China for example, the MCH system is responsible for primary immunization and ambulatory health care of infants into their second year of life. Beyond this age and during acute illnesses, children are managed by pediatricians. Children are typically given an immunization book that they bring to each visit; this book constitutes the sole record of ongoing care for subsequent practitioners. In many cases, MCH hospitals may be completely separate from pediatric hospitals, and practitioners are rarely in direct communication with one another. This can be highly problematic for HIV-exposed infants as they grow older and are in need of ongoing monitoring and treatment by a different care provider in a different health-care facility.

Optimal care of HIV-exposed and HIV-infected children requires effective communication between different sets of care providers. For example, the World Health Organization (WHO) guidelines now recommend that bacillus Calmette-Guérin (BCG) vaccination be withheld from symptomatic HIV-exposed children in whom the risk of disseminated BCG outweighs the benefit of vaccination. For such children, the immunizing clinician will need to know the HIV exposure status of the child. This raises the issue of the need for confidentiality, which accompanies the need for patient information. Confidential communication regarding a patient’s HIV status can be especially challenging in developing world settings. Clinics may be extremely crowded, and clinicians may not have adequate training in the importance of confidentiality and how it can be preserved.

**Laboratory Capacity**

The most vulnerable population of patients with HIV infection is the very young. High mortality rates have frequently been documented in HIV-infected infants less than one year of age. For instance, the Children with HIV Early Antiretroviral Therapy (CHER) study conducted in South Africa randomized infants to immediate early antiretroviral therapy or close observation and follow-up of immunologically “normal” infants and found that those randomized to observation and follow-up had a mortality rate of 25 per 100 person-years, compared with only 6 per 100 person-years in the early treatment group. However, it is in this group of children under one year of age that HIV infection is particularly difficult to diagnose. Standard antibody testing may produce false positives, and definitive polymerase chain reaction (PCR) testing is technically difficult and costly, making it inaccessible to many treatment programs. Many children will therefore die of HIV-amplified common illnesses before they are diagnosed with HIV infection. It is a common misconception that in the absence of PCR diagnosis, HIV-exposed infants are not eligible for antiretroviral therapy. Clinicians are not comfortable with their clinical judgment as an acceptable surrogate for a laboratory test, which could potentially lead to a young infant receiving unnecessary treatment if it is incorrect. Medications for HIV are felt to be too toxic to give to infants without a definitive laboratory test. This reluctance comes despite clear guidance from WHO and most country program guidelines. The combination of reluctance on the part of families to have testing because of stigma and discrimination and the inability of many centers to perform PCR testing in young infants can result in a perceived lack of patients, which in turn may lead to a lack of program development.

The integration of HIV care into general pediatric systems of care requires that HIV be considered a common and urgent problem. Since the majority of HIV-associated morbidity and mortality comes from other common childhood diseases
like pneumonia, tuberculosis, and diarrhea, the significance of HIV infection in this population frequently goes unnoticed.

**Training and Human Resources**

One important factor contributing to the spread of HIV infection in communities is a lack of adequate health-care infrastructure and limited access to HIV-related services. These disparities are most pronounced in remote areas of the developing world. The burden of HIV disease is often greatest where capacity for care and treatment is weakest. Human resource limitations are particularly acute in peripheral sites away from urban areas and major referral centers. Recruitment of physicians and other providers to remote sites is extremely difficult, and these sites experience frequent staff turnover. Temporary staffing works well for episodic acute care, but it is not effective for the chronic care of illnesses that require specialized and ongoing training. For HIV treatment to move from the referral centers to routine child health programs at peripheral sites, strategies are needed to recruit, retain, and adequately train health-care providers at these sites.

Integrated Management of Childhood Illness, or IMCI, was developed to guide the provision of care by individuals who lack specific training for the management of common acute conditions. IMCI is a WHO-sponsored program that has been adopted worldwide and provides an algorithmic framework for syndromic management of various conditions with recommendations for appropriate referral procedures. Until recently, IMCI has generally focused on episodic acute care of children, rather than on the type of longitudinal care and health-care maintenance that is necessary for effective HIV treatment. Yet, IMCI forms the foundation of most pediatric care in many resource-poor countries, with clinical officers, nurses, village doctors, and other health-care providers all trained in this framework. These are the same frontline providers who will see HIV-exposed and HIV-infected children presenting with treatable opportunistic infections and other stigmata of HIV disease.

To address this gap, IMCI has recently been updated to include HIV management and appropriate referrals, yet many countries have not begun incorporating these changes into routine practice. Ensuring that the revisions in IMCI become standards of care requires a massive training effort that reaches caregivers even in the most remote settings. Keeping IMCI guidelines current with the rapidly changing standards of care for HIV medicine is another major challenge affecting health-care systems everywhere.

**Stigma**

The unique nature of HIV infection makes integration of HIV management into existing systems of care particularly difficult. Stigma, discrimination, and ignorance among health-care workers, health-care recipients, and the greater community remain commonplace, despite the fact that more than 25 years have passed since HIV was first discovered. There is often a legitimate concern on the part of patients that their HIV-positive status could cause medical care providers to be reluctant to provide necessary services and could lead to ostracism and violence in their communities and within their families. For instance, many anecdotal reports exist where care providers have refused services to HIV-positive patients and insisted on testing particularly of pregnant women. The BBC recently reported cases of HIV-infected persons being buried alive in their villages in Papua New Guinea. In light of this hostility, even if uncommon and only patient perception, it is understandable why HIV testing may often be refused or why patients may not return to receive their results or disclose their status or the status of their children to other care providers.
ADDRESSING THE HUNGER NEEDS OF THE FAMILY AND COMMUNITY: A NUTRITION INITIATIVE WITHIN AN HIV CARE PROGRAM

Elizabeth Dufort, a Winstone Nyandiko, b and Joseph I. Harwell a,c

aThe Warren Alpert Medical School of Brown University, United States
bMoi University School of Medicine, Kenya
cClinton Foundation HIV/AIDS Initiative, United States

A comprehensive, family-centered HIV care model that includes care for children living with HIV can effectively increase access to pediatric HIV care, especially in remote settings. For example, food insecurity is an issue that cannot be addressed through an individual, patient-centered approach; interventions to relieve food insecurity must target the broader environmental and social causes of food shortages while focusing on ways to effect change at the household and community levels. The Academic Model for Providing Access to Healthcare (AMPATH) program, in partnership with the United States Agency for International Development (USAID), has successfully applied this approach to the problem of malnutrition in the communities it serves in western Kenya.

Malnutrition and food insecurity are common in western Kenya, as in many other regions heavily affected by HIV/AIDS. Agricultural output and economic productivity have been greatly impacted due to the severity of the local HIV epidemic and other common illnesses. In addition, HIV-related stigma sometimes affects the ability of caregivers and those living with HIV to support themselves and their dependants financially. Medical expenses and lack of income from those who were formerly the most productive members of the household lead to further poverty and food insecurity. Young children are most vulnerable to these conditions, as lack of proper nutrition can inhibit proper growth and development. Those living with HIV are also highly vulnerable, since they require increased calories and nutrients to maintain optimal health and maximize the benefits of antiretroviral therapy (ART).

The cycle of disease and poverty, along with the need for adequate nutrition to reach optimal health, requires specific attention within an HIV care program. Food insecurity, in particular, needs to be considered as part of comprehensive HIV care for pediatric patients, given their unique needs in growth and nutrition, the effect of HIV on an immature immune system, and the vulnerability within the economic structure of society. Yet children living with HIV cannot be supported in a sustainable manner without addressing the nutritional needs of the entire family. If food supplementation is only given to an individual patient, regardless of their age, this supplementation may be divided among multiple family members also suffering from hunger and malnutrition. Furthermore, plans must be in place for when the food supplementation is discontinued to ensure the long-term nutritional health of the entire family.

The USAID-AMPATH partnership in western Kenya is one program that has successfully integrated pediatric care into the
comprehensive care of the family. The USAID-AMPATH partnership is an HIV care program borne out of a unique collaboration between Moi University, Moi Teaching and Referral Hospital, the Kenyan Ministry of Health, Indiana University, USAID, and the ASANTE (America/sub-Saharan Africa Network for Training and Education in Medicine) educational exchange consortium. The program strives to provide comprehensive HIV care through a multifaceted approach that includes ART, prevention of mother-to-child transmission (PMTCT), outreach services, support services, the HAART (highly active antiretroviral therapy) and Harvest Initiative (HHI), and the Family Preservation Initiative (FPI). As each family is enrolled into the HIV care program, they are interviewed and assessed by a trained nutritionist, social worker, support group staff, nurse, and trained HIV care provider.

There are approximately 80,000 patients receiving HIV care through the USAID-AMPATH partnership system in western Kenya, 13,000 of which are children exposed or infected. Of these, individuals with advanced HIV infection who will begin ART, as well as their families, are eligible for HHI assistance. Children with malnutrition and families deemed by the assessing nutritionist and social worker to have food insecurity at home are entered into the HHI. Roughly 20% of individuals needing ART are felt to be in need of some food assistance. Through the HHI, initial food support is provided to the family for a three- to six-month period while family members are entered into HIV care and started on ART. Families are given food vouchers based on their needs assessment by the social worker and nutritionist. This food is meant to supplement the food currently available in the home in order to provide 100% of the family’s daily nutritional requirements. The goal of the initial phase of food supplementation is to support healthy immune function through the combination of adequate food and ART.

Food assistance is provided by the World Food Bank in the form of maize, oil, and beans. In addition, fresh vegetables, milk, and eggs are supplied by HHI high-production farms, employing many individuals in need of work. The use of the HHI farms is dual in purpose. The farms also serve as demonstration plots that are used to train subsistence farmers in agricultural techniques that can increase crop yields and provide income generation opportunities. Through these means, food assistance is provided to approximately 30,000 people per week.

Patients who are unable to support themselves and their dependent family members after six months of support from the HHI program are entered into a food-weaning program. During that time, they are also entered into FPI, a program that aims to improve the financial stability of the family through skills and business training, agricultural initiatives, and extensive social support. The goal of this program is to give families the means to provide a sustainable source of income.

The issue of food insecurity needs to be considered as an essential component of comprehensive HIV care in resource-limited settings, especially in light of the worldwide scale-up of ART. The family-centered approach to HIV care employed by the USAID-AMPATH partnership also highlights the importance of approaching pediatric care within the context of the medical, social, and economic condition of other household members.
CHALLENGES OF INTEGRATING PEDIATRIC HIV CARE INTO FAMILY-CENTERED MODELS OF CARE

Structural and Organizational Barriers
To prevent caregivers from having to make multiple, separate visits in different locations—which can result in additional transportation costs, time away from work, and inconvenience—many programs have adopted a family-centered approach to HIV treatment. This approach is better suited to chronic care than the individual patient care model and is more common in remote settings, where there tends to be a single health post for the provision of all health care. In urban settings, particularly at large referral hospitals that tend to be centers of excellence for HIV care, a significant barrier to integration of pediatric HIV care into care for other members of the family is the fragmented nature of subspecialty care. Different services are frequently offered in separate areas of the hospital or may be in completely different hospitals. Perhaps even more problematic for the integration of pediatric HIV care, MCH care, pediatric care, adult general medical care, adult HIV care, and other subspecialty care is that they are often managed through different divisions of the ministry of health, commonly referred to as “silos.”

Integrating TB and HIV Care for Children
In light of the long-standing and severe TB epidemic in many countries, TB control programs are often established as unique departments within a country’s health-care system. Health provider training, drug procurement, laboratory infrastructure, and even patient payment systems for TB programs may be completely separate from programs offering routine medical care. Unfortunately, TB is the number one cause of mortality for HIV-positive patients worldwide,7,8 and management of both infections is complex and specialized. Drug therapy for HIV and TB may require collaboration between TB specialists and HIV specialists to prevent potential drug interactions and toxicities. In some circumstances, pediatric TB programs may also be separate from adult TB treatment programs. The task of integration thus expands from merging two programs, adult and pediatric TB programs, into a collective marriage of up to four programs from two different branches of the ministry of health requiring separate memoranda of understanding, training programs, personnel, and hospitals.

Integrating MCH Programs with Pediatric HIV Treatment Programs
The most effective way to identify children at risk for HIV infection and to initiate treatment in a timely fashion is through the identification of HIV in pregnant women. Obstetrical care and MCH also are generally the responsibility of a different branch of the ministry of health than that which deals with adult and pediatric medicine. In many countries, routine child health consists entirely of immunization visits. This immunization function may also fall to MCH care providers, as in the China example, while care of acute illness in children will fall to the pediatrician. The health-care provider performing immunizations may have longitudinal contact with children, but they may not be trained to recognize the signs and symptoms of HIV infection and its progression. A truly integrated program of pediatric HIV care will need to bring together the expertise and health-care delivery functions of many disciplines, many hospitals, and many branches of government.

Beyond the administrative separation of medical specialties serving mothers and their children, there is usually physical separation as well. In Phnom Penh, Cambodia, there are three large children’s hospitals, several large adult hospitals, a large public MCH hospital, and several
HIV treatment clinics. With the exception of the Médecins Sans Frontières HIV treatment center, which is located on the grounds of the largest adult referral hospital, none of these facilities is within easy walking distance of the others, making family-centered HIV care impractical.

**Barriers to Integration: Training and Human Resources**

Approaches to health-care provider training vary from country to country. In China, there are no pediatricians with specialty training in infectious diseases. In Papua New Guinea, most services in hospitals are performed by doctors in training, but these services may not be counted toward certification if not supervised by a certified specialist. In this context, it is difficult to encourage a trainee interested in pediatrics to work in a hospital that doesn’t yet have a pediatrician on staff. In order for a truly integrated, family-centered HIV care program to be successful, there needs to be a multidisciplinary team based at one easily accessible location. Since the availability of different specialty care providers varies greatly by region and within countries, cross-training may be required for a site to provide adequate multidisciplinary services.

In reality, there may be no physicians on staff at many health outposts in more rural settings. Since public sector salaries tend to be low, it can be difficult to recruit doctors for work in remote settings, where there are few if any opportunities for more lucrative private consultations. Although working in an underserved setting may be a requirement for training, doctors rarely remain at their rural posts after their service requirement is fulfilled. As a result, these posts are often served by medical officers with little postgraduate training (as is the case in district hospitals in India) or by nurses or other allied health professionals. These sites may be adequate for follow-up of stable patients, but caregivers often do not have the necessary training to recognize, diagnose, and treat drug toxicities or complex opportunistic infections (OIs). To overcome these shortcomings, appropriate training materials need to be developed for the wide variety of possible care providers to ensure that quality pediatric HIV care can be implemented at all health facility levels throughout the country.

**INTEGRATION OF PEDIATRIC HIV CARE INTO ROUTINE CHILD HEALTH-CARE MODELS**

Supporting national programs to train health-care providers on the updated IMCI is essential. The recognition and early diagnosis of HIV in children and the treatment of common OIs can be emphasized as part of the IMCI training format. A further challenge is the implementation of the newest IMCI HIV care guidelines through a more chronic care model as proposed by WHO. This model differs from the episodic acute-care model used to treat the other five leading causes of mortality in children (i.e., pneumonia, diarrhea, malaria, measles, and malnutrition) and requires a stable infrastructure and longitudinal approach. This shift will require the sustained support of governmental organizations aimed at improving and expanding the existing health infrastructure and health-care workforce.

There is evidence that an IMCI-based approach to HIV management is gaining acceptance. For example, there is now an Integrated Management of Adult and Adolescent Illness (IMAI) framework, which forms the basis of HIV training in Papua New Guinea, and all practitioners who will prescribe antiretroviral drugs must complete IMAI training. India has developed its own version, the Integrated Management of Neonatal and Childhood Illnesses, which incorporates HIV management. For IMCI to form the basis for the integration of chronic HIV care of children into routine child health-care systems, governments must ensure that the political
THE MONDOL MITH CHUOY MITH CENTER AND THE CAMBODIAN CONTINUUM OF CARE

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THE HIV EPIDEMIC IN CAMBODIA has reached a mature stage, as evidenced by the decline of prevalence rates among the general adult population (aged 15–49) from 2% in 1998 to 0.9% in 2006. Although HIV prevalence has been decreasing since 1998, the number of Cambodians suffering from AIDS and related illnesses is increasing among both adults and children. In 2003, there were an estimated 21,500 people living with AIDS and roughly 6,500 deaths attributed to AIDS. In that same year, there were approximately 12,000 children living with AIDS in Cambodia.

Children living with HIV have a wide range of needs and, as such, require a continuum of care approach that includes medical care as well as nutritional and psychosocial support. It is therefore necessary to integrate different types of services for children into established HIV care structures, including institutional and home-based care.

Due to an increasing demand for HIV care throughout the country, the Cambodian Ministry of Health approved the Operational Framework for Continuum of Care (COC) in April 2003. The COC program was implemented through government health facilities at the operational district level. All stakeholders are involved in the coordination of the program, including community members, governmental organizations, local and international nongovernmental organizations (NGOs), and donors. The COC model aims to provide comprehensive, continuous, multilevel care incorporating all of the components of care including voluntary confidential counseling and testing (VCCT); health-facility-based care, which includes clinical care for opportunistic infections, ART, TB/HIV care, and PMTCT; community- and home-based care; and support groups for people living with HIV. The COC model not only focuses on medical care but also incorporates a range of support and prevention activities, such as health promotion and education for patients and their families. Because of its multifaceted nature, the COC approach requires careful planning, coordination, monitoring, referral, and medical information systems.

Children living with HIV in Cambodia generally receive clinical care in a pediatric HIV clinic adjacent to the general pediatric ward. The clinic is separate from the HIV clinic for adults. Trained pediatric clinicians provide the majority of care for children living with HIV. However, the COC model is designed to link the pediatric services to the adult services in a family-centered way. The “glue” that links pediatric and adult services is a unique feature.
of this program. One component of this glue is the Mondol Mith Chuoy Mith (MMM) Center (translated from Khmer as the Friend Support Friend Center). The MMM service is one of the essential elements of the operational framework for the COC for people living with HIV. The MMM is a comfortable gathering place for HIV-positive families, including children, and is a primary focus for HIV care activities in the operational district. Each MMM has its own building and is attached to a referral hospital, to a health center, or even to a community location (for example, the local Buddhist pagoda). MMM is a family-centered gathering spot and serves as a bridge of communication between pediatric and adult services. MMM holds monthly meetings to facilitate patients’ access to care and treatment and fosters partnerships between patients of all ages and genders and their health-care providers. Children are welcome and actively participate in MMM activities. MMM also serves as a vital linkage mechanism to improve access for HIV-infected children to medical care, ART, and nutritional support. For example, MMM provides linkages between (1) HIV-positive children and the outpatient department HIV clinic and (2) VCCT services for children in need of HIV testing. MMM also promotes linkages between adults and children living with HIV to access care and treatment. For example, HIV-positive women often come to the MMM Center with their children during MMM meetings. Counselors attending the MMM meeting are trained to identify and refer these children for appropriate testing and care.

The Cambodian model for the integration of clinical HIV care ensures an effective linkage of HIV-exposed children from PMTCT to pediatric care, and from pediatric care to other services as needed, thus increasing the number of HIV-infected children accessing ART and psychosocial support. Rather than creating an entirely new system of medical care that was not previously in place in Cambodia, the MMM meeting was created as a way for patients who receive care under the different components of the existing system (antenatal clinic, TB, adult, and pediatric) to gather in one place. The MMM staff can then make sure that newborns receive appropriate referrals, that TB patients receiving new medications notify their HIV doctors, and that patients with symptoms are evaluated appropriately.

In addition to improving linkages, MMM offers support groups for HIV-positive families, including special support groups for children. The MMM is a place where those living with HIV, including children, feel safe and at home. Therefore, the MMM model reduces HIV-related stigma and discrimination.

Planning is now under way for the implementation of a MMM program specifically aimed at addressing the needs of children affected by HIV. This program will further expand access for HIV-affected children to general medical care as well as pediatric HIV clinical care (see Figure 1). MMM staff will be trained to identify the more general medical needs of children and make appropriate referrals for HIV-negative children as well. With this expansion, the MMM program will serve as an important provider of comprehensive care for orphans and vulnerable children, including child-friendly peer support groups for HIV-affected children.
The high early mortality rates in infancy and possible decrease in mortality with early antiretroviral therapy, it is essential to increase HIV testing for young children. Furthermore, children account for only 6% of those with access to antiretroviral therapy (ART) worldwide, while they comprise 14% of those in need. Given this disparity, the pediatric population needs to be targeted for expanded HIV testing and subsequent improved access to care.

Another way to facilitate integration of HIV care into routine child care is to make HIV testing a part of the existing structure. Pediatric patients congenitally infected with HIV face an estimated 33% mortality rate in their first year of life, increasing to more than 50% by two years of age. Given the high early mortality rates in infancy and possible decrease in mortality with early antiretroviral therapy, it is essential to increase HIV testing for young children. Furthermore, children account for only 6% of those with access to antiretroviral therapy (ART) worldwide, while they comprise 14% of those in need. Given this disparity, the pediatric population needs to be targeted for expanded HIV testing and subsequent improved access to care.
The 2007 WHO HIV testing guidelines for the generalized epidemic setting recommend provider-initiated HIV testing of all children cared for in pediatric health services. Pediatric patient contact with the health-care system in many resource-limited settings occurs primarily in the immunization/well-child care clinics and in association with episodic acute care. The USAID-AMPATH partnership in western Kenya (see associated sidebar for a description of this program) strives to offer provider-initiated HIV testing of all pediatric inpatients. Similar strategies have been successfully implemented and reported in Zambia and Uganda. A strategy that routinely offers HIV testing in the context of childhood immunization could potentially provide broad coverage of testing at earlier stages of illness, rather than when acute illness brings a patient to the hospital. Investigators in the CHER trial found that most of the deaths in their cohort occurred in the home. Since many (close to 80% in Kenya) children are seen in immunization clinics for at least one vaccination, this might be one possible site where children at risk of HIV infection in high-prevalence settings can be identified.

Systems need to be put in place that allow and promote HIV testing for young patients in locations other than traditional voluntary counseling and testing (VCT) centers. The use of virologic testing for accurate diagnosis in young infants also needs to be expanded as access to pediatric ART is increasingly available. While virologic testing can be expensive and technically challenging, dried blood spot HIV PCR has shown promise and proven useful in resource-limited settings around the world. This method of specimen collection is simple and requires very little training. Blood is collected from capillary blood, and therefore, difficult phlebotomy is not necessary. Specimens are dried and can be kept at room temperature and shipped to a centralized location without expensive or time-consuming preparation or shipping requirements.

More efforts need to be focused on reducing the barriers to testing in high-prevalence settings. Surprisingly, health-care providers often represent a greater barrier to testing than their patients. Providers may be uncomfortable talking to patients about risk factors, or they may simply not have enough time to perform pre- and posttest counseling. Novel approaches, such as group pretest counseling of pregnant women and routine testing of all hospital inpatients, can help to simplify the process and reduce stigma associated with HIV testing. Providers should also be trained to recognize signs and comorbidities associated with HIV and to routinely provide rapid testing at the point of care to ensure patients receive their results. Treatment of HIV can only be integrated into routine care when HIV testing also becomes part of routine care, rather than treating it as a special test that patients have to go somewhere else to receive. Study of the implementation of routine HIV testing approaches, use of virologic testing for young infants, and determination of optimal methods for linkage of routine medical services to HIV care should all be undertaken to ensure expanded access to quality pediatric HIV care.

In order to include pediatric HIV care as part of a family-centered model of health service delivery, different stakeholders must be brought together to improve linkages and reduce structural barriers. Historically, these various stakeholders may have had very little interaction, since many are physically and administratively separate. To promote integration, care providers from different departments and different hospitals should be introduced to each other and a forum created for developing a program and for working out problems. When individuals are introduced to one another, the framework naturally develops for referral and consultation. The natural first step for building a
collaborative family care program is to develop a local protocol based on national guidelines for management of HIV-exposed infants. This requires collaboration between MCH providers and the general medical providers to ensure that adequate baseline data are collected and communicated to those responsible for ongoing care. Such a collaborative process can also ensure that women living with HIV who become pregnant will have appropriate continuity of care as they move between general HIV care providers and obstetric care providers, should they be different.

Care providers in a family-centered model generally have a very broad skill base but often lack experience and resources for the management of more complex problems. For a family-centered care model to work, subspecialty consultation must be available to routine health-care providers. Regular meetings could be arranged to discuss problem cases among a multidisciplinary team. This allows general care providers to gain experience with problem cases and to have access to specialist referrals when necessary. A comprehensive resource guide for referrals for nutritional support services, rehabilitation services, medical subspecialists, and social services can be provided to those working in a family-centered care setting.

HIV care that caters to the entire family can maximize economies of scale by consolidating resources for common tasks. The most important place to start with this consolidation is in the laboratory. Not every care center needs to have on-site CD4 lymphocyte monitoring or viral load testing. Centralization of these high-cost and relatively low-volume laboratory tests can improve collaboration between facilities and minimize costs. Support staff, such as adherence counselors, pharmacists, nurses, and outreach workers, can provide care to all age groups, because the skill sets required in these areas do not vary significantly with the age of the patient.

In order to facilitate integration of care and services for families living with HIV, public health officials need to work together to remove funding disincentives for integration. When care is provided in a fee-for-service system, shifting patients from one site to a common site may be viewed as lost revenue by hospitals or doctors. When patients have to pay for laboratory tests, every care center will want to have instrumentation to perform these assays, even though it is more costly and inefficient.

As groups come together to try to facilitate integration of care programs, it can be helpful for them to jointly devise referral guidelines. Similar to the IMCI algorithms, family care providers can work together with TB programs, obstetrical programs, and other subspecialists to devise an approach for collaboration. If expectations are jointly written, there will be minimal confusion about when patients should be managed, in which facility, and by which providers.

When scaling up treatment for family-centered care, it can be helpful to identify sites as primary treatment centers based on their ability to provide comprehensive care to parents and children alike. Hospitals with adult and pediatric services in close proximity that have unified pharmacy and laboratory services, and where obstetrical care is provided, are good facilities for this type of integrated program. With increased experience, these sites can then serve as training centers and demonstration projects for other providers.

Training in pediatric care and management of HIV-infected pregnant women is often not part of standard programs. Since children represent a smaller proportion of the HIV-infected population, programs typically do not focus attention on pediatric care when systems of care are developed. If a family-centered approach is desired, it can be extremely helpful to include pediatric treatment in the approach from the beginning. This can be accomplished in two ways. First, pediatric treatment recommendations can be included in
Integrating the care of children living with HIV into existing systems of medical care is an enormous challenge. It requires an understanding of the existing health-care system and local culture and attitudes. Here we recommend two different approaches to integration. In some cases the best approach should be integration of HIV care into routine pediatric care in systems where comprehensive, patient-centered strategies are well established. In other cases, an integrated, family-centered approach may be better suited to the available resources and methods already in place. Regardless of the approach that is chosen, building pediatric HIV care services from the ground up requires careful planning from the outset, with a focus on designing activities that work together as one harmonious program capable of optimizing health outcomes for parents and children alike.

To further improve the uptake and implementation of an integrated family-centered approach to pediatric HIV care, training in pediatric treatment can be included in all training programs. Every provider who attends HIV treatment workshops would then be exposed to a pediatric HIV treatment knowledge base and would understand that children must be considered as part of the system and not separate and unique problems to be addressed by a specialty practitioner.

National treatment guidelines, not in a separate document. Throughout the guidelines document, attention should be paid to child-specific needs, rather than treating children as exceptions. In this way, every practitioner and program manager who reads the guidelines will be aware of the needs of children and not be tempted to neglect the “pediatric section” as ancillary or irrelevant.


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The Role of Social and Behavior Change Communication in Combating HIV/AIDS

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Although there have been significant advances in prevention and treatment since HIV was first discovered, the virus continues to spread unabated in many parts of the world. Strategies to prevent new infections must match both the complexity and the multifaceted nature of the epidemic. Social and behavior change communication is one such strategy that to date has been underutilized, despite its proven effectiveness in many settings. This chapter will discuss the role of social and behavior change communication in HIV prevention and its implementation in resource-limited settings.

AIDS is often characterized as a disease of intolerance and ignorance, compounded by social and economic issues such as gender inequity, poverty, and lack of political will, among others. Common myths and misinformation about HIV/AIDS stand in the way of greater awareness, discussion, and acceptance of individual and societal behavior change to reduce risk of infection. HIV-related stigma can also be a barrier to the uptake of HIV testing and can prevent those living with HIV from accessing resources for positive living and compassionate care. Inadequate counseling services can make it difficult for someone who is infected to understand their options and make an informed choice about appropriate treatment, reproductive health, and other issues. Fortunately, strategic health communication interventions can make a difference informing, equipping, and motivating people to make appropriate choices about HIV prevention and care.

HIV/AIDS communication efforts, like any HIV/AIDS strategy, must address the whole care continuum (i.e., prevention, care, support, and treatment) to be effective. A holistic approach goes well beyond prevention to include tools for the biological, psychological, and social care of people living with HIV, their families, and communities.

Evolution of Social and Behavior Change Communication for HIV/AIDS

In the past, strategic planning for HIV/AIDS communication focused on determining the knowledge, attitudes, and practices of individuals deemed at risk for infection. In the process of designing a communication strategy, the variables contributing to behavior were identified, and then a theory was developed to explain how these variables were linked together. An intervention was then designed...
to influence these variables with the goal of producing a desired effect. As a result, approaches to behavior change in the early years of the HIV pandemic focused on providing correct information about transmission and prevention, based on the theory that lack of accurate information about HIV transmission and acquisition was a primary catalyst for the spread of infections. Unfortunately, this approach fell short of producing the desired effect, and it became clear that more complex, multilayered strategies would have to be developed.

More recently, frameworks such as the Joint United Nations Program on HIV/AIDS (UNAIDS) communications framework and the Health Communication Partnership (HCP) Pathways framework seek to understand and explain the role of sociocultural influences (e.g., socioeconomic status, gender relations, cultural norms, and spirituality) and environmental influences (e.g., government policy, access to services, and occupational risks) on human behavior. These frameworks are based on the understanding that beyond an individual’s social network exist larger structural and environmental determinants that affect HIV/AIDS-related behaviors. Such an approach to communication reflects a greater appreciation of the complexity of the HIV epidemic, and a greater emphasis on social groups and contextual factors rather than individual behavior alone.

**MAXIMIZING IMPACT THROUGH STRATEGIC HEALTH COMMUNICATION**

Throughout the past 20 years, health communicators have learned that health communication strategies that are collaboratively and strategically designed, implemented, and evaluated can help to improve health in a significant and lasting way. Positive results are achieved by empowering people to change their behavior and by facilitating social change. The field of health communication has evolved into what may be called the “strategic era,” which is characterized by utilizing many different channels of communication, multiple stakeholders, and an increased emphasis on evaluation and evidence-based programming. Large-scale impact at the national level, more pervasive use of mass media, and a communication process in which participants (“senders and receivers”) both create and share together are also increasingly being emphasized. Additionally, there is an ever greater push for communication to be an integral component of an HIV/AIDS program design, not a secondary consideration or an afterthought.

**Grounding HIV/AIDS Communication in Research and Theory**

Effective communication strategies are evidence based. Evidence provides information about what individual and social behaviors, knowledge, norms, and practices need to change. Effective strategic health communication programs are also based in theory. The theory employed need not be complex, but it does need to be appropriate. In other words, the theory should reflect the evidence and the environmental and sociocultural variables specific to the target population(s).

The research or evidence needed for strategic health communication can be split into three categories: formative, process, and summative. Formative research is used to learn more about a problem in a specific social context and gathers both qualitative and quantitative data. Formative research helps identify the extent of the problem, given the parameters of the specific situation, and the factors that explain its existence. It is typically conducted near the start of the program. Examples of formative research activities include using a baseline questionnaire to define and understand populations at greatest risk for HIV, determining the relationship among potential implementing partners in care and treatment, and focus group discussions.
with most-at-risk populations to determine exposure risks associated with specific behaviors.

Process evaluation can be used to track program activities and how well they are received by the target audience, thereby providing information for midcourse changes, if necessary. An example of a process evaluation activity is conducting in-depth interviews with those affected by the intervention (e.g., exposure to a prevention message about the risk of needle sharing) to assess the effectiveness of the intervention.

Summative evaluation assesses how well the program achieves its objectives. This usually occurs at the end of the program and provides information on whether or not the program has been effective and what needs to be changed to achieve the desired result. An example of a summative evaluation activity is the distribution of a final questionnaire, to be compared with a baseline questionnaire that was collected prior to the start of the program.

Just as there are different research options, there are also many theories that can be used as a basis for designing strategic health communication. This chapter provides examples of three theories that are particularly relevant to HIV/AIDS programming.

The Extended Parallel Process Model
The Extended Parallel Process Model (EPPM) seeks to explain when and why fear appeals work and when they fail. It is based on the idea that in order to motivate people to take action to protect their health, messages must accomplish two tasks. First, people must be made to feel that the threat posed by the health problem is real and serious. In other words, both perceived susceptibility and perceived severity of the threat must be high. This is the part of the theory that addresses the fear component. Second, once people are in a heightened state of awareness because of the fear, they must believe that they have the capability to take action that will avert the threat. At this stage, people's confidence in their ability to act (i.e., their self-efficacy) and their belief about the effectiveness of the act (i.e., the response efficacy) must both be high. This is the part of the theory that addresses the efficacy component. The theory further states that the combination of high fear and low efficacy can be counterproductive; if people's fear levels have been aroused and then they are led to believe that there is nothing they can do, then they will avoid dealing with the issue altogether. This is known as a “fear-control strategy,” which people use to manage heightened levels of negative emotions, like anxiety. If, however, high levels of fear are combined with high levels of efficacy, then people invoke a “danger-control strategy,” which prompts them to take meaningful steps that will minimize the threat, including taking precautions or preventive measures.

Using aspects of EPPM, the BRIDGE project in Malawi sought to persuade people to take preventive actions against HIV/AIDS. BRIDGE did this by informing people about their risk of HIV infection and providing them with concrete steps that they could take to avert the threat. In this way, the campaign sought to increase both perceptions of risk and self-efficacy. The campaign messages were designed to enhance self-efficacy by promoting small, doable steps that people could take to remain free of HIV. The campaign slogan Nditha! means “I can!” in Chichewa (read more about this campaign in the EPPM case study in this chapter).

It should be noted that EPPM is intended for application in any setting, even though the theory itself was developed in the United States. Although

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From the Ground Up: Developing Pathways and Partnerships

Communication for Social Change

Communication for Social Change (CFSC) is not an actual theory but rather a model that synthesizes two competing approaches to development communication. For many years, arguments raged over whether the role of communication in support of development was to deliver top-down, high-quality information and motivational messages to mass audiences or to enhance bottom-up communication that originated from participatory communication processes and that expressed the needs and priorities of communities. CFSC emphasizes the complementary role of both top-down and bottom-up communication in engaging communities, in building on local wisdom, in expanding horizontal communication (i.e., communication that occurs between individuals operating at the same “level”) and through increased access to media. At the heart of the CFSC approach is a process of

Factors that lead to risk perceptions and efficacy beliefs are culturally defined, the theory’s central claim—that both threat and efficacy perceptions must be high in order for people to take action—is believed by the theory’s creators to hold true across different cultures.

EPPM: The Malawi BRIDGE Project’s Nditha! Campaign

The Nditha! Campaign, the multimedia cornerstone activity of the Malawi BRIDGE project, combines nationwide radio with targeted print materials and community outreach to underscore the message that Malawians can prevent the spread of HIV/AIDS. Nditha is a word in the Chichewa language of Malawi that means “I can.”

The Nditha! campaign strategy is based on the BRIDGE project’s formative research findings, which demonstrated a high level of HIV knowledge among the target population of males and females of reproductive age. The research also showed that corresponding prevention efforts have been hampered since many Malawians do not believe there is anything they can do to prevent HIV infection.

Inaction was found to be compounded by a lack of open communication around HIV/AIDS issues and a relative lack of personal risk perception.

In response to these findings, the campaign highlights the many small, doable actions that people can take to foster an environment of openness and support that is believed will lead to a reduction of HIV risk exposure. The campaign is being rolled out in three phases, with the first phase having begun in 2005.

As predicted, results from the first two phases indicate that increased exposure to the campaign is linked to greater self-efficacy to enact HIV prevention behaviors, including abstinence, mutual fidelity, and particularly condom use.6

For more information on the Nditha! campaign and other components of the BRIDGE project, please visit http://www.jhuccp.org/africa/malawi/.

For more information on CFSC visit http://www.communicationforsocialchange.org.
community dialogue and collective action through which the community itself identifies priorities, develops a vision and plan of action, and mobilizes internal and external resources to carry it out. Every time a community goes through this process, changes in both individual outcomes (such as increased knowledge and healthier behavior) as well as social outcomes (such as strengthened community leadership, broader participation, and social cohesion) are expected to occur. The model can be used to describe and explain why previous community projects were successful or unsuccessful (descriptive function), and it can also be used to increase the likelihood that community action will be successful (prescriptive function).7

Social Learning Theory
The foundation of social learning theory8 (also called social cognitive or observational learning theory) is the belief that people learn to act by observing the actions of others, observing what happens as a result of those actions, evaluating the results in relation to their own lives, and then rehearsing and attempting to reproduce those actions themselves. The most common application of social learning in health communication is the use of role models (e.g., celebrities, authority figures) for the delivery of program messages. The role models are people whom the target audience can identify with and who perform the behavior being promoted so that audience members can observe, learn, and evaluate the results for themselves. A key concept in social learning is self-efficacy, which is confidence in one’s ability to perform an action and achieve the desired results (e.g., as in condom negotiation or malaria prevention). Program planners and researchers use social learning theory to guide program decision making in several ways. For instance, the theoretical framework helps to pinpoint what types of messages will be most compelling. Questions that are raised may include the following:

- Which role models will be appealing and compelling?
- How should the behavior be visually represented?
- How can you stimulate and/or reinforce behavior rehearsal?
- How can trials of the desired behavior be encouraged?
- How can feedback about the results of the behavior be provided?
- How can incentives for performance be provided?

GUIDING PRINCIPLES OF STRATEGIC HEALTH COMMUNICATION
After being grounded in research and theory, strategic health communication should be guided by the following principles:

Target social norms as well as individual behavior. Individual behavior must be looked at as a product of overlapping social and environmental influences. Figure 1 shows how family, community, and peers, as well as environmental factors, all affect individual behavior.9

Expand beyond ad hoc activities to a coordinated social movement. The rapid growth of the HIV epidemic in many countries has intensified the worldwide commitment to combat HIV/AIDS and has brought many new actors to the table. However, organizations often act quickly and without reaching out to other stakeholders in the interest of launching efforts as soon as possible. This lack of coordination with like-minded partners

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8 For more information on social learning theory, visit http://www.learning-theories.com/social-learning-theory-bandura.html.
Bring community-level activities to scale through mass media. Community mobilization is a critical component of social mobilization; individual communities must be fully engaged as partners before a society’s response to the epidemic can evolve. Mass media is a powerful tool in the health communicator’s toolbox, with the ability to reach...
on HIV/AIDS. The four key elements of harmonization are as follows:

- **Consistent messaging.** Consistency is of paramount importance when there are multiple programs operating in a small area. If messages conflict, the target audience will lose trust in all of the messages relating to the epidemic. This can result in communication efforts that cause more harm than good.

- **Reducing duplication.** Some programs may focus on prevention messages, while others may focus on prevention and testing. To maximize the impact of scarce resources, implementing partners should seek to avoid duplicating messages so that they may reach the widest possible target audience with messages from across the entire continuum of care.

- **Maximizing resources.** Coordinating health communication messages with other implementing partners to avoid duplication and inconsistencies ensures that resources can be used efficiently.

- **Prioritizing resources.** Coordination among implementing partners provides an opportunity for all partners to determine together which issues are given the highest priority.

**Strategic communication design**

Strategic communication is a promising response to the HIV epidemic that to date has been underutilized. Barriers that have prevented the use of strategic communication include lack of funds, lack of knowledge regarding accurate HIV information among marginalized groups, lack of defined processes, and misunderstanding of the communication approach for health. The process of designing strategic communication requires a systematic approach that includes use of data, careful planning, creativity, linkages to other program elements, and stakeholder participation. This contrasts sharply millions and provide much-needed information, stimulate discussion on important issues, and influence social norms and behaviors. Frequently, these two levels of intervention (i.e., community-level and mass media) are treated as separate, parallel programs. When effectively coordinated, they can be mutually reinforcing and complementary interventions, resulting in a greater overall impact. 

**Design the communication program to fit the epidemic.** An effective HIV/AIDS communication program needs to be designed in response to the specific characteristics of the epidemic in the target setting. It is important to make the distinction between generalized epidemics and concentrated epidemics, as communication messages will differ according to the type of epidemic. According to UNAIDS, a generalized HIV epidemic is one in which adult HIV prevalence in the general population is at least 1%, and the main route of transmission is sexual. A concentrated HIV epidemic occurs when HIV is concentrated in certain groups that engage in behaviors exposing them to a high risk of HIV. (See the “Understanding Different Audiences” section in this chapter for more information.)

**Link to services.** Successful communication interventions provide a clear call to action for the audience. Communication can greatly improve the uptake of services by promoting specific types of services and sites. Communication can also improve the quality of services through interventions designed to enhance the client-provider relationship. (See the “Creating Linkages to HIV/AIDS Clinical Services through Communication” section in this chapter for more information.)

**Harmonize interventions.** Various groups work together and separately to provide a continuum of prevention, testing, counseling, treatment, care, and support. When implementing strategic health communication programs, it is important for implementing partners to work together to deliver effective and coordinated communication.
HARMONIZATION OF INTERVENTIONS: THE HEALTH COMMUNICATION PARTNERSHIP IN ZAMBIA

The number of international and national nongovernmental organizations, local organizations, and government departments working on HIV/AIDS issues in Zambia is almost too numerous to count. While most groups have a specific, well-defined focus, there is still the likelihood and risk of redundancies, inconsistencies, and overlap in messages, programs, and tool creation. Even more harmful is the potential for gaps that will not be filled and key intervention areas that will be omitted altogether.

The Health Communication Partnership—Zambia (HCP-Z) sought to avoid such pitfalls and to strengthen collaboration and partnerships by bringing all the relevant players together to map out where each was working, which audiences were being addressed, and which approaches and tools were being used. This exercise was undertaken to see what, if any, essential HIV/AIDS communication tools were missing. More than three dozen participants took part in the mapping meeting, which highlighted the wide diversity and coverage of interventions. In the course of the mapping exercise, a critical gap was discovered: none of the groups present had developed a user-friendly guide for people living with HIV to help navigate the challenges of living positively.

HCP-Z took the lead on producing a handbook to address this gap, while receiving feedback at each stage of design and development from multiple stakeholders (including partners working in antiretroviral therapy delivery, the Zambia Ministry of Health, people living with HIV, and various peer educators and counselors). While this collaborative approach slowed the pace of progress, it ensured that the messaging and approach was consistent with what was already being done on the ground. Equally, if not more important, stakeholder buy-in of the final product ensured that the handbook, entitled “The Positive Living Handbook,” would be widely accepted and used. The handbook featured color-coded chapter headings and easy-to-understand language and graphics. Topics covered ranged from food selection and sexual and reproductive health to opportunistic infections and the rights of people living with HIV. To date, more than 40,000 copies of the handbook have been ordered and distributed throughout Zambia, and it has been adapted for use in three other countries.

Due to the success of this collaborative approach, HCP-Z has continued to involve a wide range of stakeholders whenever communication materials intended for mass distribution are being produced. Other examples of products developed by this process include three very popular and widely distributed videos: Mwana Wwanga, three short stories about prevention of mother-to-child transmission; Road to Hope, an honest portrayal of the challenges of being HIV-positive and dealing with antiretroviral therapy; and Our Family Our Choice, which looks at the fertility options and related decisions faced by HIV-positive couples.

The initial survey of available HIV/AIDS communication responses and existing materials prompted the National AIDS Council (Zambia’s coordinating body for HIV/AIDS response) to ask HCP for help in compiling a national database of communication activities and materials. This effort served as the foundation of the newly established HIV/AIDS Resource Center at the National AIDS Council.
with the common, ad hoc practice of designing posters or other materials to address a specific cause. Ensuring that all stakeholders are involved in the planning process, implementation, and evaluation of the health communication program is paramount to the success of any communication effort.³

Utilizing the P-Process
Behavioral change interventions should utilize a systematic approach in their design and implementation. The systematic approach refers to a sequence of steps that guide program planning and implementation, and one model is called the “P-Process.” This process entails five steps: analysis, strategic design, development and testing, implementation and monitoring, and evaluation and replanning.

Understanding Different Audiences
Before designing a communication program, it is important to understand the characteristic of the HIV epidemic in the target setting. In some countries, for example, in southern India and Afghanistan, the epidemic is mostly confined to a certain group of people, for example, sex workers in India, men who have sex with men (MSM), or injecting drug users (IDUs) in Central Asia. These types of epidemics are referred to as concentrated or nongeneralized epidemics. In other countries (e.g., South Africa), the epidemic is affecting the general population rather than any specific subgroup. This type of epidemic is referred to as a generalized epidemic.

As stated earlier, a generalized HIV epidemic is when adult HIV prevalence in the general population is at least 1%, and a concentrated epidemic is when HIV is concentrated in certain groups who engage in behaviors that expose them to a high risk of HIV infection.⁹ The HIV epidemics in countries in sub-Saharan Africa are generalized epidemics.

Characteristics of nongeneralized (concentrated) epidemics include the following:
- Usually driven by sexual and injecting practices, especially among vulnerable groups, including sex workers and men who have sex with men
- Target population usually harder to reach than the general population; tend to be underground or do not want to be identified according to their behavior
- Require large-scale but targeted activities to reach HIV-vulnerable groups

Figure 2. Steps in strategic communication: the P-Process
Source: Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs.⁷

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³For more information on the P-Process, visit http://www.hcpartnership.org/Publications/P-Process.pdf.
Characteristics of generalized epidemics include the following:
- Driven primarily by sexual behavior in the general population
- Require large-scale changes in social norms, sexual values, and practices
- Social change critical to the success of interventions
- Can be impacted by broad-based, national (versus targeted) campaigns

Due to these differences in the nature of epidemics, communication messages must be tailored to address the behaviors for each type of affected group. In short, there is no “one size fits all” strategy that can be used to address all of the issues surrounding HIV transmission across a variety of settings.

Communicating to Different Audiences
When designing messages for any audience, communicators should consider the seven Cs of effective communication.

### Box 1. The Seven Cs of Effective Communication

1. **Command attention.** Attract and hold the audience’s attention. Make the message stand out so that it draws people’s attention and is memorable.
2. **Cater to the heart and the head.** People are swayed by both facts and emotion. Use both approaches to maximize the persuasiveness of the message.
3. **Clarify the message.** Ensure the message is clear and easily understood so that the audience can respond.
4. **Communicate a benefit.** Stress the advantages of adopting the new behavior being promoted.
5. **Create trust.** The credibility of the message is important. Without trust and credibility, the message will go unheeded.
6. **Call to action.** Include a clear call to action. Tell the audience precisely what they should do.
7. **Be consistent.** Repeat the same message consistently. This will avoid confusion and enhance the impact of the message through repetition.

**Communicating to the General Population**
Communication strategies targeting generalized epidemics must promote fundamental changes in social processes and norms. Yet communicating to the general public about HIV is challenging, given the number of issues that need to be addressed. The following are some guidelines to assist with the creation of messages for general audiences:

- **Emphasize “you can’t tell by looking.”** Many people think that someone who looks healthy cannot possibly have the virus and therefore do not take precautions to avoid infection.
- **Focus on risk behavior.** Seek to persuade those engaging in risky behavior to change, instead of focusing on risk groups, as this can lead to stigma and discrimination.
- **Focus on the ABCs.** Messages should focus on the ABC three-pronged prevention strategy of abstinence, being faithful, and correct and consistent condom use, along with a strategy for partner reduction.
- **Promote available services.** Promote the available HIV/AIDS services, such as counseling and testing, care and treatment, and support groups. Communication should stress the availability and ease of use of these services.
- **Emphasize the importance of getting tested.** Getting tested should be emphasized as an entry point to accessing needed services, making positive life changes and getting connected with groups that can provide support.
- **Address stigma.** Stigma plays an important role in fueling the epidemic. Generalized epidemic campaigns should explain how stigma (language, attitudes, and behavior) allows the epidemic to thrive, and how people often stigmatize others without realizing it. In addition to these guidelines, there are a number of myths surrounding HIV that should be dispelled whenever possible. Some of these myths have
proven to be as deadly as the epidemic itself, and this is another area where communication can play a pivotal role in slowing the spread of HIV. Responses to common, widely circulated myths are as follows:

- Sex with a virgin does not cure HIV/AIDS.
- Condoms are not infected with the virus by foreign governments.
- AIDS is not caused by witchcraft.
- HIV is not transmitted by touch.
- HIV/AIDS is not limited to drug users and homosexuals.¹⁰

**Addressing Social Factors that Contribute to the Epidemic**

There are many social factors that fuel the epidemic, including, but not limited to, gender, alcohol use, multiple partners, cross-generational sex, and transactional sex. This section briefly discusses key messages that address the role these factors may play in the spread of HIV.

**Gender**

There are many gender-related factors that are believed to fuel the spread of HIV. The following are some key areas that communication efforts can focus on to bring about positive change:

- **Gender equity.** Clearly communicate the need for gender equity. Gender roles are socially determined and can therefore be changed. Communication can challenge these roles to provide a more equitable environment.
- **Power imbalances in relationships.** Communicate (in a culturally sensitive manner) that power imbalances in a relationship increase HIV risk. Messages should address the power imbalances and the consequences of these imbalances and can emphasize that a man’s self-worth is determined by caring for his partner’s well-being.
- **Inclusion of men.** Men have often been ignored in many programmatic gender interventions, including communication, and should be included as partners to fight against gender inequality.

- **Targeting men and women together.** Provide opportunities for men and women to work together toward decreasing their risk. Gender-based activities are largely focused on women, or if they do include men, they separate targets by gender. Instead, communication efforts should seek to bring the two genders together to openly discuss gender norms.³

**Alcohol Use**

The consumption of alcohol is now recognized as a key determinant of sexual risk behavior, and indirectly, as a contributor to HIV transmission. Cross-sectional studies conducted among adults have shown that alcohol use is associated with HIV infection.¹¹ Additional studies have discovered associations between alcohol consumption and unprotected sex, timing of sexual debut, and multiple sex partners, all of which lead to an increased risk for HIV infection.¹² Addressing the complex motivations behind excessive alcohol consumption is challenging; however, key areas of focus for communication efforts are as follows:

- **Risk behaviors.** Messages should seek to persuade those engaging in excessive alcohol consumption to change their behavior by moderately consuming alcohol, as excessive consumption is associated with high-risk sexual behavior.
- **Consuming alcohol minimizes perception of risk.** Because alcohol use reduces inhibitions and self-control, communication efforts should stress that consumption alters self-perception of risk.¹³
- **Utilize counselors to promote partner communication.** Educate counselors on how to help female clients talk to their partners about how consumption impedes communication about HIV prevention.¹⁴
AFRICAN TRANSFORMATION (AT) is a package of tools designed to promote gender equity, participatory development, improved health, and community action. The package includes a facilitator’s guide and nine profiles portraying women, men, and couples from Tanzania, Uganda, and Zambia who, through their actions, overcame gender barriers to reach their goals and became positive role models in their communities. Their stories feature the challenges they faced and triumphed over when dealing with issues ranging from traditional and cultural values and reproductive health to violence between partners and networking and life skills. AT was developed by the Health Communication Partnership.

AT provides the means for men and women to discuss and debate how gender influences their lives. Through this process, AT helps men and women chart a way forward to transform harmful gender norms and reinforce positive ones. The overall goal of AT is to generate and reinforce gender-equitable normative behavior concerning health, decision making, and resource distribution among men and women in African countries. Topics covered in the profiles and guide include social roles, traditional and cultural norms, women’s and men’s reproductive health, sexually transmitted infections and HIV/AIDS, life skills, violence between partners, joint management of resources, and the benefits of networking.

AT has been recently evaluated in Uganda with positive results. The evaluation was a posttest consisting of in-depth interviews and a survey to evaluate changes in self-efficacy, views about gender norms, participation in community groups, household decision-making, and other topics associated with participation in the project.

Highlights from the findings include the following:

**Improved self-efficacy.** Compared to nonparticipants, AT participants expressed significantly higher levels of confidence in their ability to take action, particularly with respect to community activities to eliminate or reduce harmful traditional practices.

**More equitable gender norms.** Both male and female participants expressed a significantly more equitable view of men’s and women’s roles than was true of nonparticipants; participants were also significantly more likely to agree that both men and women can clean, cook, collect water, and shop for household goods compared to nonparticipants. AT had a significant and positive effect on men’s perceptions of men who assumed nontraditional roles; men who had not participated in the project reported disapproval of nontraditional men at twice the rate of participants. Participants who had taken part in five or more sessions scored significantly higher on the Gender Equitable Men (GEM) scale than those who participated in less than five sessions. (The GEM scale examines men’s normative gender perceptions and was adapted for this evaluation to incorporate attitudes about women that parallel those about men.)

**Greater participation in community groups.** Compared with 70% of nonparticipants, 95% of participants had taken part in at least one community meeting.
Multiple Partners

Multiple concurrent partnerships (MCPs), the practice of people having more than one sexual partner at the same time, are a major driver of the HIV epidemics found in much of sub-Saharan Africa. The rate of change of sexual partners—and especially the number of concurrent partners—is a key determinant in the spread of HIV. Reducing the number of partners and more specifically the rate of change of sexual partners is therefore a key risk reduction strategy. Individuals in acute stages of HIV infection are highly infectious and messages to prevent transmission should specifically target this group.17 The following are some key areas of focus for communication efforts targeting those engaging in MCPs.

- **Reduce the number of partners and limit the rate at which sexual partners are changed.** Advocate for the reduction of sexual partners and fewer changes of sexual partners, stressing the fact that multiple partners leads to increased chances of transmission. MCPs are estimated to increase HIV risk tenfold.18

- **“Zero grazing.”** Uganda mounted a successful national campaign to encourage people to stick with their regular partners to reduce the risk of HIV exposure. This was termed “zero grazing” in light of the fact that many people in Uganda raise cattle and are therefore familiar with this term. The campaign reported that multiple partner behavior dropped noticeably after the campaign was initiated.17

- **Address gender-defined roles.** Create awareness about gender-defined roles and behaviors that place expectations on men to act in a dominant or womanizing fashion. Men may also experience psychological pressure to fulfill family obligations, which sometimes results in having multiple sexual partners.18 I In cultures where polygamy is the social norm, messages should be modified to take into account the local context.

- **Facilitate dialogue among partners.** Research conducted in southern Africa indicates a lack of communication between partners on sexual issues in relationships. Open dialogue can clarify expectations and enhance the quality of a relationship. Communication interventions can play a pivotal role in promoting the benefits of monogamous long-term relationships.

- **Link MCP interventions.** MCP interventions should be linked with ongoing prevention strategies and programs. Messages on partner reduction and serial monogamy should complement, not replace, messages about abstinence, condom use, or faithfulness.
THE SCRUTINIZE CAMPAIGN

The Scrutinize campaign was created in partnership with United States Agency for International Development (USAID), Johns Hopkins Health Education in South Africa (JHHESA), and designer jeans label Levi’s to encourage and equip young people to take responsibility to reduce their risk of HIV infection. The campaign, which was launched in 2008, involves a series of short animated commercials known as animerts. It uses animated township characters who illustrate daily life encounters that place young people at risk of HIV infection. The animerts, which are intended for 18–32 year-olds in South Africa, aim to equip viewers with a new HIV fact or insight to help them examine (or scrutinize) their own risky behaviors and beliefs. The main topics addressed by the series are perceptions of risk, multiple and concurrent partnerships, faithfulness, condom use and safety, transactional intergenerational sex, and alcohol and sex. The animerts are broadcast on national television and are used to stimulate discussions in a series of organized youth conversations. The initiative is also supported by organized campaigns in higher education institutions.

Communication Strategies

According to the producers, the Scrutinize series makes use of township characters, slang, and symbology that the youth in South Africa can easily relate to. Created by communications company Matchboxology, each of the animated commercials is about 40–60 seconds long and is based on the everyday realities that place young South Africans at risk of HIV infection. The lead character is a taxi driver named Victor who is on a mission “to flip HIV to H-I-Victory.” His character was created in collaboration with a well-known South African comedian, Joey Rasdien. He is joined by a cast of four other local actors and comedians. The characters include a shebeen queen (a female owner of a small drinking establishment, usually in her home), a sugar daddy (an older man who dates young girls), a young girl, a businessman, and a teenage boy.

Personifying HIV as a ninja character is part of the series’ HIV communication strategy. According to the producers, research indicates that HIV messages become far more effective when presented in a way that people can easily relate to. The ninja pops up in many different situations: alongside sugar daddies and mommas, hanging around when there is drunken sex in shebeens, and never far away from the stigma and prejudice that help it grow stronger. Qualitative research was conducted by JHHESA to ensure that each animert communicates the correct message clearly and with impact.

The first eight animerts will be broadcast on local television in South Africa for a period of a year. The aim will be to reach target audiences during peak hours and at times when youth programs are broadcast. The campaign will also be taken to local communities, where the commercials will be used as discussion starters for a series of planned youth conversations around HIV/AIDS. The series of animerts will also appear in public health clinics via Mindset Health television, an initiative which delivers content through satellite broadcast and datacast into hospitals and clinics. Levi’s will also feature the characters on T-shirts as part of its “Red for Life” range in shops nationwide.

MULTIPLE PARTNER REDUCTION: ZERO GRAZING AND CHANGING SOCIAL NORMS IN UGANDA

In response to the HIV/AIDS epidemic in the late 1980s and early 1990s, Uganda encouraged a “zero grazing” policy, which encouraged people to reduce their number of sexual partners. The policy in Uganda utilized a combination of explicit and repeated pronouncements and the committed engagement of faith-based organizations, government, the military, and the national health system, aided by mass communications focused on the reality of people dying from AIDS. The combination of these efforts achieved a tipping point, and avoiding risky sex became the social norm. This experience stresses the importance of having reinforcing messages delivered from a variety of different sources. Additionally, this approach to behavior change originated from within,

Cross-Generational Sex
There has been a recent heightened interest in relationships between younger women and older men, where the woman is significantly younger than her male partner. The motivations for a woman to engage in a sexual relationship with an older partner are numerous and include strategies to gain love and affection, a marriage partner, and monetary gifts. Unfortunately, studies have shown that larger age differences within partnerships are associated with decreased condom usage. A multivariate analysis in rural Zimbabwe showed that a one-year increase in age difference between partners is associated with a 4% increase in the risk of HIV infection. Another study in Kenya and Zambia among women showed that there was a significant positive association between large age difference with one’s husband and HIV infection. The following are key areas of focus for communication efforts addressing cross-generational sex:

- **Social norms around cross-generational sex.** Sexual relationships with older men are a social norm in many countries. Reducing the acceptability of the practice is a key strategy.  

- **Power imbalances in relationships.** Similar focus should be given as efforts to address power imbalances specifically (see subsection “Gender”).

- **Prevention for young people.** Youth easily discount the risk of infection, since the consequences are perceived as something that may occur in the distant future. Messages that focus on prevention, such as preventing unintended pregnancy and the dangers associated with abortion and sexually transmitted infections (STIs), are more likely to influence behavior in women in cross-generational relationships.

- **Girls’ self-esteem.** Messages should attempt to raise self-esteem among girls and young women and inform them about alternative sources of income generation.

- **Reproductive health information.** Many young girls in cross-generational relationships lack accurate reproductive health information and therefore do not even perceive that they are at risk of HIV infection. This lack of awareness makes it unlikely that they will protect themselves in sexual relationships with older men.
ADDRESSING TRANSACTIONAL SEX: THE YEAH PROJECT AND SOMETHING FOR SOMETHING LOVE CAMPAIGN

Despite Uganda’s making significant progress in the 1980s and 1990s toward decreasing HIV prevalence, recent sentinel surveillance data show infection rates increasing among 15–19-year-olds. The risk is particularly serious for young women, who are more than twice as likely as men to become infected with HIV between the ages of 18 and 19.¹¹

According to studies conducted in Uganda between 1997 and 2001, anywhere from 31% to 90% of girls age 14 to 19 had been involved in sexual relationships in exchange for gifts or money.¹⁹ In addition, the Ugandan government estimates that as many as 30% of girls age 15 to 24 are involved in transactional relationships with men 10 years or more their senior.²²

To address these risk factors, Young Empowered and Healthy (YEAH), a national sexual and reproductive health/behavior change communication program for young people, developed the “Something for Something Love” (SFSL) campaign to address transactional sex. Utilizing the MARCH (Modeling and Reinforcement to Combat AIDS) approach, the radio serial drama Rock Point 256 was developed as the centerpiece of the SFSL campaign. Characters model positive behavior change over time, and the campaign incorporates reinforcing radio spots, print and outdoor media, and a wide range of communication tools (e.g., publications, training kits, drama scripts, music, interactive DVDs) to create a supportive environment through community participation.

Rock Point 256 is broadcast to 14 radio stations and reaches an estimated weekly audience of five million youth. This audience was established through youth advisory groups, which decided that listening to this broadcast was important to their healthy development. In 2007, Rock Point 256 won the AfriComNet Award for Best Folk Media Initiative for a radio serial drama and comic book series.

- **Need for men to take responsibility.** Men must be equally involved in efforts to minimize transmission risk in cross-generational relationships. Messages should encourage men to be sexually responsible by knowing their status, being faithful, and using condoms.¹⁹

**Transactional Sex**

Transactional sex is the act of engaging in sexual relations for money or gifts, and it is not the same as cross-generational sex. The economic power of women, especially in Africa and other resource-limited settings, has decreased for the last century. As a result, women are increasingly financially dependent on men. In this situation, women’s sexuality has been used as a source of economic potential.¹⁹ Transactional sexual relationships are a social norm in many countries. Therefore, social norms are a key area of focus for communication efforts targeting transactional sex. Reducing the acceptability of this practice is a key strategy.¹⁹
COMBATING STIGMA: THE MALAWI BRIDGE PROJECT RADIO DIARIES

Malawi is rated as one of the 10 countries worldwide most affected by HIV/AIDS. In response to this need, the Malawi BRIDGE Project embarked on the Radio Diaries project. The Radio Diaries, which are incorporated as part of weekly programming on a variety of radio stations nationally, present the personal narratives of two diarists, one male and one female, who are HIV-positive. The Diaries are personal, powerful accounts that engage the audience in the lives of the diarists, humanizing those living with the disease. The Radio Diaries’ main objectives are reducing stigma and discrimination against people living with and affected by HIV/AIDS in Malawi communities, increasing understanding of personal risk and vulnerability to HIV/AIDS among the general population, and increasing involvement of the general Malawian population in HIV and AIDS issues. It is also hoped that the program will foster a more compassionate environment in which problems and solutions can be discussed in a positive, constructive fashion, both at the community level and hopefully at the government and policy level.

BRIDGE Project research has shown positive effects of the Radio Diaries on both the listeners and the direct participants (e.g., the producers and diarists). Since the program first began airing, there has been a significant reduction of stigma observed toward people living with HIV, increased use of voluntary counseling and testing services, and increased membership in support groups for people living with HIV. The program has also had a significant impact on national media, encouraging new production methods at radio stations, increasing capacity and knowledge on HIV/AIDS among producers, strengthening radio station management response to HIV/AIDS, and increasing donor support for other health programming at the radio stations.23 For more information about the Radio Diaries, visit http://www.jhuccp.org/africa/malawi/docs/RadioDiariesFactsheet.pdf.

Stigma
HIV/AIDS-related stigma is a reality anywhere in the world where there are people known to be living with HIV. It is a significant obstacle to creating change in social norms and individual behavior, and therefore every communication campaign should seek to address stigma by creating awareness around the language, attitudes, and behavior that perpetuate stigma and discrimination. Communication efforts have the unique ability to present the human face of the epidemic, thereby challenging the pervasive “us and them” mentality among the general public. The following are key areas of focus for communication efforts targeting stigma:

- **“Us and them” mentality.** HIV-related stigma is often layered upon preexisting stigmas concerning socially marginalized and vulnerable groups (e.g., IDUs, MSM, sex workers). Messages should stress that there is no difference between “us” and people living with or at risk of HIV infection.

- **Breaking the stigma cycle.** People living with HIV may be implicitly associated with
stigmatized behaviors, regardless of how they became infected. So once there is a stigmatizing environment, all sufferers of AIDS are looked at through tinted lenses and are subjected to even more suffering. Those who have been affected by HIV should be treated with respect.

- **Concepts of care and compassion.** Messages should speak to people’s hearts by appealing to their emotional nature and asking them to be compassionate toward those in their community. It should be stressed that the only way to overcome the epidemic is through a united, community-wide response.

### COMMUNICATING TO SPECIFIC AUDIENCES

Epidemics sometimes disproportionately affect specific groups, such as sex workers, MSM, IDUs, pregnant women, youth, and orphans. This section offers guidance on key messages targeting specific groups commonly at risk.

#### Sex Workers

Sex workers are predominantly women who trade sex for money and use sex as their primary means of income. They are different from women who have sex for transactional purposes, or those who engage in cross-generational relationships, both of which are discussed in another section in this chapter. Sex workers are particularly vulnerable

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### THE SONAGACHI PROJECT: SEX WORKERS USE PEER OUTREACH TO FIGHT HIV

MARAJIT JANA, AN EPIDEMIOLOGIST working in Kolkata, India, started the Sonagachi Project in 1999 to protect sex workers from HIV and other sexually transmitted infections. The project was unique in its approach due to the fact that Jana believed that sex workers could run the project. The project set up a health clinic and hired the sex workers in the area to perform peer outreach. These women wore distinctive coats over their saris, giving out free condoms and spreading the word about HIV/AIDS. They spoke with madams, police, and local ruffians who run the sex industry, persuading them to use condoms to protect their investments, and thereby, reduce HIV risk exposure. Additionally, they opened up their own bank to lend one another money. “With sex workers everywhere else, within three to four years, the prevalence has just skyrocketed,” commented Jana. But the Sonagachi Project has managed to keep HIV prevalence in these women down to just 11%. This is at a time when HIV prevalence in other red-light districts in Goa, Mumbai, and Pune has soared. The combination of the sex workers’ union along with the project increased condom use from 3% to 90%.

There is some scientific evidence that the Sonagachi model can be successful in other settings. The model of using sex workers as peer outreach workers advocating on behalf of other sex workers and empowering women is a powerful one that resulted in increased use of condoms in a West Bengal community in a controlled study at the University of California.
to infection due to multiple sexual partners, frequency of sexual acts, limited condom use, and low bargaining power in condom use with clients. Key areas of focus for messages targeting this group include the following:

- **HIV infection risk.** Sex workers and their clients carry a high risk of contracting HIV. Messages should communicate high levels of risk, as well as behavioral changes on how to lower risk.
- **Condom use.** Messages should stress that condoms must be used correctly and consistently to reduce the risk of contracting HIV.
- **Condom negotiation skills.** Sex workers may fear that insisting on condom use will result in violence or loss of income. Communication campaigns should build sex workers’ confidence and self-efficacy for effective negotiation.
- **Protection with regular partners.** Sex workers often do not use condoms with regular partners. Messages should encourage sex workers to protect themselves in all types of relationships.
- **Counseling, testing and STI treatment.** Messages should stress the benefits of diagnosis and treatment of STIs and motivate sex workers to act.3

**Pregnant Women**

Pregnant women who are HIV-positive are an important target for prevention of mother-to-child transmission (PMTCT) messages. By providing information on how a mother can prevent her unborn child from acquiring HIV, mothers are given the opportunity to protect them from the virus. Additionally, PMTCT is an essential tool in fighting the epidemic globally. Key messages for HIV-positive mothers include the following:

- **Seek care.** Persuade HIV-positive mothers to speak to a counselor about their family planning, PMTCT, and pediatric care for their children who are HIV-infected or of unknown status.
- **Treatment options.** Communicate that drugs are available to protect their children from infection during pregnancy and delivery.
- **Breastfeeding.** Promote the latest breastfeeding guidelines for HIV-positive pregnant women to inform the expectant mother about the need to adopt alternative feeding practices to reduce the risk of transmission.
- **PMTCT stigma.** Communicate the dangers of stigma against HIV-positive mothers (e.g., women suspected of being HIV-positive because they do not breastfeed).3

**Youth**

Youth represent a unique audience with special needs in regard to communication program design. Young people often believe that they are not vulnerable to HIV and, as a result, are more likely to put themselves at risk of contracting HIV than adults. About half of all new infections occur in young people between the ages of 15 and 24, warranting the need to specifically address the behaviors of this population. Key messages for youth include the following:

- **Delay sexual debut.** Motivate young people to delay sexual debut as long as possible to minimize exposure to the virus.
- **Reduce number of partners.** Advocate for the reduction of sexual partners, stressing the fact that multiple partners leads to increased chances for transmission.
- **Value condom use.** Argue that condom use is valued and expected in any type of sexual relationship.
- **HIV is not visible.** A key message is that one cannot tell if a sexual partner has HIV unless the partner has been tested.3
- **Myths surrounding HIV.** Promote the truth behind the common HIV myths that many youth may believe and tell others (see section entitled “Communicating to the General Population”).
THAILAND WAS THE FIRST ASIAN nation to realize that it had a major HIV/AIDS problem, one that was so serious that it became a top priority on the national agenda. In the early 1990s, HIV prevalence of brothel-based sex workers had reached 15.2%, up from 3.1% in 1989. Prevalence was also rising among young Thai men from 0.5% in late 1989 to 3% in late 1991. It was soon determined that the majority of new infections were occurring through commercial sex. To address this alarming trend in new infections, Thai public health officials devised a new strategy in 1989 to promote condom usage among those engaging in commercial sex in the Ratchaburi province. They called this strategy the 100% Condom Program.

The program sought to address the concern that sex-worker establishments requiring condom use would lose clients, and therefore money, to those establishments that did not require condom use. Because many clients did not want to use condoms, clients would simply go to another establishment, so there was no economic incentive for establishment owners to promote safer behavior by requiring condom use. Regional communicable disease control officials realized that the solution was to require all establishments and sex workers in the province to use condoms for every sex act. When this program was implemented, the rates of sexually transmitted infections dropped, and efforts were expanded into neighboring provinces with positive results. Even though the program was working in the provinces where it had been implemented, new problems arose—if a man could not find a sex worker willing to have unprotected sex in Ratchaburi, he could travel to a neighboring province and find someone there. To combat this trend while reinforcing the important role that sex workers played in the epidemic in Thailand, the National AIDS Committee, chaired by the prime minister, issued a resolution to implement the 100% Condom Program nationally.

Condom use was promoted through mass media, peer education, and outreach programs, and condom quality was ensured through the Ministries of Public Health and Industry. Approximately 60 million condoms a year were provided free of charge, primarily at sex establishments.

Initially, many people doubted that the program would work, as many believed that they would still be able to engage in commercial sex without a condom. Yet a number of studies, as well as surveys of sex workers, found that condom use in brothels exceeded 90%. Among approximately 2,000 sex workers interviewed in one study looking at the effectiveness of the program, 97% reported always using condoms with clients they saw once, while 93% reported always using them with clients they saw repeatedly. Consistent condom use with one-time clients was around 96% in all sex establishments and more than 99% in massage parlors.26 This points to the notion that the 100% Condom Program was most effective due to various channels of communication that were utilized to target all the people involved—sex workers, brothel owners, and clients.
SUPPORTING WOMEN ENROLLED IN PMTCT: THE MOTHERS2MOTHERS PROGRAM

The MOTHERS2MOTHERS (M2M) program was created through the Horizons Program of Population Council and Health Systems Trust to assist women enrolled in prevention of mother-to-child transmission (PMTCT) programs in facing the challenges associated with living positively and in following recommended PMTCT guidelines. The m2m program in this case study, which is located in the province of KwaZulu-Natal in South Africa, provides psychosocial support to mothers through peer counseling provided by other HIV-positive mothers who serve as mentors.

Mentor-mothers conduct daily outreach activities to inform pregnant women and new mothers about PMTCT clinic services as well as referrals. One-to-one counseling is also provided by mentor-mothers on a daily basis in the health facilities. Finally, mentor-mothers provide community outreach by visiting women in their homes to assist them with status disclosure and provide support for their chosen infant-feeding method. These visits are also used as an opportunity to promote safer sex and family planning, and to encourage mothers to return to the clinic for wellness HIV care and to have their infant tested for HIV.

A recent evaluation of the program suggests that m2m plays an important role in the care of HIV-positive women and their infants. Importantly, the program links women to health facilities, which has been commonly identified as a weakness of traditional PMTCT services. The evaluation found that a peer support approach produced an association between participation in the program and greater psychosocial well-being and increased uptake of PMTCT services.

For more information on mothers2mothers, visit http://www.m2m.org/.

People Living with HIV

The goal for health communicators in crafting messages for people living with HIV is both to promote the ways in which HIV-positive people’s quality of life can be improved and to stress the importance of measures to prevent HIV transmission and reinfection. Key messages targeting people living with HIV include the following:

- **Human rights.** Address the human rights aspect of HIV by asserting that people living with HIV enjoy the same basic rights as any other individual, and that human rights abuses should not be tolerated. Messages can also refer people to services that can help them in cases where their rights have been violated.

  - **Available services.** Promote the availability and location of health-care and support services for people living with HIV.

Any communication effort targeting those who are HIV-positive should involve people living with HIV in the design, delivery, monitoring, and evaluation of campaigns. In addition, people living positively can serve as important role models for others living with the virus and can help model behaviors leading to improved health and well-being.
Orphans

Orphans are frequently denied health care and the right to an education, and suffer stigma due to their status. Additionally, many of these children are exploited through sexual means, such as through human trafficking and prostitution. Key messages addressing issues related to orphans include the following:

- **Preserve care for orphans.** Communicate the need to help families that are caring for orphans, including the need for community and economic support. Also stress the need for linking orphans with existing support services, especially for those who do not already have a caregiver.

- **Rights of the child.** Advocate for respect and preservation of children’s human rights; in countries where these rights are not explicitly protected, policy changes or mobilization around this issue can be advocated for.

- **Capacity/potential of orphans.** Assert the need to support the capacity of children to exercise their rights and grow up to be healthy, productive members of society.

Men Who Have Sex with Men

Campaigns targeting MSM need to be comprehensive, sensitive, and culturally appropriate. Reaching MSM populations can be especially challenging in countries or regions where same-sex relationships are highly stigmatized, such as in sub-Saharan Africa. Developing successful programs will require targeting existing social networks and engaging MSM themselves to achieve the greatest impact. Key messages targeting MSM include the following:

- **Practice the ABC approach.** The ABC approach (abstinence, be faithful, use condoms) is an applicable prevention message. MSM in the West are familiar with the term “negotiated safety,” which is a practice that allows for discarding condoms among seronegative partners who negotiate and agree to have sex using condoms outside their relationship.

- **All unprotected penetrative sex is risky.** Some people believe that anal sex is less risky than vaginal sex, yet rates of HIV transmission associated with anal sex are significantly higher. It is important to stress that a condom must be used during any type of sexual penetration, including anal and oral.

- **Misconceptions about oral sex.** Penis-to-mouth sex involves some risk, especially if there are cuts or lesions through which bodily fluids can be transmitted. Messages should stress using condoms as a protective barrier for oral sex acts.

- **Consistent and correct condom use.** Correct condom usage should be stressed, including appropriate application, use, and removal. It should also be stressed that condoms may break when an oil-based lubricant is used.

Injecting Drug Users

The sharing of needles among IDUs is one of the primary behaviors responsible for HIV transmission in many countries. IDUs also contribute to increased sexual transmission, and as such serve as a gateway for HIV to enter non-IDU populations.

The fact that injecting drugs is illegal makes it hard to reach IDUs, as they are generally criminalized and marginalized. Another challenge is the issue of legality around needle exchange programs. Although research shows that needle exchange programs are one of the most effective ways to prevent the spread of infectious diseases among IDUs, these programs are outlawed in most parts of the world. Stigma is a continuing challenge as well, because many people believe IDUs are to blame for the spread of HIV.

Communication programs targeting IDUs must gain the trust of this hard-to-reach population; utilizing peer educators is important in message development. Key messages targeting IDUs include the following:
is critical. Communication can play a key role in supporting a holistic approach and improving the overall quality of care.

Clinic-based, community-oriented, and mass media interventions all have a place in facilitating the uptake and utilization of HIV/AIDS services and helping the client to successfully navigate through the continuum of care.

Specifically, communication interventions can help as follows:

• Increase awareness of and reduce barriers to the use of the services
• Influence social/community norms to support specific behaviors
• Improve the quality of counseling and provider-client interactions at these services
• Educate consumers and potential clients to make optimal use of the services
• Enable community and service delivery partnerships for effective service delivery

Client-Centered Care

A client-centered care model is one cornerstone of quality service provision. Patient-centered care is care that (1) explores the patient’s main reason

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**Creating Linkages to HIV/AIDS Clinical Services Through Communication**

The need to think and act holistically about client needs in the provision of HIV/AIDS services
for the visit, concerns, and need for information; (2) seeks an integrated understanding of the patient’s world—their whole person, emotional needs, and life issues; (3) finds common ground about the problem and reaches mutual agreement on management; (4) enhances prevention and health promotion; and (5) enhances the continuing relationship between the patient and the doctor.18

This model of care facilitates a respectful, positive, and productive interface between the client and service provider. Good provider interpersonal communication and counseling skills, as well as job aids, are important tools that facilitate a client-centered approach.

Clinic-Based Communication
The interpersonal communication and counseling skills of providers are an often-neglected component of HIV/AIDS training programs. Yet a provider’s ability to relate to and engage with a client is central to ensuring positive outcomes. The HIV/AIDS service provider should be able to put the client at ease and present information in a clear and understandable way. Providers need to elicit, understand, and respond to client concerns, as well as provide follow-up and referral information. These “soft” skills are critical to the success of initiatives such as provider-initiated HIV testing that are now being implemented in many settings. Curricula and other tools addressing HIV/AIDS interpersonal communication and counseling skills are readily available and can be adapted to suit the needs of a particular setting.19

Provider Job Aids and Client Materials
Job aids and client materials can significantly enhance the quality of the provider-client interaction. A well-designed job aid—whether it is a counseling card, flip chart, or wall chart—can help the provider to present information to the client clearly and consistently. Job aids can also be used to reinforce provider knowledge and practice, or to provide the latest technical information on emerging issues, such as male circumcision. Take-home materials for the client can reinforce information or topics discussed during the visit, provide instructions (e.g., medication dosages and timing to improve adherence), or address concerns that may not have been addressed during the clinic visit. Print materials distributed to clients can also be shared with others, including friends and family members, who may play a supporting role in client care and/or need to be reached with important health messages.

The following are some key questions to consider when designing a communication strategy aimed at improving the quality of HIV/AIDS services:
- What are current levels of quality and access to services, and what plans are in place for improvement?
- By what criteria do clients and community members judge the quality and accessibility of services?
- What factors enable or hinder clients’ ability to communicate well with service providers?
- What are the current mechanisms for community involvement in quality improvement and what opportunities exist for increasing them?
- What are provider opinions and attitudes toward the community and clients they service?
- How do providers treat people living with HIV?
- What are provider attitudes and behaviors toward vulnerable populations, such as MSM, sex workers, and IDUs?
- What factors enable and/or hinder service providers’ ability to communicate in a facilitative, supportive manner while interacting with clients?

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18 For examples of communication tools, visit: http://www.jhuccp.org/pubs/.
ENHANCING SERVICE PROMOTION: ETHIOPIA HIV/AIDS TALKLINES FOR PATIENTS AND SERVICE PROVIDERS

HIV/AIDS TELEPHONE “TALKLINES” are excellent ways of providing accurate health information and counseling. The confidential, anonymous, nonjudgmental nature of talklines enables callers to speak freely about sensitive matters without embarrassment.

In 2005, the Ethiopian AIDS Resource Center (ARC) launched the Wegen AIDS Talkline, or Wegen 952, Ethiopia’s first state-of-the-art, toll-free, national HIV/AIDS talkline. Wegen operators provide information, counseling, and referrals on a wide variety of topics related to HIV/AIDS, other sexually transmitted infections, and TB. Ethiopians access the free and anonymous service by dialing 952 from anywhere in Ethiopia. The talkline operates from 8:00 a.m. to midnight, Monday through Saturday. The information and services provided through Wegen (e.g., promotion of voluntary counseling and testing, safe sexual behaviors, and ART adherence; counseling and support) complement information that patients receive from their care providers. Wegen is promoted nationwide through many channels, including print materials produced by ARC and its partners, as well as via advertisements on local radio and TV programs.

The talkline also tracks complaints received from callers on HIV- and AIDS-related issues. Callers from across the country provide feedback on the quality and availability of HIV/AIDS services, which is then directed to the respective service providers for resolution. As one caller notes, “Wegen not only enabled me to access ART, but helped me during the time of my distress and frustration I felt after knowing that I am HIV-positive. Wegen made me understand the importance of positive living. Following the counseling I got from Wegen counselors, I became aware about the fact that I could still be a productive citizen even if I am living with the HIV virus.”

ARC has also recently established a call center service for hospitals and health centers providing ART services. This call-in line enables health service providers and clinical professionals across Ethiopia to gain immediate responses to problems they encounter while providing ART services. ARC is also exploring strategies to use the call center to address burnout issues by providing psychosocial support for HIV/AIDS service providers.

At the request of the HIV/AIDS Prevention and Control Office, ARC is supporting hospitals by overseeing the introduction of Internet connectivity at 100 hospitals nationwide, facilitating more effective data collection on HIV/AIDS services as well as the potential for enhanced information exchange with and support to providers working in HIV/AIDS services.

- What formal and informal networks exist in the community being serviced?
- Who are the formal and informal leaders in the communities being served?

Community and Mass Media Interventions

Beyond the clinic walls, community mobilization and other communication interventions can go a long way in facilitating clients’ understanding of and access to HIV/AIDS-related services.
HIV/AIDS Service Promotion
People need information on the services that are available, where, when, and at what cost. Promotion of services—from provision of condoms for prevention to antiretroviral therapy (ART) or PMTCT for treatment—can range from the simple to the sophisticated: from a signboard outside the facility listing available services, to more complex promotional efforts involving branding and promotion through mass media, local outreach events, and other promotional efforts that direct people to specific services.

The following are general guidelines for communication efforts aimed at promoting specific HIV/AIDS-related services.

VCT
- **Clearly explain voluntary counseling and testing (VCT) and its benefits.** Educational materials should explain what VCT is and what people can expect, the accuracy of results, and what results mean.
- **Promote the concept of responsibility in relation to getting tested.** Messages should promote VCT as something everyone should do, not just those who are ill or have an HIV-positive partner.
- **Emphasize confidentiality of testing.** Communication should focus on the confidentiality of VCT to build trust in the service.
- **Communicate risk to youth.** Messages should focus on behavior that puts young people at risk and the importance of getting tested if engaged in risky behavior.3

ART
- **Stress that antiretrovirals (ARVs) are not a cure.** Make it clear that ARVs treat rather than cure HIV/AIDS.
- **Communicate the importance of drug adherence.** Stress the importance of following the regimen exactly as prescribed by the doctor to obtain the most positive health outcomes.
- **Communicate the negative effects of nonadherence.** Stress that nonadherence leads to drug resistance, which in turn can render treatment ineffective.
- **Promote support groups.** Encourage people on ART to join support groups for psychosocial support.3

Pediatric ART
- **Emphasize that adherence is key.** Promote information, education, and communication materials to providers to remind them to talk to caregivers about adherence, as it is key to keeping the child healthy.
- **Promote peer support.** Partnering with an adolescent club can help dispel myths about ART and decrease the harmful effects of stigma and discrimination on young patients.
- **Involve children in drug administration.** Involving the child in drug administration helps them gain a better understanding of the dosing schedule as well as what their body needs to fight the virus.29
- **Promote the efficacy of ARVs.** Many caregivers believe that ARVs will not make a difference. Emphasize that when children take ARVs correctly, they can live longer and more productive lives.
- **Educate caregivers about drug fatigue.** Many caregivers and children may become overwhelmed knowing that they have to take drugs their entire lives. Caution caregivers and young patients against becoming careless or forgetting to take their ARVs, which can lead to treatment failure.30
**Integration of Family Planning and HIV/AIDS Care**

- **Promote spousal communication.** Through communication modeling and role play, couples can be encouraged to discuss issues that connect HIV/AIDS and family planning.

- **Deepen family planning communication.** There is more room for family planning communication in any clinical setting. Address the rumors and misconceptions surrounding family planning and HIV, and promote correct and consistent use of condoms.

- **Encourage couples’ counseling and testing.** One person in a relationship may find it difficult to disclose an HIV-positive diagnosis to a partner. Encourage couples to get tested and go to counseling as a couple.31

**Male Circumcision**

- **Male circumcision reduces risk of HIV infection.** Male circumcision should be recognized as an additional strategy for the prevention of male acquisition of HIV infection. It should be noted that male circumcision does not reduce the risk of HIV transmission from an infected male to his female partner.

- **Male circumcision does not provide complete protection against HIV.** Circumcised men can still become infected with the virus, and if HIV-positive, they can still pass the infection to others.

- **Promote consistent condom use, even with male circumcision.** Male circumcision does not provide complete protection against HIV; therefore, other HIV prevention strategies, such as male and female condoms, should be promoted.32

**CONCLUSION**

Communication is an important tool for promoting positive behavior change—educating, informing, and motivating people to improve their health and the health of their families and communities. As has been described in this chapter, various forms of communication have been successfully used in resource-limited settings to fight many of the drivers that fuel the epidemic. Only through persistent and well-conceived, comprehensive communications strategies, coupled with high-quality health services, can we reverse the tide of the HIV epidemic in the most affected regions of the world.

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REFERENCE LIST


EN YEARS AGO, IN 1997, A MEETING was convened in Geneva, Switzerland, by the Joint United Nations Program on HIV/AIDS (UNAIDS) to begin the process of examining communications approaches to HIV and AIDS globally. Four subsequent meetings were held in Abidjan, Côte d’Ivoire (1997); Washington, D.C. (1998); Bangkok, Thailand (1998); and Santo Domingo, Dominican Republic (1998). The outcome of these consultative meetings led to the development of what became the UNAIDS / Penn State communications framework (henceforth referred to as the UNAIDS framework) for HIV and AIDS.1 Since the development of the UNAIDS framework, some countries, such as Ethiopia, have used the framework as a guideline for their national HIV/AIDS communications plans.

The UNAIDS framework was developed through a participatory process that involved 103 health and communications researchers and practitioners.a The framework advanced a new approach to HIV/AIDS prevention, care, and support by focusing on one or more of five contextual domains: government policy, socioeconomic status, culture, gender relations, and spirituality.2 This framework differs from conventional strategies employed in HIV/AIDS prevention work because it focuses on the contexts within which individual behaviors occur rather than focusing primarily on individual behaviors. In this chapter, we describe the five contextual domains of the framework by using examples from Senegal (based on the experiences of the authors) to illustrate the importance and relevance of each domain. We then present an example of how this framework has been applied in Ethiopia (based on the experience of the authors) as part of its national HIV/AIDS communications plan. We conclude with case studies to illustrate the impact of this context-based framework at the national level.

FIVE CONTEXTUAL DOMAINS
As indicated, five contextual domains were identified as being the keys to successful communications strategies at the national level. The framework was published as a “house-to-home” strategy.1 This
means that at the global level, we have a framework that is identified as a house containing the five domains. To make the house into a home, each country and region would need to modify and adapt it to its own unique setting. Following is a description of the five domains.

**Contextual Domain 1: Government Policy**

Government policy arguably exerts the most influence on social change, having the power to transform social and environmental forces for the benefit of individual health outcomes, even when individuals have no intention of changing. For example, smoking and its effects are an area in which public and institutional policies in many countries have made a major difference, thereby reducing vulnerability to negative health consequences. The need for government policy is often most appreciated when it is absent, as in the case of the absence of policies to protect against HIV/AIDS stigma in many countries. While the tendency has been to focus solely on government policy, policies of institutions outside government, such as universities, multilateral donor agencies, and civil society organizations, are also central to transforming the social and environmental contexts that can encourage and normalize both positive and negative behaviors.

The leadership of each country plays an important role in communicating about HIV/AIDS. Official policies shape how the collective voices and images of the disease are perceived by the general public. Some policies, such as those that make provision for supply of antiretroviral (ARV) drugs, communicate a sense of urgency, while others, such as those that do not insist on school health education about AIDS, reinforce complacency.

In Senegal, soon after the first HIV/AIDS cases were detected in 1986, the Senegalese government publicly acknowledged that HIV and AIDS existed in Senegal and must be addressed urgently. Its position was based on scientific evidence provided by well-known Senegalese researchers. The studies carried out by Senegalese researchers in collaboration with international partners helped develop an indigenous, independent perspective and gain greater political support. The Senegalese scientific community, including researchers in the social sciences, has enjoyed easy access to the highest government authorities since the beginning of the epidemic. The fact that prevention messages about AIDS were coming from Senegalese nationals helped lend credibility to these early announcements. Building credibility among the general public was especially important during a time when the Western media were contributing to negative reactions, such as denial, by portraying negative images of those infected and, in some cases, suggesting racial links between HIV and African populations.

The Senegalese government swiftly set up a national multidisciplinary AIDS prevention program that was one of the first to be developed in Africa. The program was implemented by a National AIDS Committee under the Ministry of Health (MoH). During the early phases of the epidemic, the committee organized meetings with parliamentarians, researchers, religious leaders, and other influential groups, such as members of the media (e.g., editors and journalists), to provide them with information and training on HIV/AIDS-related issues. In 2001, the National AIDS Committee became the National Council for the Fight against AIDS and was placed under the authority of the prime minister. This change of status strengthened its multisectoral approach. The committee included representatives from a large variety of social and government sectors, as well as associations of people living with HIV, members of the private sector, and members of vulnerable groups, such as women.
At the international level, the Senegalese government is known to have played an important role in the mobilization of African heads of state and members of the international community in the struggle against the HIV/AIDS pandemic. 

**Contextual Domain 2: Socioeconomic Status**

Socioeconomic status has a significant impact on the success or failure of many public health interventions, even though it may not independently explain disparities in health outcomes. Individuals and communities that constitute the bottom rung of the socioeconomic ladder are the most vulnerable to HIV/AIDS; they have the least power to demand attention to their welfare needs and the least access to health information and treatment. They also tend to have poor nutritional status, have limited access to routine health care, and be least able to afford medical services. For these reasons, socioeconomic status influences, to a great degree, one’s vulnerability to HIV/AIDS. Government policy in some countries has been shown to help minimize a population’s vulnerability to HIV/AIDS despite limited resources. Senegal’s approach is one example of how this can be achieved.

Senegal’s poor economic status (per capita annual income of less than US$750) translates into scarce health resources. In the context of HIV/AIDS, scarce health resources translate into poor health infrastructure and a high cost for ARV drugs, making HIV treatment inaccessible for the majority of the population. Between 1992 and 1996, the government of Senegal invested in one of the highest budgets devoted to AIDS in West Africa, with about US$20 million being spent on prevention programs. In addition, the Senegalese government launched efforts to address the problem of availability of ARVs, making support and care of people living with HIV a national priority. The process of expanding access to ARVs started with the creation of the Senegalese Initiative of Access to ARVs program (Initiative Senegalaise d’Accès aux Antiretroviraux [ISAARV]) in 1998. At that time, Senegal was the first country in sub-Saharan Africa to develop a government-driven ARV treatment program for the general public. Senegal was followed by two other African countries (Uganda and Côte d’Ivoire) that started their programs under the framework of the UNAIDS initiative for better access to medicines.

ISAARV was started in the context of limited national resources and widespread poverty among the general population. The cost of ARV treatments was extremely high, and the international consensus, influenced by the donor community, often recommended prevention rather than treatment for African populations and the populations of other developing countries. Some of the major international institutions were reluctant to finance access to treatment in sub-Saharan Africa. However, after having conducted several biomedical and social operational studies, ISAARV began implementing its own treatment program in 1998 with the support of 250 million CFA francs (US$500,000) in government funds. One such effort was the country’s decision in 2000 to be among the first countries to participate in the partnership program called Accelerating Access to HIV Care, Support and Treatment. With the support of participating pharmaceutical companies, the price of ARV drugs in the country was reduced by 80%. This considerable reduction in drug prices made it possible for some people (a small portion of those in need) to obtain these drugs, while the majority of people still were unable to afford or have access to treatment. With these funds and a program in place, ISAARV lobbied the pharmaceutical industry, which agreed (contingent upon massive and coordinated purchases) to apply preferential pricing for the Senegalese government. The Senegalese policy was informed by
studies that had succeeded in demonstrating that the country had the required competencies to correctly administer treatments and that it could succeed in bringing about a reduction in the cost of ARV drugs (resulting in a 90% reduction in price) through appropriate purchasing strategies. Finally, the initiative resulted in the adoption of a government decision in 2000 to make ARVs available free of charge to all eligible individuals.

The Senegalese response to HIV/AIDS appears to have benefited from the country’s health policies that were developed prior to the outbreak of the global HIV/AIDS pandemic. Senegal had set up a number of political, legal, and social arrangements aimed at controlling a number of infectious diseases and also at improving health conditions generally (policies for blood transfusion safety, management of sexually transmitted diseases, reform of the health system, support for women’s and youth associations, etc.).

The official policy on blood transfusion safety was articulated in recognition of the fact that Senegalese society has a tradition of active community involvement in health and development issues. To face the HIV/AIDS threat, the policy was able to initiate the mobilization of religious, women’s, youth, and other community groups. According to several studies, 200 nongovernmental organizations (NGOs) were active in the fight against AIDS in Senegal by 1995. Over 400 women’s groups, with a total of half a million members, also supported a wide range of AIDS-related activities.

In a case such as this, in which there is an urgent need to respond to HIV and AIDS, it becomes even more important to understand the cultural contexts of behaviors so that prevention strategies can focus on multiple contexts and institutions.

**Contextual Domain 3: Culture**

The role of culture in understanding the contexts of preventive health behavior cannot be overemphasized. Rather than focusing exclusively on the negative aspects of culture as is often done in intervention programs, we recommend beginning a program with the positive aspects of culture. Culture is most important when health communicators understand and acknowledge the strengths that reside in a particular community so that they are able to identify the cultural strengths as they examine cultural challenges (see the PEN-3 model in Airhihenbuwa, 2007). The goal is to assess the positive and negative aspects of a culture rather than focusing solely on the negative.

Culture shapes an individual’s understanding of health concepts, since the meanings of health, drugs, treatment, and illness are all culturally constructed. Most people involved in HIV/AIDS communications have recognized the importance of culturally appropriate communications. However, efforts to ground HIV/AIDS prevention messages in local culture are apparent in some contexts and surprisingly absent in others.

Prevention efforts throughout Senegal are also conceptualized so as to correspond to traditional Senegalese culture. The president of the NGO SIDA Service, E.D. Diouf, illustrated this point by sharing the following story at the opening of the 1996 conference on AIDS and religion in Senegal:

The symposium, today, reminds me of the big community meetings that former kings of the Sine kingdom used to organize for their traditional religious leaders. When there were signs that a big calamity was getting closer, the Saltiguis (leaders) explained to the populations, in big assemblies, the seriousness of the danger, revealed the fight they took to contain it and recommended behaviors individuals had to hold to protect themselves and especially to safeguard the country.

Along the lines of what Diouf refers to in his address, the Senegalese national AIDS response
placed an emphasis on the familiar concept of *disoo*, which literally means interacting around a burden or challenge. *Disoo* refers to the images of discussion and consensus building before making a critical decision. The concept of consensus building is translated by the Wolof word *degoo*, which literally means listening to each other in a collective and interactive way. The consultations that built Senegal’s national response to AIDS were described as part of a process of peace building. The Wolof word *jamm* refers to both peace and good health. It is understood as a product of consultations and processes aimed at reducing tensions, conflicts, misunderstandings, and social exclusion.

The Senegalese case highlights the importance of social communication in the processes of sensitization. Here, collective thinking and discussion were pursued as a prerequisite to consensus building and integrating the response into social relations and networks. Successful social communication strategies recognize that societies and communities construct their own discourses, using their own socially appropriate languages and symbolic systems. Using these systems to their maximum effect helps ensure that the values and representations likely to mobilize populations to face the HIV epidemic are well understood and internalized by local populations.

The Senegalese response also highlights multiple forms of mobilization on the part of NGOs and civil society interested in serving as extensions to the national response. The approaches centered around human rights and/or women’s rights managed to achieve a high level of success due to civil society interventions. Structural responses and legal provisions were worked out to protect the rights of people living with HIV and to develop responses to abuses of those rights.

HIV prevention efforts in Senegal also built on the customary, popular, or traditional elements of Senegalese culture. Within each culture, the roles of women and men should be understood and contextualized, as will be discussed in the case studies at the end of this chapter.

**Contextual Domain 4: Gender Relations**

The impact of HIV/AIDS on women remains one of the most challenging aspects of the pandemic. Women are more vulnerable to HIV, more stigmatized, and the least empowered to control their environment. Even though discussions of women’s vulnerability tend to focus on women without equal reference to men, the positive and negative roles men play in women’s lives should be fully addressed. Gender analysis should address both male and female dynamics as they relate to HIV/AIDS communication. The notions of power and equality come into play at this level. Gender roles influence not only communication styles but also who has a voice (the opportunity to speak and be heard).

UNAIDS reports that an estimated 23,000 women in Senegal were HIV-infected by the end of 2003, representing slightly more than half (53%) of the total HIV cases in Senegal. While the overall rate of female infections has remained steadily low, in line with the country’s prevalence rates, the rate among sex workers has been rising at an alarming rate. Nationally, the prevalence rate among female sex workers grew from 1% in 1986 to 14% in 2002. Despite this increase, the overall HIV prevalence among sex workers in Senegal appears to be relatively low in comparison with that of many countries.

Prior to the discovery of HIV/AIDS, the Senegalese government had taken steps to decriminalize sex work. Laws provided protection and medical follow-up under certain conditions. Those provisions eventually helped spread awareness of HIV/AIDS among sex workers.

Efforts to implement prevention efforts with a focus on gender roles include the work of community-based women’s associations in cooperation
with the National Council for the Fight against AIDS. The role of women’s organizations within the National Council ensures that they actively participate in implementing policies related to women. In so doing, they can promote the inclusion of women’s concerns and issues related to HIV/AIDS. In addition, the work of NGOs, such as the Society for Women and AIDS in Africa (SWAA) Senegal, is a great example of how the capacity of women’s associations to communicate can be reinforced. These larger organizations can help generate a heightened awareness of the specific concerns and recommendations of women with regard to HIV/AIDS. Traditionally, women’s associations serve as support networks (natt, mbotay, tuur, Dimbatulon, Kanyalen) and help ensure that women hold prominent roles in the dissemination of information and the organization of collective responses concerning issues relating to sexuality and the health of women and children. These associations’ roles are often recognized not only as a source of social and economic support, but also as a source of spiritual support. This leads to our discussion of spirituality, another critical aspect of communications and the last domain of the framework being discussed.

**Contextual Domain 5: Spirituality**

Spirituality is a much broader and more inclusive concept than religion, even though the two terms are often used interchangeably. Spirituality embodies primarily values and beliefs and how they are shared, and the rituals that accompany the sharing is expressed. Such sharing may take place through tolerance, compassion, acceptance, support, and faith. Aspects of spirituality include questions of what is considered right and wrong and what constitutes fair and unfair. Evidence from HIV/AIDS literature shows that there is a relationship between spirituality and both positive and negative attitudes toward HIV/AIDS. When attitudes are positive, a supportive space is opened up in which persons living with HIV can feel accepted. When attitudes are negative, an environment that breeds discrimination and stigmatization is created.

In Senegal, there is a high degree of religious tolerance among religious leaders, despite differing beliefs. Muslims and Christians live together peacefully and treat one another with mutual respect. The existence of various religious groups is recognized and legitimized by the Senegalese government; major Muslim and Christian holidays are national holidays. Not only do religious groups respect each other, they also collaborate when necessary for the benefit of the country. In several instances, Muslim and Christian leaders have worked together to address national issues.

The process of mobilizing religious leaders around HIV/AIDS started with surveys of Muslim and Christian leaders. The findings from the surveys were used to produce appropriate educational materials. Training sessions were organized to help disseminate information in such a way that HIV/AIDS prevention became a regular topic in Friday sermons and in prayer sessions in mosques throughout Senegal; preeminent, well-respected religious figures even addressed the issue of HIV prevention on television and radio.

In March 1995, about 300 senior Muslim leaders gathered for a conference on HIV/AIDS in Dakar,

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*Natt* is a type of women’s group; the word *natt* literally means a contribution. Each woman gives an equal part, and the total is given to one member of the group every week or month. *Mbotay* is another type of organization that insists on the solidarity of its members. The word can be translated as a group that is carried together on the back of one mother. *Tuur* refers to women who meet in one house after another. The word refers to libation. *Dimbatulon* is a Manding word. *Dimbas* are women who do not have children or who have difficulties with childbearing and maternal health. *Dimbatulon* is a group of *Dimbas* with their activities in one neighborhood. *Kanyalen* is a Diola word for the same type of women’s organization as *Dimbatulon.*
with the presence of the head of the state. Christian leaders also attended major events during the conference. The conference firmly supported HIV/AIDS prevention efforts. During the conference, the religious leaders in attendance announced that they did not consider HIV to be a divine retribution for immoral behavior. They spoke in support of the rights of people living with HIV, including the use of condoms by married couples if one partner is infected. They also recognized the right of people to have access to full and accurate information about HIV/AIDS. In January 1996, Christian leaders gathered at another conference on AIDS, with the presence of Muslim leaders at the major sessions. The Catholic bishop of Senegal also attended. The major result was a consensus that AIDS prevention was a crucial national activity. Led by a Catholic NGO, SIDA Service, the churches gradually developed a supportive outlook toward HIV prevention. SIDA Service provided important counseling and psychosocial support, and frequently referred people to alternative providers when the organization itself could not meet needs, for example, for the distribution of condoms.

The moral support provided by religious leaders allowed NGOs and health authorities to work productively in providing specific HIV prevention services. The involvement of religious leaders helped avoid potential controversies over the distribution and use of condoms and allowed activists and health officials to work toward providing greater access to prevention, care, and treatment.

The experience in Senegal shows that even in a country that did not adopt the UNAIDS framework for its national communications plan, all the domains of the framework were both important and relevant to the success of the country’s HIV/AIDS efforts. This example reinforces the conclusion reached during the development of the framework that these domains are a reflection of what has actually worked in countries, such as Senegal, that are considered to be success stories in HIV/AIDS prevention, support, and treatment. During the final phase of the development of the framework, the following conclusions were reached:

1. Changes in behaviors should be encouraged, along with changes to the environments in which behaviors are taking place, by focusing on one or more of the five domains.

2. Interpersonal communication should be used as a strategy to promote changes in social contexts and individual behaviors, since media campaigns alone have not proven to be effective in changing behavior.

3. While the framework offers a broad direction, as in a house, each country and region must adapt it to its own particular methods to make it a home.

Following the development of the framework, an implementation process was developed to provide some direction for countries wishing to use the framework.

**COUNTRY IMPLEMENTATION PROCESS**

The overall objective is for each country to develop a communications strategy that focuses on contextual factors that promote positive individual behaviors and that have the power to change negative behaviors.

Specific country-level activities include the following:

- Identify a national HIV/AIDS plan or strategy. Within this strategy, the role of communications in prevention, support, and treatment should be identified by listing activities in the plan that require or are part of a communications strategy. As a part of the initial preparation, each country should identify and document activities (such as published or unpublished reports and articles) that show the level and range of existing HIV/AIDS prevention, care, and support
activities in each of the five contextual domains of the framework.

- Key country partners, organizations, and collaborators should be identified. A country team should typically include a research institution, such as a university, that will provide institutional continuity for monitoring, evaluation, and documentation; health communications practitioners or HIV/AIDS information, education, and communication or behavior communication specialists who will be directly involved in the implementation; local NGOs with experience in HIV/AIDS in at least one of the five domains of the framework; representatives from the national government to ensure ownership and sustainability; representatives from United Nations agencies such as the United Nations Children’s Fund (UNICEF), and/or other UNAIDS co-sponsors; and representatives from other multilateral organizations.

- The country team should organize a two- to three-day planning session that includes all the partners identified above. Local and/or international experts (such as the UNAIDS communications adviser and UNAIDS consultant for the framework) should be invited to provide technical expertise.

- At this meeting, participants should review, discuss, and document activities in communications for HIV/AIDS in the country as they relate to the five domains of the framework. Any other relevant issues should also be cited and discussed. An outline for a country framework should then be developed. The country framework outlines strategies that will focus on specific issues within the five domains (and any additional domains identified) of the UNAIDS framework. A timetable for implementation should be developed as a critical next step. Strategies to be implemented may include mass media and interpersonal communication approaches. Other issues to be addressed are identification of resources and organizations to serve as partners, identification of past national successes in working on other health issues within any of the domains, and any other strategic discussions and approaches that will enhance the implementation process. During these sessions, consultation meetings should be scheduled with key organizations and institutions with a focus on HIV, particularly those that are not represented at the planning session.

- At the end of the session, two or three of the five contextual domains (or other relevant domains that may have been identified as requiring immediate attention) of the framework should be identified as the priority focus for the first phase of implementation.

- Based on the agreed-upon priorities, an implementation plan should be developed to include a budget, timeline, and strategies for monitoring and evaluation.

- The next step is the implementation of the country framework, including the establishment of a monitoring and evaluation mechanism. A monitoring and evaluation plan should be developed as a part of the national implementation plan, to ensure that the effectiveness and impact of activities can be monitored and documented.

- The communications strategy should be integrated into other national HIV/AIDS efforts, as well as, in some cases, larger development programs.

**EXPERIENCE FROM ETHIOPIA:**

**IMPLEMENTING THE FRAMEWORK**

Ethiopia is one of the countries most severely affected by HIV/AIDS, accounting for roughly 9% of HIV infections worldwide. The disease has spread among all population groups, with a growing concentration among young men and women between the ages of 15 and 24. Ninety-one percent
ROLLING OUT AND SCALING UP

of AIDS cases reported are among people between the ages of 15 and 49, an age group that spans the most productive years of human life. HIV/AIDS has become not only a national health problem but also a serious economic and social problem for Ethiopia. The national adult prevalence rate is estimated to be 3.5% (4.0% female and 3.0% male), with an urban prevalence rate of 10.5% and a rural prevalence rate of 1.9%. There are 1.3 million people living with HIV, and annual AIDS-related deaths are estimated to be 134,000 (61,000 males and 73,000 females). The number of pregnant women testing positive for HIV annually is estimated to be 106,000, with 30,000 infants testing positive for HIV. The spread of the virus appears to be more controlled in urban areas, where prevalence rates have remained fairly steady at around 10.5% in recent years (since 2002). In contrast, new infections have increased at an alarming rate in rural areas, from 0.3% in 1990 to 2.6% in 2003, and are projected to reach 3.4% in 2008. The number of children living with HIV is estimated to be 135,000, with annual deaths of 21,000. Those who need and should receive ARVs number 43,000. The level of care and support services for people living with HIV is extremely low, reaching only 16,000 (1%) of total people living with HIV (1.3 million).14

In response to the growing HIV/AIDS epidemic in Ethiopia, various behavioral interventions have been implemented based mostly on media campaigns to create awareness about HIV. It was assumed that by changing attitudes and behaviors such an approach would lead to a reduction in vulnerability and the risk of contracting HIV/AIDS. After years of unsuccessful strategies, the limited impact of these mostly media-based approaches led to the acknowledgment that the approach needed to shift to a focus on what became known as behavior change communications (BCC). In BCC, interventions are designed to target individuals to change attitudes and behaviors, including risky sexual practices. A major strategy of BCC has been to focus on youth educating youth in the popular peer-to-peer education approach, which was later expanded to include adults in targeted population groups such as sex workers and truck drivers. This approach also became popular in mass media campaigns. However, these interventions, despite their popularity, have not yielded the intended impact in terms of reducing HIV incidence and prevalence.12

To address this problem, the HIV/AIDS Prevention and Control Office (HAPCO) in Ethiopia adopted the UNAIDS framework by focusing on the five domains discussed earlier in this chapter. Supportive guidelines were also developed for the framework to facilitate easy implementation.

The UNAIDS framework continues to acknowledge the importance of individual behaviors and decisions but does so in the context of the domains identified. It calls for a multisectoral, multilevel approach to communications strategies involving many stakeholders, including but not limited to specific ministries, local NGOs, community-based organizations (CBOs), religious organizations, and the private sector.

Both the government and NGOs have been implementing communications interventions among different target population groups using the framework and the guidelines. Since the implementation, very encouraging results have been documented in the last few years.15

Implementation Process

To facilitate effective implementation of programs at all levels within Ethiopia, the national and regional AIDS councils, with their secretariats, have been used as coordinating bodies for the implementation of the framework. At a grassroots level, work is being done by the woreda (district) AIDS councils and kebele (local) AIDS committees, NGOs, CBOs, religious and traditional organizations, and others.
The process of adopting the UNAIDS framework began after a program manager from Pact Ethiopia, an NGO, participated in the development of the UNAIDS framework and committed to coordinate the adoption process in Ethiopia. With technical and financial assistance from UNAIDS and Penn State University, the NGO facilitated the adoption process by taking the following steps:

- Discussed the project idea with MOH and UNAIDS Ethiopia.
- Formed a task force with members from MOH, the National Office of Population (NOP), Addis Ababa University (AAU), UNAIDS, UNICEF, and Pact Ethiopia.
- Held a consultative workshop with key stakeholders to introduce the UNAIDS framework and identify domain-related issues in the Ethiopian context. The workshop was facilitated by the UNAIDS Africa regional office, Penn State University, and Pact Ethiopia.
- Held a second workshop to adopt the UNAIDS framework and drafted a strategy for the framework to be piloted by NGOs. At this point, the National AIDS Council and its secretariat came into being and took over responsibility from MOH for coordinating all HIV/AIDS-related matters in the country. For this reason it took some time to begin advocacy work to influence the National AIDS Council/Secretariat (NACS).
- NACS subsequently decided to adopt the UNAIDS framework as a national communications framework for HIV/AIDS instead of piloting it with NGOs. A workshop was held on the adoption of the framework with the participation of broader stakeholders, including key actors such as NACS at the national and regional levels, MOH, the Ministry of Labor and Social Affairs (MOLSA), UNAIDS, UNICEF, the Policy Project, the Centers for Disease Control and Prevention (CDC), Family Health International (FHI), faith-based organizations (FBOs), NGOs, CBOs, and others.

- Launched in October 2002, the national communications framework was divided into three regional clusters based on similarities in context. Having the framework in place, however, was only the beginning. There was an expressed need to develop regionally specific guidelines for the use of the framework, and thus workshops were held to develop communications guidelines for each of the three regions. The guidelines contained an outline of concepts, the framework, steps to follow in implementing the framework, and instructions for monitoring and evaluation of the communications interventions. These guidelines became the main implementation tool for the framework.

Challenges at the Country Implementation Level

The entire process of adopting the framework took more than two years to complete, due to a variety of factors. Some of the more notable are the following:

- Because the leading NGO, Pact Ethiopia, was from civil society, the government offices involved often slowed the process. It is typical for an NGO-initiated national program to take a long time to gain acceptance, although it took longer than anticipated in this case.
- There was resistance to new communications concepts among other international NGOs employing different concepts, strategies, and theories. However, strong commitment at the individual and organizational level and persistence in policy advocacy helped overcome this challenge.
- National priority programs, such as those targeting HIV/AIDS, must be anchored within the relevant government bodies to ensure sound overall coordination among stakeholders. However, it was difficult to coordinate and obtain feedback from relevant government...
bodies on the use of the framework. Eventually they were successful and the framework was adapted to the Ethiopian context.

When the Ethiopia National Communications Framework for HIV/AIDS, with consolidated guidelines for its use, was in place, 11 regional/provincial HIV/AIDS secretariats formed HIV communications teams and started using the framework. As part of this action, the Southern Regional HAPCO translated the framework into one of the national languages (Amharic) and distributed it to HIV/AIDS stakeholders in the region.

Pact Ethiopia, which led the communications framework adoption process, has provided training on the use of the framework to more than 40 of its local NGO partners and youth associations. The NGOs and partner associations have since been using the communications framework and guidelines for HIV and reproductive health communications interventions among different target population groups (community leaders to address cultural and traditional practices that aggravate the problem of HIV/AIDS, urban and rural youth, sex workers, employees of various companies, housewives, rural communities, etc.) through the use of interpersonal and mass media communications.

In what follows, we present three case studies from Ethiopia to illustrate the importance and relevance of the framework at the country level. Of note is how one case is used to highlight the intersection of multiple contexts that may need to be addressed at the same time.

Ethiopia Case 1: Gender Relations, Culture, and Spirituality
In the Kembatta district of the Southern Regional State, an NGO called Kembata Women’s Help Center led a process of identifying communication problems and issues and from this helped develop communication objectives and messages for different segments of the population, such as women. This process involved identifying the proper channels for message transmission as well as monitoring and evaluating the activities of other partners during the implementation process. Specifically, a “community conversation” approach was used—an approach that brought community members together to identify the major problems and challenges the community was facing, prioritize issues, and take action by setting and enforcing community laws themselves. During this process, harmful cultural practices and related issues were identified that affect the health of women. These problems were then prioritized, and the community was encouraged to seek common solutions. Female genital cutting (FGC) was identified as a major problem that exposes females to various health risks, including HIV/AIDS. The issues identified as being related to the problem of FGC were resistance of males to marry uncircumcised females, support and acceptance of the practice by community and religious leaders, and dependence of circumcisers/practitioners on circumcision for their livelihood. During these community conversation sessions, community leaders, male and female community members, and circumcisers participated. These sessions were complemented by targeted message transmission in a variety of forums, such as live drama performances, debates, and informal group discussions during coffee ceremonies. Messages were targeted to reach different groups, including males, females, circumcisers, community and religious leaders, and others. As a result of this intervention, the community has totally abandoned FGC. At the beginning of the intervention, more than 200 girls refused to undergo circumcision,

*The coffee ceremony is a well-established cultural practice in Ethiopia. An invitation to attend a coffee ceremony is considered a mark of friendship or respect.*
men started marrying uncircumcised women, and community leaders started penalizing families that were having their daughters circumcised.

**Ethiopia Case 2: Government Policy and Culture**

Stigma and discrimination against people living with HIV is a significant problem throughout the country. Losing one’s home and job, having trouble accessing public services, and encountering difficulty in obtaining accurate health information are just some of the problems that people living with HIV and their families can encounter.

The African Initiative for Democratic World Order (AIDWO) is an NGO involved in non-formal civic education. In 2003, AIDWO initiated a pilot project on HIV/AIDS prevention using a human rights approach in collaboration with the NGO Pact Ethiopia. The main objective of the project was to encourage behavioral and attitudinal change toward people living with HIV through the provision of human-rights-based education on HIV/AIDS. It was hoped that this type of education would help prevent the spread of HIV/AIDS, as well as reduce stigma and discrimination against people living with HIV.

The primary target populations were members of traditional community groups such as the *idir,* youth in and out of school, women, and government policymakers in two districts of the Addis Ababa region. AIDWO used its existing relationship with the district administration (developed during the election period) and *idir* chiefs as an entry point to reach the intended groups.

AIDWO’s drama group is widely used for advocacy work and has extensive experience in the field of advocacy and lobbying. The group used drama and songs, case presentations, testimonies by people living with HIV, and panel discussions on human rights in general and the rights of people living with HIV in particular—through mass media and in mass gatherings—to sensitize the target populations and open a dialogue on human rights issues.

Forty drama sessions were staged, each followed by a group discussion. One drama dealt purely with human rights, people living with HIV, and AIDS orphans, while the others dealt with the general issue of HIV/AIDS. Over 15,000 people in different kebeles (local administration units) of two districts attended the drama performances. The communications strategies were found to be effective in bringing about the intended behavior and attitudinal changes toward HIV/AIDS and people living with HIV, both among the traditional groups and local governments.

*Idirs* are now empowered to reorganize themselves from the local level to the district level to perform development work and to systematically address the problem of HIV/AIDS, including the handling of funerals for people with HIV, thereby working to curb the stigma and discrimination faced by children and other family members of the deceased. Currently, support from the Regional AIDS Council and local government is being provided to the group for community planning to deal with stigma and discrimination, including support for orphans and people living with HIV in the two districts. As part of this process, the community has been able to provide support to AIDS orphans, including food, clothing, and school supplies, as well as protecting them from physical attacks by other children.

The practice of supporting those in need is a deeply rooted cultural belief of Ethiopians. Calls for the continuance of this practice in the face of HIV/AIDS is an example of the kind of culturally

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*Idir groups are traditional Ethiopian burial societies that help families after a relative dies.*

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appropriate message that can help combat stigma and discrimination based on a person’s HIV status.

The following lessons were learned from this experience:
- Using existing relationships with local governments formed during the election period facilitated efforts to reach out to target populations.
- The existing government policy on freedom to speak out on human rights issues helped the education and advocacy process.
- People could act more effectively to solve their problem when they were supported through already organized traditional forums, such as idir groups in this case. Traditional leaders, if properly sensitized, can influence the community to take action or make needed changes in behavior and/or attitudes.

Ethiopia Case 3: Culture, Gender Relations, and Government Policy
A local youth reproductive health association in one district of the Amhara region began working together with rural youth clubs in order to reduce harmful traditional practices. The major objective of the communications intervention was to reduce early marriage among girls in a rural community by changing attitudes and practices relating to early marriage. Club members, in collaboration with local government officials, used community conversation to address the problems and issues associated with early marriage and the benefits of girls’ education.

After several sessions, the community issued a law forbidding the traditional practice of early marriage. According to this law, the penalty for early marriage carried a maximum fine of US$50. In addition, the local school, in collaboration with the clubs, organized a girls club in the school that assisted the girls in making their own decisions about when to marry and whom to marry. As a result, girls’ enrollment in schools has increased dramatically and early marriage has been significantly reduced in the project area.16

An exemplary case is Gebeeyehu Negash, now a 14-year-old seventh-grade student in the village. When Gebeeyehu was 13, her parents planned her marriage without her knowledge. In their culture, once the parents decide on their daughter’s marriage partner, the man whom they have selected will come to their home and work on their farm for two years. According to this traditional practice, the man whom Gebeeyehu was supposed to marry came and started working on her parents’ farm. One of her friends informed her that this man was her future husband. Upon hearing this, Gebeeyehu went to her school and reported what was happening in her home. The school, in collaboration with the local reproductive health club and local government administrators, discussed the case with her parents and convinced them to change their minds. Because of this intervention on her behalf, Gebeeyehu is continuing her education as a young unmarried woman.

Looking Forward
The national communications framework and guidelines are the foundations for promoting interpersonal communication from a country-specific perspective. Communications practitioners from the public and NGO sectors have been using the guidelines to implement targeted communications interventions, and positive impacts have been observed. However, wider use of the framework and coordination of efforts at all levels is crucial. This can be achieved by building the capacity of government coordinating offices at various levels as well as communications practitioners from civil society in order to increase their level of commitment, knowledge, and skills. Conducting research and evaluation to measure impact is also crucial.
EXPERIENCE FROM SENEGAL: HIV/AIDS RESPONSES IN THE WORKPLACE

The response of the Senegalese workplace has been in accordance with the following principles established by the International Labor Organization (ILO):

- Recognizing HIV/AIDS as an important crisis in the world of work and developing social dialogue to face the issue, namely, by establishing healthy work environments and a continuum of prevention and access to treatment and care
- Rejecting all forms of exclusion and discrimination against workers living with HIV, being respectful of confidentiality of serologic data, and rejecting test imposition or the use of test results aimed at taking exclusionary or discriminatory measures against employees
- Applying principles of gender equality and respect for women’s rights in order to reduce their vulnerability to HIV and eliminate gender-based inequality in access to treatment

To develop this approach, tripartite commissions (the state, employers, and trade unions) were organized by the government to coordinate responses in the workplace. In the public sector, an interministerial committee to combat HIV/AIDS was established under the leadership of the Ministry of Labor. This move increased capacity for reinforcement programs and sensitization in the ministries.

Partnership between the private sector, the public sector, and trade unions allowed for a synergistic approach to prevention and improved access to care, not only for workers and their families but also for other vulnerable groups throughout the country. Some companies, such as those in the chemical and mining industries, had pioneered initiatives to provide workers and their families with ARV medicines as well as to invest in preventive activities in surrounding rural and urban areas.

Company coalitions against HIV/AIDS were created to reduce the risk of infection and protect the rights of people living with HIV, as well as to supply treatment and care. Advocacy programs were undertaken by several companies in the country. A Companies Against AIDS charter was created in 2003, with the aim to reverse HIV trends by translating the ILO Code of Practice on HIV/AIDS and the World of Work into practice. Currently, more than 80 companies have signed the charter.

As indicated previously, the Senegal experience has been used to illustrate each of the five domains. Senegal continues to be hailed as an HIV/AIDS prevention success story, since the country has been able to maintain low prevalence rates throughout the years in spite of increasing rates in neighboring countries. To demonstrate the strategies contributing to this success, we present two examples that help reinforce previously cited experiences from Senegal.

Senegal Case 1: Government Policy and Socioeconomic Status

The condom distribution plan of the NGO International Movement for Development in Africa (Mouvement International pour le Development en Afrique [MIDA]) is one example of a successful HIV/AIDS prevention program.

HIV/AIDS prevention workers seeking to talk to factory employees about AIDS can ask factory supervisors to set aside work time or speak to the workers during their breaks. When doing prevention work with individuals in the informal sector, there is no such opportunity, as these informal-sector workers are in business for themselves and do not belong to any defined organizational structure. For MIDA representatives, this lack of formal structure meant that they had to rely on direct communication. This involved making regular visits to places of work and busy corners and talking
directly to people such as the young man selling sunglasses or the older woman selling umbrellas.

A challenge arising from this lack of formal structure was to make condoms accessible to workers who did not have a physical office. MIDA’s representatives used the existing communication networks of informal workers. They asked questions, such as, “Which workers communicate regularly?” “Who are the most influential workers?” and “Who are the most accessible workers?” Armed with this information, MIDA chose to provide certain workers with condoms, making it possible for others to easily access them (MIDA representative, personal communication, August 2002). This use of existing communication lines allowed MIDA to reach its goal of making condoms available to individuals who otherwise might not have received them.

Senegal Case 2: Government Policy
This case study, which draws on interviews with representatives from some of the more successful programs undertaken in Senegal, highlights the importance of understanding context in addressing an epidemic.

An understanding of context is illustrated by the changes that occurred within the Senegalese government HIV/AIDS organization in 2002. Two years later, in 2004, the organization changed from being the National Program Against AIDS (Programme National de Lutte contre le SIDA [PNLS]) to the National Council Against AIDS (Conseil National de Lutte contre le SIDA [CNLS]). A CNLS representative explained that this was not just a change in name; it represented a new approach in the fight against the AIDS epidemic in Senegal. PNLS was a program of the Senegalese health ministry, but HIV/AIDS was not only a health problem. If AIDS was beyond the realm of the health ministry, the national committee’s structure had to reflect this reality. The program was thus restructured to be under the leadership of the prime minister, who then encouraged government ministries to take ownership of the ways in which HIV/AIDS affected their departments. According to the CNLS, not everyone who should play an important role in HIV/AIDS prevention work should be under the minister of health. These individuals should have their own programs and coordinate them with a global, multisectoral vision.

The fact that this restructuring occurred in the government agency leading all HIV prevention activities in Senegal is very important. It shows that even in a country that is praised globally for its success, the agency leading the efforts has not become complacent. This change displays a continuous commitment to maintain and even improve upon strategies demonstrated to be effective.

Senegalese HIV/AIDS organizations often look for new frameworks for activities and new areas in which to direct their HIV prevention efforts. The CNLS representative explained how the council was always looking to identify new areas of focus to strengthen its efforts. For example, he referred to the new programs in Matam (northeastern region of Senegal), an area with considerable emigration.

An SWAA representative provided another example of the dynamism of the Senegalese HIV/AIDS prevention organization. She explained how one of their programs selected the region of Ziguinchor because of its instability. SWAA believed that donors had abandoned Ziguinchor because of civil unrest in that area, and the organization wanted to make sure that the region was included in prevention efforts.

Finally, an Environment and Development Action in the Third World (ENDA) health representative revealed another example. He discussed ENDA’s activities and showed how this NGO has evolved in its approaches as it has learned more about HIV/AIDS in Senegal. The HYGEA 1997 behavior survey showed that knowledge of HIV/AIDS did not necessarily translate into a change
in behavior. To respond to this finding, ENDA integrated its strategies for strengthening community response. This involved preparing community members to create their own prevention programs. By doing so, communities had the opportunity to gain ownership, and, as the representative explained, “Sustainable action can only be created by a population’s members.”

Dynamism in organizations was not limited to these examples. In explaining their activities, interviewees constantly gave examples of how they adapted their programs and activities as they learned more about HIV/AIDS, their community members’ behaviors, and HIV prevention work in general.

**CONCLUSION**

The UNAIDS framework is becoming increasingly relevant in the battle against HIV/AIDS. The successes achieved in Senegal and the embracing of the framework in Ethiopia are just two examples showing the importance of a contextual response to HIV rather than a focus on individuals alone. With both governmental and nongovernmental agencies calling for an increased emphasis on communication for social change, the framework represents a proven approach for assembling multidisciplinary and multisectoral teams to collectively develop effective strategies for reducing vulnerability to HIV and providing greater access to treatment for people living with HIV.
REFERENCE LIST


COMMUNITY-BASED CARE
The Growing Importance of Community-Based Care
Joia S. Mukherjee and Fernet Leandre

In 1981, when the mysterious occurrences of Kaposi’s sarcoma and Pneumocystis carinii pneumonia—which later were known to be associated with AIDS—were first reported in gay men in New York and San Francisco, a wave of stigma began. In 1983, the first cases of AIDS in children were reported as occurring in "children born to promiscuous and drug addicted mothers." AIDS was thought to be a gay men’s disease and a disease of the badly behaved—an exceptional disease in exceptional populations. The gay community rose above the stigma to work together in an organized fashion to both advocate for prevention and reach out to those affected. Community organization was a key factor in reversing the trend of new infections in the early 1980s among the gay community, yet this lesson was not translated as the epidemic spread. Similarly, the reasons for the success of the HIV-prevention programs in Thailand and Uganda were not well understood and thus not replicated or adapted in other settings.

Subsequently, in the 27 years since the discovery of AIDS, transmission of HIV, predominantly through heterosexual relationships, has led to a pandemic previously unknown in world history. AIDS has gone far beyond the exceptional—it is one of the most common causes of death in the developing countries of sub-Saharan Africa. Today, the disease affects millions of people. It affects parents and children; it affects both urban and rural communities. As AIDS prevention, treatment, and care are scaled up, it is imperative that the availability of effective treatment reflects the nature of the epidemic and as such is based in the community—at primary health centers and with community-based, participatory care.

THE ADVENT OF ANTIRETROVIRAL THERAPY: ACCESS THROUGH CLINICAL TRIALS VS. REAL-WORLD EXPERIENCE
The advent of antiretroviral therapy (ART) caused AIDS mortality to plunge sharply in industrialized countries. ART was first made available through clinical trials in 1995 and 1996. In the United States and Europe at that time, one had to be enrolled in a study to receive this lifesaving therapy, which required living close to an academic center so that frequent visits could be made and specialists could administer all necessary care. These trials demonstrated significant success and
was responsible for changes in practice throughout the developed world.13

While trials taught us much about optimizing therapy for HIV, dramatically reducing both morbidity and mortality, it was often noted that the outcomes in real populations were less ideal. The difference between real-life settings and clinical trials is that trials are performed in a setting of exquisite follow-up and adherence. Studies have shown that adherence (as estimated by self-reports and viral suppression) in clinical trials often approaches 90% compared to 40%-75% in the general population.14-26 As new information on antiretroviral regimens was generated from such trials, the responsibility for improving patient outcomes fell to specialists in infectious diseases rather than primary-care clinicians, and there was little focus on methods to address adherence. Yet it has been widely understood that adherence to ART is critical in delaying the development of resistance. When protease inhibitors were first used in the United States, groups thought to be at high risk for poor adherence were denied access to ART based on the assumption that such individuals would develop HIV strains resistant to these important drugs and that resistance would spread to the “general population.”27 Similar arguments were used as justification for not delivering ART to those living in resource-limited settings—then, as now, 90% of those affected.28

MOVEMENT TO DELIVER ART TO RESOURCE-LIMITED SETTINGS

Fully six years after ART had shown remarkable benefits in the United States, Europe, and Brazil, AIDS remained the world’s leading infectious cause of adult death in sub-Saharan Africa and Haiti, and ART was not available owing to the cost of the drugs and the fear of drug resistance. In 1998, as a matter of good medicine and justice, Partners In Health’s Haitian program, Zanmi Lasante, began treating patients who had advanced AIDS with ART. These patients had in many cases been identified years before but no longer responded to the treatment of opportunistic infections. Because CD4 count and viral load testing were not available to clinical programs in Haiti at the time, clinical criteria alone were used to initiate therapy. The clinical response of these patients to ART was no less remarkable than it had been in New York, San Francisco, or Paris. Patients demonstrated the “Lazarus effect,” returning to health and productive life. Because patients lived many hours’ walking distance from the clinic and would now be receiving lifelong therapy, we employed a system of community health workers (“accompagnateurs”) to provide daily visits to supply medications, offer psychosocial support, and evaluate side effects. Not only did this system provide a large community support network, but it also reassured the public-health world, concerned about the specter of drug resistance, that our patients were receiving their medicines more reliably than those in developed settings.

DECENTRALIZING CARE

The subspecialist-driven care used in Europe and the United States is impossible to replicate in countries where doctors and nurses are in scarce supply. Moreover, this model has not proven to be adequate in terms of assuring adherence to medications or retention in care. In the global pandemic, many of those living with HIV reside in rural areas, far from capital cities or “centers of excellence.” The movement to scale up access to ART necessitated a new approach that would take these challenges into account.

First, it was necessary to move care from tertiary centers to the district and primary health-care level. To do this, health-care workers had to be trained in the triage of HIV-positive persons who needed prophylaxis, treatment of opportunistic infections, or ART. Generic-drug manufacturers
developed fixed-dose combination therapy—specifically, the combination of stavudine, lamivudine, and nevirapine—which, given twice daily, minimized the complexity and pill burden and facilitated adherence. In 2002, the World Health Organization (WHO) created a working group to develop simplified and standardized ART recommendations for resource-limited settings.29 These guidelines suggested first-line and second-line regimens, which helped to streamline ART-related procurement and training. Simplified regimens helped move therapy closer to the community level, as nonspecialist physicians, nurses, and clinical officers could be trained to administer ART.

COMMUNITY HEALTH WORKERS: TESTING, ADHERENCE, ACCOMPANIMENT

Even with simplified care delivered at the district level, the reach of ART is dependent on the utilization of services. Many studies have addressed the utility of community health workers and peer counselors in HIV prevention programs.30,31 Yet community members also can have an important role in increasing uptake of testing and utilization of services. In 2009, in most parts of sub-Saharan Africa, many people do not have access to HIV testing and do not know their status. The lack of uptake of testing has been attributed to lack of access as well as social factors such as stigma and lack of knowledge about HIV. Studies have shown that knowing one’s HIV status enhances the ability to adopt targeted prevention strategies, from both individual and programmatic perspectives. In Haiti, we quickly discovered that providing treatment with ART led to an enormous increase in demand for voluntary counseling and testing. Many of our community health workers and community educators are people living with HIV and are on ART. These community members serve as powerful voices to encourage testing and are a living testimony to the effects of ART.32

Community health workers engage in active case finding, looking for families with HIV contacts who have not yet been tested as well as referring people who are ill to the clinic.

Peer counselors, community health workers, and groups of people living with AIDS have a critical role in many resource-limited settings in promoting adherence to ART.33,34 In Partners In Health’s project in rural Haiti, community health workers—accompagnateurs—began supervising therapy for TB in 1988 and soon saw the end of deaths from that disease. A decade later, accompagnateurs began providing essentially the same services for HIV by delivering ART for AIDS treatment.35 Accompanateurs serve as a vital link between village and clinic, administering therapy and ensuring adherence. They identify people who are ill and who have not yet been evaluated, as well as alerting clinic staff to complications in patients already receiving therapy. The accompagnateurs, who are members of the communities they serve, help attend to the pressing social problems—including lack of access to food, potable water, housing, and education—that the vast majority of patients face. It is in this role of “accompagnement” that they are most valuable to the patients they serve. Our patients in Haiti, Rwanda, and elsewhere describe their accompagnateurs as their angels, friends, and supporters. When we have conducted focus groups of patients and accompagnateurs in Haiti and asked if this system is necessary, the large majority of patients and accompagnateurs have expressed the belief that those with a chronic disease need ongoing psychological support.

At Partners In Health, the goal of the accompagnateurs is to promote social justice by ensuring access to care and to provide solidarity by reaching out to members of the community who are sick and vulnerable. As such, their work is focused not only on their medical role but also on their...
role in the community at large. This includes community mobilization, education, destigmatization, and work with communities of faith to reduce the social isolation of affected individuals and households. Because accompagnateurs are very active in reaching community members who might be ill with HIV or family members or partners of known HIV contacts, new HIV patients are identified promptly, often well before they are extremely ill. This affords them the chance to maintain health and have a more effective response to ART, and also allows the promotion of safe sexual practices in couples where one partner is infected and the other not. The follow-up provided by the accompagnateur has reduced the time between identification of an HIV patient’s need for ART and actual initiation of therapy to just two weeks on average, and few patients are lost to follow-up in this critical period.

Lastly and of critical importance is the accompagnateurs’ promotion of individual patient adherence and retention in care. Our projects in Haiti, Rwanda, Lesotho, and Malawi have an extremely low lost to follow-up rate (approx. 2% per year), and only 1%–2% of patients per year switch to second-line therapy. Given the chronic nature of HIV, the cost of second-line therapy, and the morbidity and mortality that is embedded in lost to follow-up rates (as high as 40% per year in some projects), we feel the integration of paid accompagnateurs is well worth the cost. With each accompagnateur following roughly 5 to 10 patients, the added cost to an individual’s therapy is US$50 to $100 per year. This represents a significant savings when compared to the cost of second-line therapy, increased morbidity, and the enormous social costs of having a chronically ill member of the community.

THE GROWING IMPORTANCE OF COMMUNITY-BASED CARE

Although we first used this approach in rural Haiti, the accompagnateur model has been successfully exported to slums in Peru and communities in Tomsk, Siberia, for the treatment of multi-drug-resistant tuberculosis (MDR-TB), and to inner-city Boston, Rwanda, Lesotho, and Malawi for AIDS therapy. Our own experience across these different sites permits us to argue that this model may be adapted to work effectively in widely diverse settings.

In the last four years (2003 to 2007) the movement to provide access to ART to those living with HIV in resource-limited settings has succeeded in providing lifesaving medication to over two million people. Since the majority of those living with HIV often reside in rural areas with little infrastructure, moving care to communities is critical if we are to reach the six to nine million people who need therapy. This process is improved if the community is involved in providing a linkage to the clinic through community health workers, treatment supporters, or peer counselors who can participate in active case finding, accompaniment of patients, and adherence support.
REFERENCE LIST


Although the world is full of suffering, it is full also of the overcoming of it.
—Helen Keller

Although palliative care is one of the most important forms of care for individuals with active, progressive, or far-advanced illness, it is frequently unavailable to those who need it. Every year, millions live and die in pain, or endure distressing psychosocial and spiritual suffering. Millions more struggle to care for sick loved ones or grieve their loss. And while a vast number of children need palliative care every year, pediatric palliative care programs are even more limited in their availability than are programs for adults.¹

Reducing suffering and increasing quality of life for people living with HIV and their families
Access to better HIV care, including antiretroviral therapy (ART), has meant that millions of people living with HIV have been able to live longer with their disease with strengthened immune function and reduced morbidities. At the same time, many people living with HIV, both those with and without access to ART, experience physical pain and discomfort, aggravating symptoms from HIV disease or comorbidities, the fear of disability and dying, discrimination, the side effects of medicines, spiritual distress, and worries about the future—all of which can lead to chronic suffering and a diminished quality of life.

In the past two decades, with the increasing burden of HIV, cancer, and other life-threatening diseases, there has been a revolution in the scope and availability of palliative care services. Such services are now available in more than 84 countries, both rich and poor.² For many, however, access to services remains limited due to a lack of national policies and guidance, barriers to accessing essential palliative care medicines such as oral morphine, and limited availability of pre- and in-service training in palliative care. As a result, millions go without palliative care despite the fact that, as Pampallona and Bollini (2003) explain: “Medical knowledge existing today can control the suffering of most of the many millions of . . . patients worldwide if that knowledge were applied appropriately.”³ (p172)
### Box 1. Definition of Palliative Care

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

—World Health Organization

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**Definition of Palliative Care**

The World Health Organization (WHO) defines palliative care as care that is focused on reducing pain and suffering and increasing quality of life for people with life-limiting illness, such as HIV, and their families (see Box 1). Palliative care can be provided to people living with life-limiting illness from the time they receive their diagnosis until death, and can be offered to family members during the illness of their loved one and through the bereavement process. In many cases, people living with HIV can now spend many years benefiting from treatment that, while not curative, can delay the onset of AIDS for an indefinite period of time. When people living with HIV are relatively asymptomatic or doing well on treatment, their quality of life can be enhanced through palliative care, which translates into the relief of all forms of suffering, including side effects, opportunistic infections (OIs), and emotional and spiritual stress. As these individuals fall ill, palliative care may become increasingly important. The needs of the patient and the affected family will vary over time, but access to palliative care services over the course of the disease enables both the patient and the family to better anticipate and address these needs.

**Principles of Palliative Care**

The overall guiding principles for palliative care in resource-limited settings are:

- **Emphasis on quality of life.** Quality of life is defined by the individual, not by the service provider. Serious effort must be made to improve quality of life, regardless of the stage of illness or individual circumstances.
- **Respectful and participatory.** Palliative care services must respect the rights of the patient and family to make choices, exercise their unique cultural and personal values, receive confidential services, and be treated with dignity.
- **Holistic.** Needs are viewed holistically, with physical, emotional, spiritual, and social aspects of care and support equally attended. Services are provided by interdisciplinary teams, which are better equipped to address diverse needs. They support people living with HIV to shape, lead, and provide services.
- **Family centered.** The unit of care is the family (as defined by the patient). Providers involve families in the care process, providing them with needed confidence, information, and skills to support their loved one with HIV.
- **Sustainable.** The provision of services can be accessed, sustained, and integrated into the local system, community, and environment. Services must strive to be cost-effective to ensure the greatest benefit for all.
- **Integrated.** Palliative care services are provided through existing health, psychosocial, and spiritual support services, including HIV and orphans and vulnerable children (OVC) programs.
Where and How Is Palliative Care Provided?

Palliative care services are sometimes provided in stand-alone facilities such as hospices or specialized palliative care units in tertiary hospitals. While there is a place for these services, palliative care can be more effective when it is provided in combination with services that offer treatment of OIs and underlying disease. This approach ensures that care is holistic and helps people with HIV to live both longer and better lives.

Increasingly, palliative care is being integrated into existing HIV care services such as outpatient clinics, inpatient departments, and home-based care teams. This integration translates into pain and other symptoms and psychosocial problems being assessed and treated as part of routine HIV care.

Integration can be achieved through training HIV care providers in palliative care and ensuring they have the medicines needed to treat pain and other symptoms.

What Are the Benefits of Palliative Care?

The benefits of palliative care to individuals with life-limiting illness, their families, and society are numerous. Several studies have documented the impact of palliative care on physical, emotional, social, and spiritual well-being, as well as macro-economic advantages.

Improving Quality of Life
Addressing physical, emotional, social, and spiritual needs, and helping people achieve a sense of peace and life meaning, can prevent end-of-life suffering and despair. Studies show an intrinsic link between the overall physical health of people with HIV and their emotional, social, and spiritual well-being. Palliative care has demonstrated improvements in quality of life through a variety of services offered in diverse settings across high-, middle-, and low-income countries. In Uganda, a recent study on the impact of a linked outpatient clinic and home-based care program for people living with HIV found that it improved social aspects of quality of life.

Promoting Better Health Outcomes, Adherence, and Service Retention
Palliative care services can greatly enhance outcomes for people on ART. Recent studies in Malawi and one conducted in several HIV care programs in Africa and the Caribbean found much lower loss to follow-up rates among people living with HIV who were enrolled in comprehensive programs (palliative care plus ART) versus those enrolled in programs with limited palliative care services. The Malawi study also documented significantly lower deaths among those enrolled in the comprehensive program (3.5% versus 15.5%). Another study among a predominantly injecting drug user population in Vietnam found that in a comprehensive palliative care and treatment program in Vietnam, adherence rates of more than 95% were found in 98% of participants.

Reducing Stigma
Palliative care offers an opportunity for providers to help family members and neighbors better understand HIV and learn how to provide care for loved ones living with HIV. It has helped reduce stigma and discrimination in some settings. For example, in Cambodia, as a result of an integrated palliative care and ART program, reported stigma among people with HIV decreased from 10% at the beginning of the program to 0% after one year. In Vietnam, similar results were documented.

Providing Cost-Effective Services
Comprehensive palliative care, where people have access to inpatient and outpatient care and home-based care when they need it, has proved cost-
effective. The evidence also shows related improvements in daily adjusted life years, increased rational use of health-care services, reductions in hospitalization, and improved quality of care.\textsuperscript{15-17}

**PALLIATIVE CARE AND HIV**

**Need for and Role of Palliative Care in HIV**

Study after study shows that people with HIV, cancer, and other life-limiting illnesses experience high rates of pain and other physical symptoms, as well as psychosocial and spiritual distress. Between 53\% and 97\% of people with HIV will experience pain that generally increases in frequency and severity toward the end of life.\textsuperscript{18} Pain experienced varies from country to country. In South Africa, two studies among rural and urban palliative care patients living with HIV/AIDS found the incidence of pain to be from 91\% to 98\%.\textsuperscript{19} Physical symptoms, including pain, can also be experienced early on in the disease process, during ambulatory periods of disease, and while on treatment. Studies show that pain is also prevalent in those on ART.\textsuperscript{20} Neuropathic pain, often as a side effect of certain antiretrovirals (ARVs), is also common in people living with HIV.\textsuperscript{21}

While pain is prevalent among people living with HIV, it is often underdiagnosed and therefore undertreated.\textsuperscript{22,23} Essential medicines to treat pain are highly regulated, resulting in multiple barriers for providers in accessing opioids such as codeine and morphine to treat pain. Prohibitive regulations regarding certain medicines to treat pain include time limits on prescriptions, mandatory morphine ampoule recovery for pharmacies, fines and removal of licenses for physicians who are unable to account for ampoules or otherwise transgress regulations, complicated licensing and procurement regulations, and others, depending on the region. When regulations make it difficult for health-care workers to prescribe these medications, the number of clients being treated for pain is relatively limited and the supply of opioids dwindles. The chilling impact of these regulations can be seen in the quantities of morphine use reported annually per capita. Only countries with balanced opioid control and use laws and policies report levels of consumption that indicate adequate management of pain. In 2003, six developed countries accounted for 79\% of the global use of opioids. Developing countries, which comprise 80\% of the world's population, accounted for only 6\% of annual opioid consumption, despite morphine being very inexpensive to produce and procure.\textsuperscript{24}

The prevalence of other symptoms is also high among people living with HIV. Distressing symptoms can range from fatigue to nausea and insomnia. The following symptoms are particularly prevalent in people living with HIV: anorexia (63.1\%), fatigue (60.1\%), fever (47.6\%), and cough (37.5\%).\textsuperscript{25}

While it may be assumed that individuals taking ART no longer need palliative care, the reality is that the need is just as intense. People on ART experience multiple, distressing side effects, some of which are major contributors to low adherence. They also may experience immune reconstitution inflammatory syndrome, chronic pain due to previous illness, other chronic illness such as heart disease or cancer, or multiple psychosocial issues.\textsuperscript{26} Depression and lack of social support are associated with significantly reduced adherence.\textsuperscript{27} Among people on ART, studies show that reports of pain vary from 30\% to 60\%.\textsuperscript{20,28}

Psychological distress is also common. People with HIV in the United States are three times more likely to have psychiatric illness than are those who are HIV-negative. Studies show that about 20\% of people living with HIV experience sadness, 20\% major depression, and 20\% to 25\% dementia.\textsuperscript{29,30} In a recent study from Vietnam, 82\% of people living with HIV reported being unhappy or very unhappy
most of the time. A growing body of literature indicates that while ART increases immune function, reduces morbidity, and improves prognosis, it does not always lead to major improvements in psychosocial well-being, and in some cases leads to reduced quality of life.

Spiritual suffering has been documented as a significant source of existential pain. Research, including a spiritual well-being and palliative care study conducted in 2003, has found a strong correlation between low scores in spiritual well-being (i.e., lack of peace, feeling that one’s life does not have meaning or purpose) and the desire for a hastened death, hopelessness, and suicidal ideation.

Palliative care also encompasses end-of-life care. While the needs of people living with HIV and others may be different from community to community, research findings on palliative care needs during this time of life are strikingly similar. The following conclusion from a 2006 study in Uganda on end-of-life needs among 178 people living with HIV illustrates this: “A ‘good death’ in a developing country occurs when the dying person is being cared for at home, is free from pain or other distressing symptoms, feels no stigma, is at peace, and has their basic needs met without feeling dependent on others.”

**Palliative Care Service Delivery Approach: Offering a Continuum of Care**

Palliative care is, in essence, a continuum of care because it focuses on relieving suffering throughout the course of HIV and through all stages of life (Figure 1). Therefore, palliative care services need to be available to people with HIV at all levels of the health-care system. This includes tertiary, secondary, primary, and community levels of care. As a person moves through the continuum of care, palliative care must be available at each point to provide relief and support for the client and affected family members.

The key to ensuring availability of palliative care across the continuum is not to establish stand-alone services, although they have their place, but rather to integrate palliative care into existing HIV care services. The need for integration of palliative care into other HIV care services cannot be overemphasized. Because palliative care covers the continuum from diagnosis through death and bereavement, it must also be integrated at every service point relevant to each stage of disease progression. Providing a holistic, palliative care approach involves the use of all HIV interventions, such as counseling and testing, ART, and prevention of mother-to-child transmission (PMTCT). The family-centered orientation of palliative care programs also integrates pediatric, adolescent, and geriatric services.

The following sections provide guidance on how palliative care can be integrated into various essential HIV services.

**HIV Counseling and Testing: A Bridge to Palliative Care**

Since palliative care begins at the point of diagnosis, individuals who test HIV-positive may need a number of services to reduce suffering, including counseling, help with disclosure, and links to HIV care services. HIV counselors must at minimum be trained in how to provide basic counseling and know where to refer clients for HIV care services. The earlier people with HIV are referred to palliative care services the better, since significant suffering can be mitigated through early identification and treatment of pain and other symptoms and psychosocial issues, and by ensuring that clients are empowered and able to access care when they need it.

To help relieve further suffering, other members of the family should also be offered HIV testing and counseling because children, spouses, and others may go undiagnosed until they are already
very sick. Home-based care teams in some areas are equipped to test family members for HIV in their homes. If home-based testing is not available, providers can maintain a two-way referral relationship with the nearest testing site. If the testing site identifies patients in need of palliative care, it makes a referral to the nearest program and/or provider. Status disclosure counseling for patients is another critical component of holistic palliative care for HIV-positive patients.

**HIV Outpatient Clinics: Nexus of Palliative Care and Treatment**

Palliative care and treatment are complementary therapies that together enhance the quality of life for people with life-limiting illnesses. Under no circumstances should palliative care be provided without available treatment of OIs and ART, unless this is the patient’s choice. All people living with HIV have a right to receive both forms of care.
HIV outpatient clinics provide an excellent opportunity for integrated care. Where a clinic provides only treatment for OIs and ART, palliative care can be incorporated into the services the clinic offers with training and some added medicines (e.g., oral morphine). The result is more holistic care for clients, including more complete clinical assessment and care for OIs, pain and other symptoms, nutritional needs, and psychosocial concerns.

While palliative care and treatment must be provided in tandem, the intensity of treatment versus palliative care needs will change over time. As HIV progresses, patients may require more intensive support in managing pain and other physical symptoms and in addressing spiritual concerns around death and dying. Figure 2 illustrates this relationship.

**Providing Palliative Care through Home-Based Care**

In many countries, people with HIV prefer to receive care at home at some point over the course of their disease. The preference for care at home or dying at home has been found to be common in both developed and developing countries.31,38

Care in the home offers many advantages; it can help people live comfortably in their home environments with their families through the ambulatory stages of the disease to the end of life. Home-based care is often provided by family members, sometimes with support from lay helpers in the community (religious workers, peer groups of people living with HIV, women’s group members, etc.).

Home-based care teams are also an important source of support to patients and families, providing them with a range of services and linking them to HIV outpatient and inpatient care facilities. However, for home-based care teams to be able to provide a minimum level of quality palliative care, they need to be trained, supervised, and equipped with a basic supply of palliative care medicines. The trained home-based care team can provide many services such as basic nursing, pain and symptom assessment and care, counseling, self-care empowerment, respite, and referrals to other community resources. Team members can also help reduce stigma in the family and
community, and encourage prevention of HIV and disclosure within the family. Home-based care staff are increasingly utilized in the important role of promoting ART adherence. Home-based care supplies should, where possible, include analgesics for Step 1 and 2 pain management on the WHO pain ladder as well as other medicines to treat mild symptoms in the home. In Uganda and a few other countries in Africa, home-based care teams are directly administering oral morphine.39

Because of the comprehensive nature of palliative care, home-based care must also be supported by the community. The home-based care staff are often volunteers or paid staff from community organizations. Teams are often comprised of a variety of people with different and important skills sets, such as people living with HIV, healthcare professionals, and social workers.

**Palliative Care and OVC Services**

Children living with and affected by HIV, like all children, require special attention because of needs unique to their physical and emotional development. Children require a safe and nurturing environment for their well-being and survival. Palliative care services can provide such an environment to ensure that children in a variety of circumstances receive appropriate help. Children can require assistance when they are living with an ill family member or when they are themselves HIV-positive, when they have recently lost a loved one, or when they have been orphaned.

Palliative care services can address the needs of these children through the application of a family-centered care approach. Examples of a family-centered care approach include (1) providing HIV care to both parents and children in the same facility so they are able to receive care together; (2) training palliative care providers in the palliative care needs of children and in how to communicate with children; (3) ensuring that home-based care teams are trained to be able to assess the needs of the children in the household alongside assessment of adults; (4) developing linkages with programs and services in the locality of the palliative care clinic or home-based care team that can help OVC enroll and stay in school, provide legal support, assist with providing alternative care if needed, offer child protection and abuse aftercare, and so on; and (5) helping parents plan for the future of their children and prepare succession plans.

Whether or not both parents are seriously ill, it is wise to discuss their wishes, together with their children, and to assist them in writing their wills stating a common agreement about where and by whom the children will be taken care of in the future. When plans have not been made for the care of orphaned children, they may suffer serious consequences such as inadequate food, shelter, and education, with accompanying emotional and social distress. The family can help its children avoid these dire situations by preparing a will that secures the family’s possessions for the children’s future and appoints a guardian. Usually, guardianship of the children naturally falls to the remaining parent. However, if both parents die, a guardian will need to be appointed.

**Palliative Care in Inpatient Settings**

While it would seem natural that palliative care be offered in inpatient settings (i.e., hospitals or hospices), there may not be adequate training and support staff in these facilities or essential palliative care medicines to ensure that such services are available. People who are being cared for within hospital and hospice settings are often there because they suffer from serious illness. Pain management and symptom care, along with emotional, social, and spiritual support, are all essential aspects of care for those who are hospitalized. At a minimum, health workers should be trained in the principles and practice of palliative care and efforts.
should be made to ensure access to morphine. In particular, the staff should feel adequately skilled to communicate difficult news sensitively to patients and families and to help them know what to expect over the course of the disease.

The staff of inpatient care settings should work closely with home-based care services so that people living with HIV have the option of transitioning back to their home or another care site if they prefer to do so.

**Palliative Care and TB/HIV Integration**

TB is a major cause of serious illness and death for HIV-positive people, including those on ART. In many resource-limited settings, there is a very high risk among people with HIV of acquiring TB. Palliative care programs for people living with HIV must link closely with TB clinics and provide support for adherence to TB treatment, as well as support family members, including children, in being tested and treated for TB. Many palliative care providers assist with TB treatment through directly observed therapy short course (DOTS) support and through community caregivers who are trained in how to refer and support TB testing and treatment.

**Role of Palliative Care in HIV Prevention**

All palliative care programs must recognize the primary importance of prevention in their work with people living with HIV and their families. Strong relationships between caregivers (family members and/or health workers), people living with HIV, and their families are an important opportunity for sharing prevention messages and providing counseling, often during times when these services are most needed.

Family caregivers should be offered guidance on how to reduce the risk of infection in the home (universal precautions). For people living with HIV and their spouses or partners (regardless of their HIV status), education on reducing the risk of infection or reinfection should be offered, as well as information on the reduction of mother-to-child transmission through PMTCT programs and family planning. Needle and syringe exchange programs should be promoted for known or suspected injecting drug users. For youth, involvement with prevention programs targeted specifically to their age group, if available, should be encouraged.

**PALLIATIVE CARE AND SPECIAL POPULATIONS**

**Injecting Drug Users**

Palliative care services are oriented differently according to the needs of the population they serve. In regions or settings where the majority of people living with HIV are injecting drug users, addiction and addiction treatment must be linked and/or integrated with palliative care services. Specialized training and sensitization of health-care workers is needed so that they can better understand issues specific to injecting drug users living with HIV, such as hypersensitivity to pain, how to manage pain for injecting drug users on opioid substitution therapy (e.g., methadone), and fear related to further addiction and medicine diversion. Despite these additional considerations, substance users should receive the same level of palliative care, including pain control, as all other clients.

**Care in Closed Settings**

Care for populations living in closed settings, such as prisons, rehabilitation centers, and refugee camps, will also require special consideration. Since HIV care services may not always be available in closed settings, it is important that, where possible, palliative care programs forge partnerships with the staff or administration to build access to palliative care services. They can also support the families of prisoners and help them communicate with
their loved ones. In some cases, it may be possible for the care provider to help negotiate a compassionate release, especially if the person is extremely ill and/or requires specialized care. Care providers can also help facilitate individuals’ reintegration into the community after their release or return to their home.

Other special populations, including sex workers, men who have sex with men (MSM), and migrants, may have a number of specific support needs that should be explored and adopted by palliative care programs serving these populations.

**TRAINING AND TEAMWORK IN PALLIATIVE CARE**

**Interdisciplinary Teams**

Palliative care is patient-focused, helping people living with HIV to address their needs at any given point in time. As such, a diversity of providers is needed since very few individuals will be able to wear the many required “hats” at a level of effectiveness that ensures quality care and support.

Palliative care employs an interdisciplinary form of teamwork. The care team consists of professionals representing different disciplines, as well as lay caregivers and support workers who bring in other expertise, viewpoints, and approaches. It may not always be possible to have representatives of all relevant disciplines on a care team, but it is important to create strong linkages with people who can provide input from a variety of disciplines or backgrounds. For example, if a pharmacist is not able to be a regular team member, a nurse may be able to identify issues that require input from the pharmacist and seek consultation for a particular team concern. The possible members of an interdisciplinary team are as follows:

- Nurse
- Medical doctor, clinical officer
- Community- or home-based caregiver
- Pharmacist
- Person living with HIV, peer, “expert patient”
- Social worker, case manager
- Counselor
- Spiritual counselor (priest, monk, imam, etc.)
- Nutritionist
- Traditional healer
- Physiotherapist
- Vocational counselor
- Substance use counselor

Palliative care is offered through a diverse range of services, so where the team is based and who the team is composed of is dependent on this factor. The team can be part of a district HIV outpatient clinic, a community health center, a community-based nongovernmental organization (NGO), or a tertiary hospital.

**Patient and Family Caregivers in a Leadership Role**

The patient and family caregivers are part of the care team. Patients are supported as they learn about every aspect of care, diagnosis, and treatment so they are able to make decisions, prioritize resources, and be involved as much as possible throughout the course of their care. When a patient is not able to make decisions, the family caregiver or caregivers must have enough information to make “good” decisions for the patient in line with the family’s values, culture, and traditions. In situations in which children are the caregivers, the palliative care team must offer as much support as possible, including age-appropriate education about care, prevention of infection, and emotional and spiritual support.

**Preparing and Supporting Interdisciplinary Palliative Care Teams**

Teamwork requires team building and clear roles and responsibilities. It is important that the team meet regularly, have the requisite skills and
training, and agree on a consistent approach to care. While access to formal training (e.g., a palliative care curriculum offered by a medical school) may be limited in resource-limited settings, training should be encouraged and advocated for as much as possible. Palliative care training and information are the basis for quality care, and the continuum of care relies on the depth of knowledge within the care team. All members of the team, whether formally trained or not, must have a basic understanding of the principles and practices of palliative care before working with clients and their families.

Training
Many organizations, regardless of their size, are capable of providing palliative care training. However, it is important that the information provided is in accordance with national guidelines and that the curriculum is developed with the assistance of experienced palliative care professionals. Training and certification should involve, if possible, a national program authorized to certify palliative care providers. A vast international network of palliative care organizations is able to support comprehensive and appropriate palliative care training. As much as possible, the training should include hands-on experience and mentoring in addition to didactic (classroom) learning.

Skill Sets
In 1998, WHO recommended a core training curriculum in palliative care for all levels of care that has been used and adapted worldwide. The following are key subject areas for training, based on these recommendations:

- Philosophy of palliative care
- Ethics and human rights
- The continuum of care
- Interdisciplinary teamwork
- The family as the unit of care
- Personal attitudes toward HIV, pain, dying, death, and bereavement
- Illness as a complex state with physical, psychological, social, and spiritual dimensions
- Communication
- Common symptoms and changes associated with disease
- Assessment and management of pain
- Assessment and management of symptoms
- Assessment and management of psychological problems
- HIV and ART
- Human sexuality and family planning
- Nutrition
- Drug and alcohol use
- Care of the caregivers
- Appropriate care of children and adolescents
- Spiritual support
- Future planning
- Social support
- Standard precautions
- Referral system and community resources
- Counseling / emotional support
- Death and dying
- Grief and bereavement
- Goal setting in physical, psychological, social, and spiritual dimensions
- Development of a family care plan
- Monitoring of pain and symptom management
- Monitoring and evaluation
- Teaching caring skills to others
- Reporting

Supportive Supervision
Training is an ongoing process and should be a regular part of supervision and team meetings. When much of the care is provided by trained community caregivers, routine supervision should be provided by a nurse or other health professional.

The interdisciplinary team should meet at least once a week to focus on the following areas:
Basic principles for care of the carer include the following:

- Realistic expectations
- Clear roles and responsibilities
- Regular supervision and emotional support
- Manageable workloads
- Skills and information to ensure competency
- Time off or respite
- Incentives and recognition
- Support for personal and interpersonal problems
- Support in dealing with fears and feelings of powerlessness
- Personal health and wellness
- Promotion of self-care by the client and family

Mentorship

Mentorship is an important way to build capacity within the care team to provide quality palliative care services. Mentoring can occur at both the individual and organizational levels. Mentorship involves guidance, support, leadership, supervision, advocacy, and training. The mentoring process should be a voluntary learning relationship between the parties that is of mutual benefit. Care providers and organizations new to palliative care should be encouraged to establish mentoring relationships with experts through national associations, if available, or through international palliative care organizations.

Care of the Carer

Because of the intense nature of palliative care, supervisors should look after the emotional, social, spiritual, and physical well-being of all team members. Stress and the accompanying burnout must be watched for and managed. Palliative care organizations must ensure that all members of the care team have access to the resources required to carry out their work (e.g., supplies for care and transportation for site visits and meetings). Similarly, conditions that can accelerate worker burnout, such as understaffing and a high demand for services, should be managed and addressed.

THE ROLE OF FAMILY IN PALLIATIVE CARE

The patient and family (as defined by the patient) is the primary unit of care. Because of the holistic nature of palliative care, all aspects of a person’s life must be considered. The family represents the main relationships that can support or hinder good care in the home. In resource-limited settings, as in most settings, the well-being of family members depends, to large extent, on the patient’s quality of life. Children are often required to provide care for their ill parents, and the worry and stress of facing a life-threatening illness is a shared concern.

When family-centered care is implemented within the continuum of care, it can save the lives of both parents and their children. It establishes a system of care in which family members are included in care assessments and in which their needs are identified and acted upon in a timely manner (e.g., referring a client’s sick child who has not yet been tested for HIV).

PALLIATIVE CARE FOR ADULTS

Establishing a standard of palliative care is essential to ensure a basis for quality care. Guidelines
and standard operating procedures (SOPs) for palliative care should be available at a national level. If these are not available, WHO, as well as many countries and organizations, has developed quality guidelines and SOPs that can be adapted for use in other settings. The following is a summary of the process of providing palliative care.

The Process of Providing Palliative Care

**Assessment**
A palliative care assessment (Box 2) addresses the physical, emotional, social, and spiritual needs of the patient and family. It is useful to think of the assessment as focusing on three areas: the illness (physical), the whole person (emotional and spiritual), and the situation and/or environment (social), including how the illness is affecting the other members of the family.

The assessment includes a thorough history to identify past and presenting illness and symptoms. Pain and other symptoms are routinely assessed, and severity of pain is measured using a pain scale. A nutritional assessment is also important, particularly in settings where food may be scarce.

Clinical depression, anxiety, dementia, and generalized anxiety disorder (GAD), as well as other neurological and mental health problems, are very common in people living with HIV but are often overlooked. Conditions can change dramatically over time and should be routinely assessed.

Assessment of ART treatment adherence, as well as adherence to other treatments, is another important part of the assessment. If a person is about to be started on ART, a holistic ART readiness assessment should be conducted, with particular attention given to the supportive environment in the home, community, and workplace. Assistance with disclosure to significant others is a step toward treatment readiness and is an important role for the palliative care provider or referred resource persons.

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Box 2. Initial Palliative Care Assessment of People Living with HIV

<table>
<thead>
<tr>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present illnesses and treatments</td>
</tr>
<tr>
<td>Past medical history, including all comorbidities (e.g., TB), HIV-related complications, other major illnesses, hospitalizations, surgeries, and date of HIV diagnosis</td>
</tr>
<tr>
<td>Medication history (including past history of ART exposure)</td>
</tr>
<tr>
<td>Drug allergies</td>
</tr>
<tr>
<td>Substance use and dependence history, including treatment</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Social history</td>
</tr>
<tr>
<td>Social resources</td>
</tr>
<tr>
<td>Spiritual support</td>
</tr>
<tr>
<td>Financial issues</td>
</tr>
<tr>
<td>Nutrition</td>
</tr>
<tr>
<td>Current symptoms (pain, weight loss, anorexia, fatigue, lack of energy or weakness, fevers, night sweats, insomnia, sadness, anxiety, dyspnea, cough, nausea/vomiting, diarrhea, etc.)</td>
</tr>
</tbody>
</table>

| Chronology of symptoms |
| Exacerbating and relieving factors |
| Current medications or other treatment for symptoms |
| Cause, type, and grade of pain |
| Symptom cause, type, and characteristics |
| Impact |
| of symptoms on functional capabilities |
| of symptoms on each other |
| of specific therapies on each symptom |
| of symptoms on patient’s quality of life |
| Mental health history and treatment (e.g., depression, anxiety disorder, delirium, psychosis) and any current mental health problems |

<table>
<thead>
<tr>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full clinical examination</td>
</tr>
<tr>
<td>Systems review, including:</td>
</tr>
<tr>
<td>constitutional (fatigue, anorexia, fevers, weight loss)</td>
</tr>
<tr>
<td>neurological</td>
</tr>
<tr>
<td>mental status</td>
</tr>
<tr>
<td>dermatological</td>
</tr>
</tbody>
</table>

| Other examinations and investigations as required |

| Assessment including differential diagnosis |

| Development of care plan |
In addition, the psychosocial needs of the patient are reviewed and actions for how to address these needs are included in the care plan.

Care Plans
Care plans help address the care needs identified during the assessment. Care plans are developed either by the interdisciplinary care team (ICT) or by a health-care worker who may receive input from the ICT. Care plans are always developed with the patient’s input and recognize the priorities and preferences of the patient and family. In addition to the steps to be taken, the care plan will also define who is responsible for each step, including family caregivers. The plan includes mention of any problems identified during the assessment process and any important physical, emotional, social, and spiritual issues.

Referrals
A strong referral system is essential to the success of a palliative care program. Primary palliative care providers, including home-based care teams, HIV outpatient clinics, or hospices, will need to initiate and support a strong referral system that includes referral forms, focal people, a feedback system, a resource directory, and a referral network. Links with essential supportive services should be formalized and maintained with the help of supervisory staff. Designated palliative care staff should serve as members of the local referral committee, or, if one is not available, a referral network committee should be developed. This will help promote stronger, more effective relationships with referral agencies and partners.

Client confidentiality must be maintained for all referrals. While services such as home-based care and social services are important and helpful to people living with HIV and their families, these services must only be provided with the explicit consent of the patient and/or affected family members.

At a minimum, referral relationships should be established with the following:
- HIV outpatient clinics
- Interhealthcare facility services (e.g., inpatient departments, tuberculosis inpatient department [TB-ID], maternal and child health [MCH] / antenatal clinic [ANC], sexually transmitted infections [STIs], pediatrics, lab, radiology, RH/FP, and other relevant services)
- Tertiary general and specialty hospitals (e.g., infectious diseases, MCH, TB, cancer)
- Support groups for people living with HIV
- Home-based care teams
- Hospice (if any)
- Faith-based organizations (FBOs)
- Social welfare agencies
- Child care and protection organizations

In addition, referral relationships should be pursued with the following:
- Economic support / employment services (e.g., skills training, job placement, microfinance)
- Substance use–related services (e.g., needle and syringe exchange/distribution, 12-step programs, opioid substitution therapy)
- Legal aid
- Transportation assistance

Essential Palliative Care Medicines
In order to provide a minimum quality of palliative care, essential palliative care medicines must be available. At the request of WHO, the International Association for Hospice and Palliative Care (IAHPC) recently updated the essential palliative list to address the most prevalent symptoms of cancer and HIV. This list, which includes 33 medicines, can be accessed through the IAHPC Web site.42
Pain Management
The goal of pain management is freedom from pain and prevention of the recurrence of pain. Successful pain management is achieved when the patient feels no more pain, is comfortable, and is able to carry out the normal activities of his or her daily life. At the end of life, pain relief allows the patient to die in peace. Palliative care respects and recognizes the patient’s assessment of his or her own pain, based on the belief that “pain is what the patient says it is.”

All patients should be assessed for pain during each clinic visit (Box 3). Pain is very common in people living with HIV and can result in extreme suffering, but it is often overlooked because clinicians do not ask about it. The onset of pain cannot be predicted. If a patient presents without pain on previous visits, this does not mean he or she will be without pain at the subsequent visit. All patients who are suffering from pain must be treated to relieve their pain and improve their quality of life, regardless of the stage of their illness. Depression, anxiety, fear, or stress can exacerbate the pain experienced by people living with HIV. Pain management must always pay attention to psychological, social, and spiritual issues, in addition to the physical.

Care providers in community- and home-based care teams, outpatient clinics, and hospital
Certain analgesics and opioids (e.g., codeine and morphine), in particular, may be difficult to access in district health-care settings either because of Ministry of Health regulations restricting access or lack of supply due to infrequent assessment of pain in the health-care setting. The role of the prescribing clinician is to work within analgesic prescription regulations while actively ensuring that all legal medicines for pain treatment are available in the hospital, clinic, or home setting.

Emotional Care
An essential component of palliative care is assessing and attending to mental health needs among patients and families. HIV care providers working in home-based care and in- and outpatient care services can be trained in basic mental health
assessment and care provision, including how to make appropriate referrals to specialty services. Support can also be provided by family members, neighbors, friends, or other people living with HIV. Support groups for people living with HIV are a critical resource that helps the patient and family members respond to problems causing distress and suffering.

**Spiritual Care**

Spirituality is defined as a belief that provides individuals with a sense of meaning and importance in their lives. Life-limiting illness often brings up painful questions associated with facing death, losing faith, or reconnecting with one’s belief and/or support system. An important aspect of spiritual care is assuring the patient and family that their spiritual beliefs and traditions will be honored, especially at the time of death and during funeral arrangements. Developing a relationship that allows for open communication is a basic tenet of palliative care and enables important conversations about spiritual issues to take place.

**Social Support and Referrals**

Many people living with HIV and their families struggle with inadequate financial resources, especially when the breadwinner has been ill for some time and then dies. They may be without enough food to eat; face stigma, discrimination, and isolation; or be unable to work. An essential part of coping is making plans for the future in an attempt to address these challenges. Palliative care providers should assist patients and families in preparing future plans that address more immediate survival needs, and in preparing wills and other legal arrangements, deciding how to say good-bye to friends and family, appointing a guardian for children, and determining end-of-life care arrangements.

It is also important for palliative care programs to establish linkages with social service providers, such as the following:

- Legal services to assist with succession planning, inheritance rights, and legal documentation (such as a living will or power of attorney)
- Government grants, housing, or health-care agencies

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**Figure 4. Three-step analgesic ladder for treating pain**

Source: WHO.
Table 1 presents a general prognostic time frame for approaching the end of life, describing typical patient features and interventions that may be helpful during this time.

Grief and Bereavement
Bereavement support is required as the patient and family pass through the various stages of disease progression. People experiencing anticipatory grief (i.e., knowing that loss is imminent) require emotional support prior to a loved one’s death. Bereavement does not occur over a set period of time or according to a certain course, but varies greatly from one individual to the next, even despite similar circumstances. Bereavement support should be individualized and culturally sensitive. Support for children is just as important as support to a surviving spouse or adult member of the family.
HIV brings with it many levels of complication related to grief and bereavement. For example, HIV is largely associated with sexual transmission. In many cultures and communities, sex is a taboo subject. HIV and death is another potentially controversial subject. Stigma in any form can seriously compound the grief associated with HIV by preventing people from being open about what has happened. As a result, they are unable to talk to others and can miss out on this vital source of support.

When a family is affected by HIV, people are often experiencing multiple losses. In some cases, both parents and one or more members of the extended family (brothers, sisters, aunts, uncles) are living with HIV. Multiple losses are not only

Table 1. Clinical Care Issues in End-of-Life Care

<table>
<thead>
<tr>
<th>Type of Manifestation</th>
<th>Last Months</th>
<th>Last Weeks</th>
<th>Last Days</th>
<th>Last 24–28 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased fatigue</td>
<td>More time in bed</td>
<td>Incontinence</td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td>Increased sleep</td>
<td>Insomnia</td>
<td>Sleep pattern reversal</td>
<td>Restlessness</td>
</tr>
<tr>
<td></td>
<td>Decreased interest in eating</td>
<td>Less interest in food and drink</td>
<td>Sweats</td>
<td>Agitation</td>
</tr>
<tr>
<td></td>
<td>Increase in pain or other symptoms</td>
<td>Decreased energy</td>
<td>Confusion</td>
<td>Gradual or sudden loss of consciousness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficulty walking</td>
<td>Cognitive failure</td>
<td>Further changes in skin color</td>
</tr>
<tr>
<td>Emotional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased need for closeness, talking, physical contact</td>
<td>Desire to talk about funeral arrangements</td>
<td>Greater peacefulness, quiet</td>
<td>May be unresponsive or minimally responsive</td>
</tr>
<tr>
<td></td>
<td>Social withdrawal</td>
<td>Periods of intense emotional expression</td>
<td>Increased communication</td>
<td>Confusion, delirium, inability to express emotions clearly</td>
</tr>
<tr>
<td></td>
<td>Increased sadness, crying</td>
<td>Bargaining</td>
<td>Signs of closure/saying good-bye</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seeking closure, expressing feelings of love</td>
<td>Life review, discussion of past events</td>
<td>Increased anxiety</td>
<td></td>
</tr>
<tr>
<td>Spiritual</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased interest in spiritual matters</td>
<td>Dreams or visions of deceased loved ones</td>
<td>Increased clarity in thinking and emotions</td>
<td>Perception of other dimensions of experience</td>
</tr>
<tr>
<td></td>
<td>Prayer</td>
<td>Increased faith in God</td>
<td>Increased sense of peace and transcendence</td>
<td>Increased sense of peace</td>
</tr>
<tr>
<td></td>
<td>Desire for contact with religious/spiritual leader</td>
<td>Periods of quiet reflection</td>
<td></td>
<td>Deep, peaceful sleep</td>
</tr>
<tr>
<td></td>
<td>Questioning of faith</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
difficult because of the amount of grief but also because of the frequency of occurrence; one death may come right on the heels of another, leaving little or no time to complete the bereavement process before losing another loved one. This creates a very heavy psychological burden and can lead to unresolved grief.

Surviving family members need to be encouraged to take care of their health, as grief can take a heavy physical and emotional toll. With HIV, disclosure of one’s HIV-positive status prior to death is helpful, so that appropriate emotional and physical support can be provided to surviving family members. Other known or potentially HIV-positive family members should be monitored and encouraged to receive appropriate medical attention or testing.

PALLIATIVE CARE FOR CHILDREN AND ADOLESCENTS

Parents
Parents and caregivers need to receive support when a child is ill. Parents will vary in their level of ability to cope with their child’s illness or death. Parents should be allowed to cope in their own way and be offered clear information about their child’s illness and what they can do to help. It is also important to provide support to other family members, including siblings, grandparents, aunts, and uncles. Often parents may be ill at the same time as their children. This creates many layers of stress, and the palliative care program helps support the parent and child together through a family-centered approach.

Children
Children require special consideration in the provision of palliative care. Providing comprehensive palliative care for a child must include care for the mother or primary caretaker as well as for other members of the family, as the child is dependent on the support of the family for survival.

Children are unique; they do not have the communication skills of adults and express much of their suffering through action or inaction (e.g., silence, refusing to eat, or crying). Children require different clinical interventions appropriate to their stage of development. Nutrition is a vital component of healthy growth, and safe infant feeding must be promoted to ensure HIV prevention. Table 2 provides brief guidelines for the different stages and reactions of children and adolescents to illness. Children may regress developmentally as a result of illness. Because children will experience different aspects of the health system, their care must be given within a continuum of care, with strong linkages between different providers (e.g., PMTCT, ART, MCH, outpatient clinics, immunization, nutrition).

Adolescents
Adolescents with HIV are a diverse population. Some may have been infected from birth, while others may have acquired HIV through sexual abuse, their own sexual activity, blood transfusions, or drug use. For the HIV-infected adolescent, the family or caregiver must help make a plan to discuss disclosure of the individual’s HIV status. Clear information about HIV must be provided so that the adolescent is able to make informed decisions about his or her health and other important areas of life.

Adolescents in need of palliative care are assessed in a similar manner to adults, but with involvement of their parents or guardians and consideration of their stage of development and maturity level. Maturity levels vary enormously, and emotional, mental, social, and spiritual needs may be very complex. Referrals for social, spiritual, and psychological support should direct young patients
toward services particularly targeting youth, when available.

Adolescence is a time of rapid change and development. The care plan for adolescents will need to be reassessed frequently in order to stay relevant. Many adolescents are also parents and will need information about caring for their children.

Clinical Care

Adolescents
Palliative care for adolescents is the same as for adults, including the management of pain and other symptoms, with the important exception that weight changes must be monitored to adjust dosing of medicines as needed. As noted above, the adolescents must be respected and included in the decisions affecting their health and general well-being.

Children
It is important to diagnose children with HIV as soon as possible. Comprehensive care and treatment for HIV-positive children must be delivered in a timely manner, as the disease progresses much more rapidly in children than in adults. Care and support must be in line with their developmental stages, which will also determine their ability to cope with illness, as outlined in Table 2.

Symptom Management
Children and adolescents living with HIV/AIDS can suffer from a number of preventable and/or treatable symptoms. Certain symptoms are more common in children, including skin disorders, mouth sores, and convulsions. Table 3 addresses some common symptoms.

Pain Management
Pain is often not diagnosed or is underdiagnosed in children because of communication gaps between adults and children, fears about giving children medications (e.g., potential side effects, overdose, addiction), and denial. In addition to taking medication, children who are in pain can be helped by being comforted through the company of others.

The principles of pain management for children follow the WHO analgesic ladder, as in pain management for adults. Aspirin should generally be avoided in children.

To assess pain in a child, it is useful to
- ask the parents or caregivers what signs or symptoms they have noticed;
- ask the child, if he or she is old enough, to show where it hurts and describe the pain and what makes it better or worse;
- ask the child to draw a picture of the pain or use a faces scale (i.e., smiling, frowning, crying); and
- observe the child and note irritability; crying; wincing; changes in mood, sleep pattern, or appetite; or lack of interest.

Emotional Care
Depending on their developmental stage, children may need much more comfort and nurturing than adults, as they have much less life experience and emotional maturity with which to cope with difficult situations. Older children and adolescents who are already dealing with issues of self-image and self-esteem will find it harder to cope with the additional burden and stigma that HIV presents.

Openness with children relieves their fears, as they often make irrational links between their actions and illness. Answering their questions, giving age-appropriate information, and offering help in a nonjudgmental manner will allow them to ask questions and express feelings that they may find difficult to verbalize. For children of all ages, nonverbal means of expressing feelings through play or the creation of art can be very helpful.
<table>
<thead>
<tr>
<th>Developmental Task</th>
<th>Infant</th>
<th>Toddler</th>
<th>Preschooler</th>
<th>School-Age Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achievement of awareness of being separate from significant others</td>
<td>Initiation of autonomy</td>
<td>Creation of a sense of initiative</td>
<td>Development of a sense of industry</td>
<td>Achievement of a sense of identity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impact of Illness</th>
<th>Infant</th>
<th>Toddler</th>
<th>Preschooler</th>
<th>School-Age Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential distortion of differentiation of self from parent or significant others</td>
<td>Interference with or loss of developing sense of control, independence</td>
<td>Interference with or loss of accomplishments such as walking, talking, controlling basic bodily functions</td>
<td>Potential feelings of inadequacy or inferiority if autonomy and independence are compromised</td>
<td>Potential alteration or relinquishment of newly acquired roles and responsibilities</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive Age/Stage</th>
<th>Infant</th>
<th>Toddler</th>
<th>Preschooler</th>
<th>School-Age Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensorimotor (birth through 2 years)</td>
<td>Preoperational thought (2–7 years): Egocentric Magical Little concept of body integrity</td>
<td>Preoperational thought: Egocentric Magical Tendency to use and repeat words they don’t understand, providing own explanations and definitions Literal translation of words Inability to abstract</td>
<td>Concrete operational thought (7–10+ years); beginning of local thought but tendency to be literal</td>
<td>Formal operational thought (11+ years): Beginning of ability to think abstractly Existence of some magical thinking (e.g., feeling guilty for illness) and egocentrism</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Fears</th>
<th>Infant</th>
<th>Toddler</th>
<th>Preschooler</th>
<th>School-Age Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separation</td>
<td>Separation</td>
<td>Bodily injury and mutilation Loss of control</td>
<td>Loss of control Bodily injury and mutilation Failure to live up to expectations of important others</td>
<td>Loss of control Altered body image Separation from peer group</td>
<td></td>
</tr>
<tr>
<td>Strangers</td>
<td>Loss of control</td>
<td>The unknown “The dark” Being left alone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. The Illness Experience for Children and Adolescents**
Table 2. The Illness Experience for Children and Adolescents (continued)

<table>
<thead>
<tr>
<th>Concept of Illness</th>
<th>Infant</th>
<th>Toddler</th>
<th>Preschooler</th>
<th>School-Age Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenomenism (2–7 years):</td>
<td>N/A</td>
<td>Phenomenism</td>
<td>Phenomenism: Contagion</td>
<td>Contamination:</td>
<td>Physiologic:</td>
</tr>
<tr>
<td>■ Perceives external, unrelated, concrete phenomena as cause of illness, e.g., “being sick because you don’t feel well”</td>
<td></td>
<td>■ Contagion</td>
<td></td>
<td>■ Perceives cause as a person, object, or action external to the child that is “bad” or “harmful” to the body, e.g., “getting a cold because you didn’t wear a hat”</td>
<td></td>
</tr>
<tr>
<td>■ Contagion</td>
<td></td>
<td></td>
<td></td>
<td>Internalization:</td>
<td></td>
</tr>
<tr>
<td>■ Perceives cause of illness as proximity between two events that occurs for “magic,” e.g., “getting a cold because you are near someone who has a cold”</td>
<td></td>
<td></td>
<td></td>
<td>■ Perceives illness as having an external cause but being located inside the body, e.g., “getting a cold by breathing in air and bacteria”</td>
<td></td>
</tr>
</tbody>
</table>

| Interventions | ■ Provide consistent caretakers | ■ Minimize separation from parents or significant others | ■ Provide simple, concrete explanations | ■ Provide choices whenever possible to increase the child’s sense of control | ■ Allow adolescent to be an integral part of decision making regarding care |
| | ■ Minimize separation from parents or significant others | ■ Keep security objects at hand | ■ Advance preparation is important: days for major events, hours for minor events | ■ Stress contact with peer group | ■ Give information sensitively, since this age group reacts to the content of information as well as the manner in which it is delivered |
| | ■ Decrease parental anxiety, which is projected onto infant | ■ Provide simple, brief explanations | ■ Verbal explanations are usually insufficient, so use pictures, models, actual equipment, and medical play | ■ Use diagrams, pictures, and models for explanations because thinking is concrete | ■ Allow as many choices and as much control as possible |
| | ■ Maintain crib or bed as “safe place” in which no invasive procedures are performed | ■ Explain and maintain consistent limits | ■ Encourage participation in daily care, etc. | ■ Emphasize the “normal” things the child can do, because the child does not want to be seen as different | ■ Be honest about treatment and consequences |
| | | ■ Provide opportunities for play and play therapy | | ■ Reassure the child that he or she has done nothing wrong and hospitalization, etc., is not “punishment” | ■ Stress what the adolescent can do for himself or herself and the importance of cooperation and compliance |
| | | | | Allow adolescent to be in maintaining contact with peer group | | ■ Assist in maintaining contact with peer group |

Source: Data obtained from Bibace and Walsh and Armstrong-Dailey and Zarbock.
Social Support and referrals

Schools

Schools are an important institution in most communities and can play a pivotal role in supporting palliative care interventions with children and their families. Many children are given the daunting task of becoming carers for their ill parents. Other children may be HIV-positive and on ART and/or dealing with their own health problems. For children of school age, school and friends are an important social support system. If teachers and pupils can become aware of how to support bereaved children,
children whose parents are ill, and/or children who are HIV-positive, it will make a very positive difference to those children and their families. Simple information about the issues they face and the reactions or behavior that such children may exhibit can give teachers and heads of schools an understanding that could curtail further problems.

Referrals
Referrals to appropriate providers, especially social welfare services, provide necessary support for children and their families. Children who have been orphaned and are in the care of an elderly relative are particularly vulnerable, as are children who are left to fend for themselves. Orphan-headed households should always be referred for social support from government and nongovernment providers.

End-of-Life Care
What Parents and Others Are Likely to Feel When a Child Is Dying
Giving parents information about HIV helps them understand and face the reality of their child’s situation. Knowing what to expect as the disease progresses and knowing what they can do to help will ease, but not eliminate, their stress. Parents or caregivers may have fears about how the illness will develop and about how their child will die. It is important to help every person in the family talk about his or her experience. This will help each individual identify what help is needed. Of course, alleviation of the child’s suffering through palliative care, particularly through pain and symptom management, is vital in reducing the parents’ level of stress.

Parents of HIV-positive children need a great deal of support, especially because they often feel that a child’s illness is their fault. These feelings of guilt can be especially difficult for the mother, who may feel responsible for passing the virus to the child at birth. This is where it is vital to provide counseling and support throughout the continuum of care for mother and child through counseling and testing, ANC, PMTCT, MCH, and ART.

What a Dying Child Is Likely to Feel
Children will have different feelings about dying, depending on how old they are, how much they understand about death, and how much they have been told. It is helpful to talk with children about dying and what to expect so they do not feel alone and become frightened or confused.

Very young children will not be able to say how they feel, but they may be unsettled and insecure, sleeping badly, and not wanting to be left alone. An older child may have fears about the illness and what is happening to his or her body. Leading a normal childhood during this time can be difficult. Teenagers can feel bitter and angry when they realize that they will not have time to accomplish their goals. Sometimes they may take chances with their lives, as though they are trying to “control” death. For instance, they may refuse to take medicines or eat healthy food.

Angry children need help to put their feelings into words. Anger may be felt toward a parent who passed on the virus, toward someone who abused them sexually, or toward God. Because there is often stigma about HIV/AIDS, a child may feel guilty and ashamed about the illness. Palliative care providers need to be sensitive to these issues and provide appropriate information and emotional support. Allowing for the expression of feelings and answering questions should be supported by open communication between parents, caregivers, and the child.

Grief and Bereavement
Children will pass through all the stages that adults encounter as part of the bereavement process, but the expression and depth of their grief will vary greatly depending on their developmental stage.
<table>
<thead>
<tr>
<th>Age</th>
<th>Thoughts</th>
<th>Feelings</th>
<th>Actions</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 years</td>
<td>■ Loved one will return; loved one is just away</td>
<td>■ Confused</td>
<td>■ Cry</td>
<td>■ Hold the child</td>
</tr>
<tr>
<td></td>
<td>■ Anxious</td>
<td>■ Anxious</td>
<td>■ Cling</td>
<td>■ Reassure calmly</td>
</tr>
<tr>
<td></td>
<td>■ Fearful</td>
<td>■ Fearful</td>
<td>■ Exhibit regressive behavior</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Separation anxiety</td>
<td>■ Separation anxiety</td>
<td>■Nightmares</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Sad</td>
<td>■ Sad</td>
<td>■ Regress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Angry</td>
<td>■ Angry</td>
<td>■ Cling</td>
<td></td>
</tr>
<tr>
<td>3–5 years</td>
<td>■ Wonder if loved one can return</td>
<td>■ Confused</td>
<td>■ Cry</td>
<td>■ Provide extra attention</td>
</tr>
<tr>
<td></td>
<td>■ Believe deceased can still function</td>
<td>■ Anxious</td>
<td>■ Temper tantrum</td>
<td>■ Reassure calmly</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Fearful</td>
<td>■ Nightmares</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Fearful they might die too</td>
<td>■ Separation anxiety</td>
<td>■ Regress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Sad or angry</td>
<td>■ Sad or angry</td>
<td>■ Cling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Confused</td>
<td>■ Confused</td>
<td>■ Difficulty in concentrating</td>
<td></td>
</tr>
<tr>
<td>6–9 years</td>
<td>■ Understand finality and irreversibility of death</td>
<td>■ Confused</td>
<td>■ Cry</td>
<td>■ Provide extra attention</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Confused</td>
<td>■ Temper tantrum</td>
<td>■ Tell the truth appropriately</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Anxious</td>
<td>■ Nightmares</td>
<td>■ Reassure (not responsible for death)</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Separation anxiety</td>
<td>■ Regress</td>
<td>■ Encourage physical or artistic expression of grief</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Sad or angry</td>
<td>■ Cling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Fearful they might die too</td>
<td>■ Fearful</td>
<td>■ Difficulty in concentrating</td>
<td></td>
</tr>
<tr>
<td>9–12 years</td>
<td>■ Understand finality, irreversibility, nonfunctionality of death</td>
<td>■ Sad</td>
<td>■ Exhibit aggressive or impulsive behavior</td>
<td>■ Provide extra attention</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Confused</td>
<td>■ Engage in risky or dangerous behavior</td>
<td>■ Tell the truth appropriately</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Anxious</td>
<td>■ Obtain worse grades at school</td>
<td>■ Reassure (not responsible for death)</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Withdrawn</td>
<td>■ Have difficulty concentrating</td>
<td>■ Encourage physical or artistic expression of grief</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Lonely</td>
<td>■ Maintain structure, limits, and rules</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Guilty</td>
<td>■ Seek community and school support</td>
<td></td>
</tr>
<tr>
<td>12–18 years</td>
<td>■ Understand finality, irreversibility, nonfunctionality of death</td>
<td>■ Sad</td>
<td>■ Exhibit aggressive or impulsive behavior</td>
<td>■ Maintain structure, limits, and rules</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Confused</td>
<td>■ Engage in risky or dangerous behavior</td>
<td>■ Encourage physical or artistic expressions of grief</td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Anxious</td>
<td>■ Obtain worse grades at school</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Believe their actions or words caused the death</td>
<td>■ Withdrawn</td>
<td>■ Have difficulty concentrating</td>
<td></td>
</tr>
</tbody>
</table>

Source: Reder.50
Palliative care providers must be aware of these important developmental differences (see Table 4).

It is important to encourage all children to express their grief and to include them in family rituals. Death will bring up fears and insecurities, and children may seek reassurance and support from family members, peers, teachers, and other children. Other relatives may need to step in to help the grieving child, as the parents may be too overwhelmed with their own grief.

Support for Children of Ill Parents and Siblings
All children facing serious illness in their family need information, reassurance, and opportunities to express their feelings. This information must be appropriate for each child’s level of understanding. It is important to not leave children out, as they are able to cope once they have an understanding of what is happening. The information does not need to be given all at once but it must be given before a parent dies. Reassurance in the form of acknowledgment that they will be taken care of is comforting. However, giving false assurances that their parent or sibling will not die sets them up for more acute feelings of loss and distrust. Many brief conversations between the child and a person with whom he or she has a close relationship will give the child the chance to ask questions, share feelings, and take in information. With information, reassurances, and sharing, the child can develop his or her own way of coping. If at all possible, children should be included in decisions about their future, such as who will care for them, and so on.

DESIGN OF LOCAL PALLIATIVE CARE PROGRAMS AND ADVOCACY FOR A NATIONAL PALLIATIVE CARE RESPONSE
This section describes local-level models of care and the essential components of a national-level palliative care program, which needs to be in place to enable access to palliative care on a broad and sustained basis.

Models of Palliative Care
A range of palliative care models are available in resource-limited countries, but the best systems of care are often found where the public health-care system has integrated palliative care throughout some or all levels of care—tertiary, secondary, primary, and community—and where NGOs, support groups for people living with HIV, FBOS, and communities are working together to complement these services.

No matter what model is implemented in a particular setting, the comprehensive nature of palliative care (see Figure 5) requires that there be a continuum-of-care network in place in the locality that links services together, adding up to a comprehensive package of services.

The following section describes four common models of local palliative care service delivery.

Community-Initiated Model
In the community-initiated model, the community identifies a need for palliative care and organizes services and care for people living with HIV in that locality. The catalyst for starting services can be support groups for people living with HIV, local religious leaders, or families of patients. There are usually no or few paid providers, and funds to provide palliative care come directly from the community. However, giving false assurances that their parent or sibling will not die sets them up for more acute feelings of loss and distrust. Many brief conversations between the child and a person with whom he or she has a close relationship will give the child the chance to ask questions, share feelings, and take in information. With information, reassurances, and sharing, the child can develop his or her own way of coping. If at all possible, children should be included in decisions about their future, such as who will care for them, and so on.
patients receive all the essential services they need. An example of this model is the Neighbourhood Network in Palliative Care (NNPC) in Kerala, India, where the community donates most of the funds for home-based palliative care and the government recently has begun contributing a small amount to this successful program.52

NGO/FBO-Led Model
In the NGO/FBO-led model, an NGO or FBO is responsible for the continuum of care for patients and their families. The coverage of these services may be broader than that of community-driven models. Services, which can include outpatient care, drop-in centers, respite for caregivers, and home-based care, are generally provided by a team that consists of health-care workers, a social worker, people living with HIV, a project coordinator, and volunteers or community caregivers who are based at and supported by the organization. The NGO or FBO acts as a coordinating structure for services provided to the families through networks and partnerships with other organizations and sectors, such as education, business, health, social welfare, and other community-based organizations and NGOs or FBOs. These models place special focus on developing linkages with hospitals where HIV palliative care and treatment are provided; however, they may not be able to ensure access to these services, as they may not exist or the hospital may not

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Figure 5. Model for comprehensive palliative care
Source: Family Health International.51

ART = antiretroviral therapy; OIs = opportunistic infections; OVC = orphans & vulnerable children; PLHIV = people living with HIV; VCT = voluntary counseling & testing; STI = sexually transmitted infections; TB = tuberculosis
have the resources to ensure quality or sustained palliative care services. A very successful example of this approach is The AIDS Service Organization (TASO) in Uganda, which leads the development of a continuum of palliative care services for clients while linking with government-based HIV palliative care and treatment and receiving support from the government to extend its services.53

Hospital-Led Model
In the hospital-led model, a hospital that is providing palliative care develops a comprehensive package of patient services, including home-based care. This model usually develops organically based on the needs of clients. The quality of these services tends to be high, but access is limited to those who live nearby. An example of a comprehensive hospital-based model is Dr. Soetomo Hospital in Surabaya, Indonesia. The palliative care unit started with a focus on cancer inpatient care in 1995 and then expanded to include outpatient care, home-based care, a day-care and respite center, and a 24-hour hotline for patients and families.54

Comprehensive Integrated Model
The comprehensive integrated model focuses on linking together and building the capacity of all the best possible providers of palliative care at different levels. The leaders of this approach tend to be from the local health system or hospital, working in partnership with NGOs or FBOs and support groups for people living with HIV. Integrated palliative care programs utilize the existing health system and the community to provide a continuum of care. An example of a successfully integrated HIV palliative care program is the Lighthouse Centre (hospice) in Malawi, which describes its services as a “circle of care.” Palliative care is provided through the district hospital outpatient clinic and inpatient clinic, and through home-based care teams. The responsibilities of the nurses who provide home-based care include administering morphine to patients in their homes to treat pain and providing ART adherence follow-up and side-effect care.55

Need for a National Palliative Care Program
In order for quality palliative care to be available on a large scale and over the long term, its development must be led by national and local government. WHO endorses a national program strategy that requires a three-part process for the development of an effective national palliative care program.56 The three prongs are as follows:

1. **Governmental policy.** National or state policy emphasizing the need to alleviate chronic HIV/AIDS-related pain through education, drug availability, and governmental support or endorsement

2. **Education.** Appropriate training for healthcare professionals (doctors, nurses, pharmacists) and others (health-care policymakers, health-care administrators, drug regulators)

3. **Drug availability.** Changes in health-care regulations and legislation to improve drug availability (especially opioids)

Former WHO cancer chief Jans Stjernsward further defines several essential steps to take in developing a national palliative care program57:

- Establish a national palliative care policy specific for the country or culture.
- Establish commitments to educate and train all health professionals by including palliative care in the curricula for physicians, nurses, pharmacists, social workers, and others.
- Develop advocacy and education programs for the public. Define freedom from pain as a basic human right.
- Ensure the availability of affordable drugs for pain control and symptom management and their use by appropriately trained professionals.
• Ensure that pain and palliative care programs are incorporated into the country’s health-care system.
• Provide interdisciplinary and multidisease approaches to health care.

All of the above are necessary and must be incorporated into a strong national effort that involves people living with HIV and cancer and other life-limiting diseases, families, and civil society. At the government level, given the legal challenges related to the use of opioids, narcotics control officials and public security should also be involved in developing a national palliative care policy. It is important to ensure that palliative care is included in the national health strategy. This can lead to better integration of palliative care into the health-care system and increased resources for operationalizing a national palliative care program. These and other important efforts can be led by a national palliative care task force, in collaboration with a national palliative care association.

In many countries, technical support is provided to ministries and other state bodies to develop and implement HIV care services. Building on these collaborative relationships, international and national palliative care technical support assists governments in
• assessing and quantifying palliative care gaps and needs,
• developing national palliative care guidelines and policies,
• reforming narcotic control laws to accommodate access to narcotics for pain relief, and
• piloting innovative palliative care services from which policy and regulatory bodies can learn and adapt current laws and programs.

Some examples of effective partnerships in establishing national palliative care programs can be found in Uganda, Romania, and Vietnam.24,58,59

Access to Essential Palliative Care Medicines and Supply Chain Management

An essential component of a national palliative care program is access to essential palliative care medicines. Most countries include some of these medicines in the national Essential Medicines List (EML).60 Palliative care advocates can identify which medicines are missing from the list and those that are difficult to access even though they are on the list and advocate with their national drug authority and ministry of health for better access to these medicines. The IAHPC recently updated the essential palliative list, which can be used as a reference document in advocacy with governments.42

In most countries it remains a challenge to access morphine—oral morphine in particular. The process of ensuring that morphine is readily available can be very complicated but is essential for a quality palliative care program. In addition to advocating for medicine availability, palliative care providers can also help the ministry of health estimate the annual need for these medicines.

Generic medicines should be used whenever possible, with drugs produced in-country being preferable as long as internationally accepted quality controls are in place. While most generic palliative care medicines are relatively inexpensive, import costs and the cost of brand-name medicines can be prohibitive. Some countries have taken the approach of importing raw materials to produce essential analgesics. Uganda imports raw morphine and prepares oral morphine of different strengths within the local health-care system for prescription in hospital, community, and home settings. Other countries, such as Vietnam, are exploring the possibility of producing long-acting morphine.

In addition to drugs, basic supplies for managing wounds, supplies for skin and mouth care, gloves, and other items necessary for managing conditions
and controlling infection need to be available to providers. Many countries’ standards for home-based care include a list of basic commodities required for supporting care at the community level.

*International Narcotics Control Board*

Opioid use is monitored by the International Narcotics Control Board (INCB). This body provides an overall legal framework for the national regulation of narcotics. The INCB has called on governments to ensure that opioids are available and used to treat pain and dyspnea. It has requested that governments assess the regulatory impact on opioid access and, based on their findings, initiate a process of reforming regulations to increase access to opioids for medical purposes. This process has been successfully undertaken in several countries, including Uganda, Romania, and Vietnam, and has resulted in an improved balance between narcotic control and access for people in pain or with other health conditions requiring opioids for treatment.24,57,59

**Networks, Linkages, and Patient Advocacy**

Community Mobilization and Leadership

No palliative care service can address all the needs of its clients. It is essential that linkages are made with services that clients need to ensure a continuum of care. As each community is unique, the composition of the comprehensive support for palliative care will vary. Each community needs to design its particular “model” for the most appropriate and effective delivery of palliative care. The development of referral protocols, service directories, and other tools to facilitate ease of referral for clients is essential for a successful program.

To build community support for people living with HIV, palliative care programs can implement community sensitization and mobilization activities aimed at reducing stigma and discrimination and improving community support for people with HIV and their families.

Several localities have instituted continuum-of-care coordination committees, which are a forum for bringing together many different organizations, government services, and other partners to plan services and mobilize resources.61 These committees develop referral guides, referral protocols, service mapping, and annual work plans. Most importantly, they have worked to mobilize support services such as social welfare, scholarships, and small business development for people living with HIV.

**Advocacy for Patients and Families**

Advocacy by palliative care providers is essential. Whether it is advocating for services or benefits, it is a critical element in the effort to ensure that patients and their families receive the help they are entitled to receive. Sickness, emotional strain, and poverty are intertwined and often leave an otherwise strong person in need of an advocate. Stigma and discrimination create added barriers. Interceding with employers, government agencies, family members, and bureaucracies is a large part of providing holistic care services.

**World of Work**

For adults, the world of work is a key part of life. Being unable to work or having to adjust to different work or limited energy levels is very difficult for employed clients. Discussing their health situation with an employer is often very difficult and risky. As with other types of disclosure, discussions with a palliative care provider help the patient know what to expect and identify the best approach to take.

With permission, the care team can support discussions and adjustments to the work environment
that could make the difference between losing a job and finding a temporary adjustment that satisfies both parties.

The support of the palliative care team could also be required to relieve part of the burden of care through respite care, which could make a big impact on other family members’ ability to cope and continue working.

MEASURING THE IMPACT OF PALLIATIVE CARE

Monitoring and evaluation (M&E) enables palliative care programs to make decisions about how to improve their programs, identify and address problem areas, and identify what is working well and how to continue to support it. These activities should be an ongoing part of the work of palliative care teams, who must be trained to use data collection tools and systems. The monitoring system should include continuous patient care planning and care activity monitoring, caregiver supervision, and technical support.

Supportive supervision and the use of quality assurance / quality improvement (QA/QI) tools are vital to ensuring quality care. Routine participatory assessment of quality, if done properly, will empower local providers to continually improve the quality of their services. Each program should develop a supportive supervision system and QA/QI tools based on local needs and definitions of quality, while reflecting national standards and guidelines.

Different models of evaluation can be used for palliative care programs, depending on what the leadership or management team would like to learn:

- Formative evaluation is conducted during the planning of the program and answers questions about the need for palliative care, how many families would benefit, where and how the program should be implemented, and what resources are required.

- Effectiveness evaluation assesses how well the palliative care program is reaching its objectives. It addresses the outcome and impact of the program, how well the program has improved quality of life, and how much of a difference it has made to the beneficiaries of the services. Quality-of-life questionnaires can be an effective tool for this type of evaluation exercise.

- Process evaluation is designed to help ensure that the planned activities are carried out correctly, effectively, and efficiently, with the given resources. The program can discover, for example, the degree to which families are satisfied with the services, how well the volunteers or caregivers are supported by their supervisors, and whether the team has the appropriate skills and materials required to do the job.

- Program cost analysis speaks for itself—it is an evaluation of the costs of the different components of the program, the use of resources, and the sustainability of the way resources are garnered or used.

Indicators

Indicators for the palliative care program could include the following:

- Number of people living with HIV receiving palliative care
- Number of people living with HIV treated for pain
- Number of people living with HIV receiving social support services
- Number of health-care workers trained in palliative care (pain, symptoms, psychosocial support)
- Number of palliative care providers trained in home-based palliative care
- Number of palliative care providers equipped with medicines to treat pain and symptoms
• Number of palliative care teams formally linked to a hospital HIV care, treatment, and support service (e.g., outpatient clinic)

Research
There is an urgent need for more research in all areas of palliative care, particularly in defining what approaches are best in resource-limited settings.2,3 Priority research areas include the following:
• The impact of palliative care–related policy change on provider practice and palliative care outcomes for people living with HIV and their families
• Tracking trends in the consumption of opioids and other essential palliative care medicines
• The impact of the introduction of pain assessment in HIV ambulatory care settings
• Identifying the quality-of-life and adherence outcomes of palliative care models
• Comparisons of the quality-of-life and adherence outcomes of services that provide only OI treatment and ART with those that integrate palliative care, including community- and home-based care
• Evaluation of specific palliative care approaches (e.g., community- and home-based care)
• Costing and comparing the cost-effectiveness of different palliative care models
• Identifying the emotional, social, and spiritual support needs of people living with HIV and effective approaches to addressing these needs.


38. Guthrie B, Nelson M, Gazzard B. In practice, are people with HIV in London able to die where they plan? *AIDS Care*. 1996;8:709-713.


The focus of this chapter is on lessons learned by members of the Hospice Palliative Care Association (HPCA) during 25 years of palliative care in South Africa. The mission statement of the HPCA—“To promote quality of life, dignity in death and support in bereavement for all those living with a life-threatening illness by supporting member hospices and partner organizations”—is based on the World Health Organization (WHO) definition of palliative care. This mission is carried out by HPCA member hospices that care for patients and families in their homes and, on occasion, in health-care facilities.

The origins of palliative care in South Africa
The catalyst for the establishment of hospice programs in South Africa, which were the predecessors to palliative care programs, was a 1979 lecture tour to the country by Dame Cecily Saunders. Saunders, a British national, was a prominent Anglican nurse, physician, and writer best known for her role in the birth of the hospice movement, which emphasized the importance of palliative care in modern medicine. South African hospice programs were initially modeled after programs in the United Kingdom and provided care almost exclusively to patients with advanced cancer. In 1988, 14 hospices came together to form a national association. The key reasons for establishing what was then called the Hospice Association of South Africa (HASA) were:

- to draw together and share scarce professional human resources,
- to promote collaboration,
- to strengthen advocacy and public relations to introduce and promote the concept of home-based hospice care throughout South Africa,
- to develop standardized training programs at a time when South Africa was excluded from the international arena due to apartheid, and
- to accommodate funders who preferred to donate to a national organization.

The name of the association was changed from HASA to HPCA in 2003 to reflect the changing focus from end-of-life care for terminally ill patients (i.e., hospice care) to a broader, life-long approach made necessary by the arrival of HIV/AIDS (i.e., palliative care). Hospices had begun to recognize the need to provide palliative care beginning at the time of HIV diagnosis, which at that time was still considered a death sentence for most people (as antiretroviral drugs [ARVs] were...
prohibitively expensive and not available at publicly run health facilities).

Today HPCA has 70 member hospices, with an aim to ensure access to palliative care resources in each of South Africa’s 174 health subdistricts. HPCA member hospices operate in a wide range of settings throughout the country, including hard-to-reach remote towns and rural villages (some of which are only reachable on foot), as well as sprawling metropolitan areas with both well-resourced suburbs and informal settlements. Programs vary in size from those caring for more than 1,000 patients to small services caring for as few as 30 patients. Access to skilled professionals and material resources, which are generally more readily available in urban areas, varies widely. Despite the diversity of programs, all HPCA member hospices are required to comply with the comprehensive HPCA hospice palliative care standards that apply to the services they deliver.

THE CHANGING FACE OF PALLIATIVE CARE IN SOUTH AFRICA

As mentioned previously, hospice programs in South Africa were initially adapted from models in the U.K. and cared almost exclusively for patients with advanced cancer. Yet before long, the devastating and far-reaching impact of HIV/AIDS throughout the country—on patients, families, and the community—fundamentally changed the way hospice care, and subsequently palliative care, were being delivered. With the arrival of HIV/AIDS, palliative care providers were confronted with a wide range of different client needs, and programs had to adapt to meet these new challenges.

Increased Demand
The demand for palliative care has increased dramatically in recent years, threatening to overwhelm available resources. By mid-2006, it was estimated that roughly 5.4 million South Africans were living with HIV and over 700,000 people were in need of ART. While antiretroviral therapy (ART) is now officially available throughout the country, widespread poverty and limited infrastructure mean that treatment still remains beyond the reach of many who need it.

In many South African hospice home-care programs, the increasing number of clients is outpacing available human resource capacity, requiring the restructuring of services, the employment of additional staff, and strengthened networking. In some cases, this gap has been addressed by the development of satellite programs or the closing of inpatient units so that all resources can be focused on home-based care. In rural areas, where large distances must be covered, care teams are organized and home visits planned according to a roster that determines the area to be visited each day, to achieve maximum coverage despite resource constraints.

Since the majority of South African hospices are nongovernmental organizations (NGOs) reliant on donor funding, they are often unable to pay competitive salaries, making it difficult for them to recruit professional staff qualified in palliative care and to cover other rising costs. These difficulties are compounded by the fact that many South African health-care professionals have emigrated to other countries, lured away by the promise of better wages and living conditions.

Changing Patient Population
Hospices are now faced with a younger patient population requiring a different type of care over a longer period of time. The large number of people living with HIV in South Africa mentioned earlier in this chapter highlight the enormous number of young adults in the 15- to 24-year-old age group who are HIV-positive, the majority of whom are female. An additional challenge is that many of these young women are single mothers with children who themselves are HIV-positive or face the...
The possibility of being orphaned. In this context, the need for social and emotional support is every bit as important as the provision of medical care.

It is important to identify potential orphans and foster parents or caregivers as early as possible so that care support can be put in place while the parent is still alive but too ill to care for young dependent children. It is common to see children as young as 10 years old being forced to take on responsibilities far beyond what is appropriate for their age, including managing households, caring for dying parents, and taking responsibility for siblings. When a child is forced to leave school to assume family responsibilities, this can have a far-reaching impact on his...

Figure 1. Sample flowchart for placement of vulnerable children
or her future options, limiting the child’s ability to grow into a self-sufficient adult.

A family conference is a good way of identifying available support so that plans can be made to keep children within an extended family. It is important that both the family and child be part of this decision-making process, as they can lend insight into the family structure that would otherwise not be available to the care team. It is also important to assist the parent in making a will in order to prevent family members from taking possessions that rightfully belong to the children. Knowing that their children will be well cared for can be very reassuring for parents or other caretakers who are in the process of dying. Figure 1 contains a sample flowchart for child placement in the context of a parent or caretaker who is terminally ill.

While providing palliative care within the home, it is important for care providers to recognize the ways in which the client’s health condition may be affecting the children in the household—as well as the serious challenges that may arise should that client die. It is therefore necessary to find ways of empowering children to cope so that they can effectively deal with these difficult issues. It is usually best for the child to remain at home, so every effort should be made to provide support to the household and for the home-care program to strengthen the local safety net and referral network.

**CATERING TO THE NEEDS OF CHILDREN**

Health-care providers have the added emotional burden of caring for children who are both living with and/or affected by HIV. Most hospices are involved in ensuring that plans are put in place for the care of orphans and that grants or other forms of support can be accessed. Recognizing that caring for children requires specialized skills, the HPCA recently established a pediatric palliative care portfolio to provide guidance and support to individual hospice programs in the care of children. A pediatric training program has been established to ensure that those caring for children at all developmental stages are equipped with specific skills, including those relating to communication, pain management, and bereavement. Advocacy for children’s HIV care and treatment is another important activity undertaken by palliative care programs at both the local and national level; advocacy is needed since ART programs are primarily designed to accommodate adults, and therefore often overlook the needs of children.

Naturally, a key intervention to ensure the health and well-being of HIV-affected children is to prolong the life of HIV-positive mothers so that they can continue to look after their own children. This involves promoting ART among mothers, assisting them with treatment compliance, and offering nutritional support. Many hospices have established day-care programs for children who are on ART or whose parents are being cared for by the hospice. These programs provide an opportunity for drug-adherence monitoring, nutritional support, educational stimulation, play, and improving school preparedness. In most cases the children’s program forms part of a comprehensive service that includes adult care, but there are currently a few HPCA member hospices that care only for children, both of which have inpatient, home-care, and day-care facilities.

**Building Resilience in Children**

In order to effectively cope with their own HIV-positive status and/or that of a parent or caregiver, children need to make sense of and find meaning in the difficulties they are experiencing. This is directly related to developing resilience, which one author describes as “the human capacity to face, overcome and be strengthened by or even transformed by the adversities of life.” While
adults may want to protect children from the seriousness of the issues affecting them, honest communication helps children cope and may give them a greater sense of control and understanding of their circumstances.

The following approaches may contribute to the development of resilience in children and are recommended for anyone involved in the care of children affected by HIV:

- Providing a safe, nurturing environment in which the child’s needs are met
- Spending time with the child, listening and showing interest in what she or he does, thinks, and feels
- Teaching children how to communicate
- Allowing for mistakes
- Involving the child in day-to-day activities
- Teaching the child family routines
- Praying with and for children
- Acknowledging children for what they are, not only for what they do
- Demonstrating trust

Developing resilience is also about allowing, even facilitating, the expression of grief and loss. Memory boxes or books are valuable tools to ensure that even very young children are able to stay connected to their roots, particularly when children are separated from their siblings after the death of a parent. In South Africa, a typical memory box would contain copies of birth and inoculation certificates, a “Road to Health” chart issued by the primary health-care clinic that shows whether the child’s growth and development are within normal percentiles, family photographs, a letter from the deceased parent, and other precious mementos that hold importance for the child.

Specially trained community caregivers who are well versed in the local culture are usually directly involved in the creation of memory boxes under the supervision of a social worker.

ESSENTIAL COMPONENTS OF COMPREHENSIVE PALLIATIVE CARE

The following sections summarize some of the key areas where palliative care programs can positively impact the lives of people living with or affected by HIV. Specific examples are provided from program activities within the HPCA network.

Reducing Stigma

HIV/AIDS-related stigma often causes people living with HIV to delay seeking treatment and can breakdown traditional support systems. Hospices have a key role to play in promoting and facilitating disclosure, in encouraging people to access counseling and testing services, in advocating for ART, and in monitoring treatment adherence. A number of hospices have run workshops on HIV/AIDS that include comprehensive information on ARVs to promote community literacy and reduce fear and stigma.

Linking Palliative Care to ART

A few of the larger faith-based hospices in South Africa have managed to secure funding to establish separate, but linked, ARV clinics where patients are assessed, medication is given, and drug adherence and progress are monitored and evaluated on an ongoing basis. Many of the hospices with inpatient units are using these facilities to admit patients with extremely low CD4 lymphocyte counts who have been started on ART and who require intensive nursing care and nutritional and psychosocial support. In KwaZulu-Natal, several hospices have developed close collaborative relationships with ARV clinics in the formal health-care sector where the promotion of drug adherence and monitoring and treatment of side effects are incorporated into home-care programs. Most pediatric day-care programs run by hospices fulfill a similar role. One program in the Western Cape has established an after-hours clinic providing HIV counseling, testing, and adherence support to cater to the needs of those who are employed and
cannot access clinic or support services during working hours. Support groups, which are run either by hospices or by networking partners, play a vital role in providing ongoing information and encouraging disclosure within a safe environment. These groups are usually run by HIV-positive people themselves and are powerful resources in promoting the rights and needs of participants.

**Training**

ART, as well as treatment for opportunistic infections, now forms a vital part of palliative care. Many health professionals and community caregivers were trained before the advent of ARVs. As ART became more widely available, hospices recognized the need to ensure that community caregivers received the necessary information and skills to care for those living with HIV. The HIV epidemic has been the catalyst for the development of a wide range of training programs for doctors, nurses, social workers, and lay caregivers and counselors on HIV prevention, care, and treatment. There are currently HPCA-supported Centers for Palliative Learning (CPLs) at 10 member hospices, providing training for hospices, community partners, tertiary institutions, and the formal health-care sector. One of the key objectives of a current donor-funded HPCA program, involving 52 member hospices, is providing palliative-care training for nurses at more than 300 primary health-care clinics.

**Health Promotion**

Health promotion has become a vital part of holistic palliative care, and each home visit provides an opportunity to promote the health of the patient and to teach the family and the community how to prevent the spread of infection. In many cases, family members are cared for by children or the elderly, and it is especially important to work with these vulnerable groups so that they have the necessary skills to cope with caring for a loved one and to protect themselves from infection. Training programs for community caregivers should also include sessions on methods for teaching families how to care for a client at home and how to keep accurate medical records. Particularly in areas of high unemployment and poverty, hospice home-care programs help families establish food gardens and network with agricultural organizations that can provide training and, at times, plants, seeds, gardening equipment, and fencing.

**Poverty Alleviation**

When providing holistic care for people living with or affected by HIV, the associated social issues of poverty, unemployment, and domestic violence cannot be ignored. For example, women in abusive and/or disempowering relationships may not be permitted by their partners to seek treatment, often resulting in devastating health outcomes for both themselves and their children.

It often becomes necessary for the family member of someone who is ill to stop work or cut back working hours, resulting in a loss of income. At the same time, household expenses can increase due to the costs of visits to the clinic, hospital, or traditional healer; food and food supplements; and transport costs.

Many hospice programs have developed locally appropriate income-generating projects such as food gardens, bead making, and sewing to help needy families survive. For example, one program within the HPCA network teaches orphans how to make beaded necklaces, bracelets, and badges, while another program teaches men and women who are members of a support group how to make beautiful embroidered cushions. For any such program, the ongoing challenge is finding outlets to sell the items that are produced. Hospice social workers also play a vital role in helping patients access any available financial assistance such as child care, foster care, or disability grants. They facilitate these
The role of the professional nurse has had to expand in the face of a variety of challenges associated with long-term HIV/AIDS care. In resource-limited settings the nurse is often the primary or sole health-care professional, advocate, educator, and social support resource for the client and family. Given the growing number of patients requiring palliative care and the distances to be covered in providing home-based care, basic nursing care is increasingly being provided by trained community caregivers. When this shift occurs, nurses are freed up to fulfill more of a supervisory/management role. Yet despite the added productivity that can be achieved through this “task shifting” approach, nurses may frequently find that the previous training they received did not prepare them for this new role. Additionally, many hospices may find it difficult or impossible to hire and retain highly experienced nurses due to limited budgets and human resource shortages, forcing them to rely heavily on retired nurses who may have difficulties adapting to an expanded role. Regardless of what strategy is used to address human resource shortfalls, additional training may be required to support nurses in taking on increased responsibilities.

Care for the Homeless
An added challenge in the delivery of palliative care is providing care to those who are homeless and live on the streets and/or who are illegal immigrants and have no access to treatment via the formal health-care system. To address this challenge, one hospice program in the center of Johannesburg has a mobile clinic that takes care to the city’s migrant population, and a number of programs have established shelters either for temporary or end-of-life care for homeless people, including street children.

Care within a Prison Environment
A number of hospices have developed innovative programs that focus on providing training to enable prison inmates to care for one another and to establish support groups. Often care is complemented by weekly visits from the hospice palliative care team.

The Changing Role of the Professional Nurse
Van Den Berg et al make the point that “it is our humanness that makes us worthy carers, but it is that same humanness that also makes us vulnerable to burnout.” Caring for caregivers is an integral part of any successful palliative care program. The three key components of effective caregiver support are: (1) training and education (i.e., empowering the caregiver), (2) providing support and supervision, and (3) encouraging self-care and early recognition of burnout or distress.
Specific organizational strategies to prevent and manage caregiver burnout should be well planned and purposeful. They can include the following:

- Preselection interviews that include a careful assessment of the applicant’s own circumstances, support, and coping skills
- Paying a living wage that minimizes workers’ financial anxiety
- Monitoring patient and task allocations to prevent overload
- Ensuring that caregivers are not expected to work unreasonable hours (40 hours a week is considered the norm for full-time employment), that they routinely take their leave, and that leave is accumulated only in exceptional circumstances
- Providing individual and group support sessions where caregivers are encouraged to talk about their personal difficulties and distress
- Creating career pathways so that skilled caregivers can be promoted within the organization and/or be given opportunities to gain formal qualifications (For example, a number of hospices have provided opportunities for those who were previously unemployed to finish their schooling and go on to obtain qualifications in nursing or social work.)
- Providing team-building and self-growth opportunities (One program, Wilderness Therapy, takes caregivers away for a weekend that includes time for them to assess their own feelings, values, and dreams, so that they return to work with renewed energy.)

THE INTEGRATED COMMUNITY HOME-BASED CARE MODEL
In order to meet the need for holistic palliative care in the context of rising numbers of people living with HIV, collaboration and networking at all levels of activity are essential. The magnitude of the HIV epidemic in South Africa makes it impossible for any one organization to adequately respond to the needs of all those affected. In order to provide a continuum of care from HIV diagnosis through to end-of-life care and bereavement, it is necessary to involve a wide range of stakeholders, including primary caregivers in the home, health professionals, community caregivers, traditional healers, NGOs, and community- and faith-based organizations (CBOs and FBOs). The flexible and evolving integrated community-based home care (ICHC) model described here promotes formal collaboration between local nongovernmental hospice home-care programs, government hospitals, and primary health-care clinics. The scope of integrated programs is varied and dynamic in response to the diverse needs of the communities being served. For instance, it is not uncommon for an ICHC program to perform a wide variety of activities, including advocacy on behalf of hospice patients in need of ART, the provision of adherence support, as well as the timely recognition and treatment of side effects. Formal health-care partners are increasingly being accredited to provide ART, which is in fact the best possible form of palliative care for HIV-positive people who are severely immunocompromised and symptomatic. Hospices that have inpatient units are now playing a vital and often lifesaving role in providing intensive nursing care for patients who initiate ART with a CD4 count of less than 50 cells/mm³.

In 1996, South Coast Hospice developed a collaborative model of integrated community-based home care that involved the collective efforts of many organizations working together (Figure 2). An NGO, such as a hospice, works closely with government hospitals and primary health-care clinics. In so doing, the hospice or other entity ensures that community caregivers are trained, and then supervised and supported. Existing community and faith-based initiatives are drawn in and strengthened by means of active networking.
and the enhancement of services that result from noncompetitive mutual support. This system allows for trust to be built between all stakeholders, an essential step in the formation of an effective referral system.

The needs of the person living with HIV and his or her family are central to the ICHC model, with the goal of all activities being to provide the client and their family with access to a continuum of care. Activities span the time from pre-diagnosis
in-depth, immediate, and frequent communication. These partnerships and collaborations have involved a broad variety of associations and have required consistent efforts that allow them to evolve over a period of time.

### THE AFRICAN PALLIATIVE CARE ASSOCIATION

Since it officially came into being in 2004, the African Palliative Care Association (APCA) has made significant progress toward meeting the objectives set out in the 2002 Cape Town Palliative Care Trainers Declaration (see Box 1). This declaration has informed APCA’s stated mission, which is “to promote and support affordable and culturally appropriate palliative care throughout Africa.”

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**Box 1. The Palliative Care Trainers Declaration of Cape Town – November 13, 2002**

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness. This includes prevention and relief of suffering by means of early identification and effective assessment and treatment of pain and other physical, psychosocial, and spiritual problems. It uses a multidisciplinary team approach to address the needs of patients and their families, including dignity in dying and bereavement support. Palliative care has only recently been recognized in Africa, which has a great need. It is therefore an essential component of health care in Africa today in light of the epidemic of HIV/AIDS and increasing cancers. The provision of palliative care requires policy, drug availability, funding, and education focused on the patients and family and integrated into the existing health services and the continuum of care.

The first meeting of palliative care trainers in Africa was held in Cape Town. Thirty participants attended from five African countries—Kenya, South Africa, Tanzania, Uganda, and Zimbabwe—along with representatives from the World Health Organization and the Diana Princess of Wales Memorial Fund.

At the end of the meeting the group made the following declarations:

1. Palliative care is a right of every adult and child with a life-limiting disease. Therefore, palliative care should be a part of national health-care strategies, making it accessible and affordable for all in sub-Saharan Africa.
2. The control of pain and symptoms is a human right, and therefore, appropriate drugs should be available in every country in sub-Saharan Africa as part of the essential drug list, including opioids such as morphine. These drugs should be available and accessible at all levels, including the community.
3. In order to provide high-quality palliative care, all members of health-care teams and care providers need training. It is therefore crucial to establish training programs at all levels (i.e., undergraduate and postgraduate, preregistration and postregistration), for community workers, caregivers, and volunteers. This should be provided for all members of the multidisciplinary team providing care.
4. Palliative care should be provided at all levels—primary, secondary, and tertiary. This necessitates a career structure for all those specializing in palliative care and in the integration of palliative care at the university and national departmental level in each country.

The organization is committed to enhancing both coverage and quality and is currently compiling guidelines for palliative care. These guidelines will be circulated to emerging national palliative care organizations together with the APCA African Pos, a palliative care outcome scale that measures patient and family perceptions of care.

**LESSONS LEARNED**

**Sound Management**
Something that many CBOs overlook is the need for sound management, which is essential to sustain the provision of home-based palliative care. Human resources, sound financial and administrative systems, and strategic planning must underpin any successful program providing HIV/AIDS care. HPCA is involved in supporting the efforts of hospices and CBOs and FBOs to incorporate sound management principles into their programs.

**Maintaining Focus**
Given the challenges involved in adapting to the changing face of palliative care, there is the danger of losing the distinctive focus on palliative care within a hospice or palliative care program and developing additional services that may be established according to donor interests rather than patient needs. Income-generating projects, food gardens, and so on are certainly important, but the key elements of palliative care, as outlined in the WHO definition, including pain and symptom management and emotional support, must remain the primary focus.

The needs in resource-limited communities with a high prevalence of HIV can be overwhelming. Hospices that have established credibility within the community and then attempt to branch out into the provision of other services or activities may risk taking on more than they can realistically manage, thus jeopardizing the quality of care they are able to provide. In hospices where there is sound management, efforts should be concentrated on building the capacity of partner organizations that can become strong networking partners able to provide complementary services.

**Standards and Mentorship**
Even though there is a wide range of palliative care settings within South Africa, it is important that patients be assured of a uniform standard of care. HPCA is committed to supporting its member hospices and helping them develop into key palliative care resources in their communities. Two tools that play a key role in achieving this goal are mentorship and accreditation. There is a comprehensive set of HPCA / Cohsasa (Council for Health Services Accreditation of Southern Africa) standards that cover all aspects of care, governance, and management. These standards were recently given recognition by the International Society for Quality in Health Care (ISQua). Improving quality is an ongoing process, and the standards, survey processes, and accreditation are more about developing a culture of quality within each hospice than meeting external requirements.

Mentorship is provided to help hospices progress from initial acceptance as HPCA members to established hospices. Once hospices are able to meet the criteria outlined in the standards, they can in turn provide support, guidance, and mentorship to newer hospice programs or CBOs with limited resources. Once a survey to assess compliance with the ISQua standards has been conducted by a team of HPCA surveyors, the report then forms the basis of an individualized hospice development plan drawn up by hospice staff and the regional mentor. This plan identifies the key areas needing additional work and specifies agreed-upon time frames to monitor progress.

Achieving the goal of full accreditation, which is valid for two years, requires a great deal of work,
treat opportunistic infections. In many instances, however, there are strong links between community programs and the local primary health-care clinics; nurses at these clinics are often overburdened and unable to perform home visits, and the community caregivers therefore represent an important additional source of support. Within this context, HPCA is piloting a project to explore the viability of expanding the reach of professional palliative care supervision by a professional hospice nurse to community caregivers at four nonhospice CBOs. If the model is found to be successful, its replication in other settings could significantly extend the coverage and quality of palliative care for people living with HIV and their families.

Hospital-Based Palliative Care
A number of hospices have made providing access to quality palliative care in their local state hospitals a priority. In some instances, hospices have facilitated the establishment of palliative care wards, with the agreement that these be staffed and maintained by the hospital and that palliative care expertise be provided by the interdisciplinary team from the hospice. In other cases, hospital palliative care teams are supported by input from the hospice staff. For example, one faith-based hospital has become a member of HPCA and is working toward applying palliative care principles throughout all of its health-care services.

Conducting and Publishing Research
There is currently very little documented evidence to reflect the wealth of clinical, educational, and organizational skills and experience of palliative care programs in South Africa. As professor Irene Higginson points out, “So that we can all learn from present efforts and ensure that the maximum benefit is gained from resources, encouragement needs to be offered to engage in monitoring and research, and especially to document work.” The
recently validated APCA African Pos, which will soon be widely implemented in South Africa to assess patient and family satisfaction with palliative care received, will provide an excellent opportunity for published research, as will the results of the pilot study mentioned earlier.

**CONCLUSION**

Palliative care in South Africa has undergone radical changes in the last 25 years, with the demands of the HIV epidemic forcing a shift in focus to include the long-term care and support of those living with HIV. The realization of the need for greater collaboration and networking, together with the parallel processes of mentorship and the implementation of standards, has led to the development of a collaborative model of care that has expanded the reach of palliative care expertise and skills throughout the country. It is hoped that the lessons learned in South Africa will be of benefit in helping organizations in other HIV-high-prevalence settings cope with the ever-increasing demand for palliative care.
REFERENCE LIST


Peer Education in HIV/AIDS Care and Treatment Programs

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Peer education is the transfer of knowledge and skills that occurs when members of a social group are trained to provide education and support to others. Used in programs seeking to shape health behaviors at the individual level and health-seeking norms at the family or community level, peer education includes a range of educational approaches such as counseling, formal classroom-based teaching, one-on-one instruction, and informal group facilitation.

Peer education can be used to accomplish a variety of goals. Examples include youth educating other youth about how to prevent HIV infection, mothers counseling new mothers about breastfeeding, patients receiving antiretroviral (ARV) drugs helping others take their medicines consistently and correctly, and men speaking out against domestic violence to other men.

Although peer education programs vary in content and structure, most share the following important characteristics: peer educators are trained laypeople; peer educators undertake specific and clearly defined activities with the clients and communities they are targeting; the peer educators’ goal is to foster specific behavioral practices among the individuals, families, and communities they are working with; and peer educators are used to complement, not to replace, the work of professional staff.

**Why Use Peer Education?**

There are several reasons to add peer education to health programs. First, it seems to work. Although evidence is limited, the data suggest that strong peer education programs can improve health-related behaviors and outcomes in a variety of settings. Second, peer educators bring unique characteristics to health programs. For example, peer educators may be more influential within a social group than people outside it and, as a result, may have a greater potential to effect change. Peer educators can also act as liaisons between program...

**Box 1. Definition of Terms**

- **Site**: Location of clinical care. May be a clinic, hospital, health center, or other venue.
- **Site staff**: All professional, paid staff of the treatment site (doctors, nurses, medical officers, counselors, etc.).
- **Patients**: HIV-positive people receiving care and treatment at the site.
- **Peer educators**: Patients who carry out educational activities with other patients.
- **Peer clients**: Patients who receive education from peers.
participants and program staff, and can provide insight into the style of communication and types of messages that are appropriate for the target group. Additionally, as a member of the group, a peer may be more aware of the group’s priorities than someone outside the group.

Peer education can provide lasting benefits to peer educators themselves, as well as to their clients, their communities, and the programs they support. For instance, clients have the opportunity to discuss their personal circumstances in a safe, comfortable environment with someone who can relate to their situation. This, in turn, can support clients’ adherence to medication and care, and their ability to navigate the health system. Peer educators can also play a role in community mobilization, helping to decrease stigma and increase support for patients enrolled in care and treatment.

Working as a peer educator can increase self-efficacy, leading to behavior change among peer educators as well as their clients, and empowering them to take better care of their own health and that of their families. The training and work experience that peer educators receive may also improve their future job opportunities in the formal economic sector. In addition, by providing a mechanism for program participants and staff to communicate with each other, peer educators can help improve the overall quality and effectiveness of health-care programs.

USE OF PEER EDUCATION IN HIV CARE AND TREATMENT PROGRAMS

When care and treatment programs include peer education initiatives, HIV-positive individuals enrolled in the program work with patients in similar circumstances. In some programs, patients newly enrolled in care and treatment work with peers who are more experienced. In others, patients with specific problems or challenges—such as medication adherence—are paired with peer educators who can assist with those specific issues. Generally, treatment peer education programs strive to

- increase treatment literacy;
- provide practical and emotional support;
- maximize adherence to care (attending appointments, tests, following instructions);
- maximize adherence to medications, especially ARV treatment;
- support internal linkages within health facilities (e.g., assisting patients as they go from the HIV clinic to the TB clinic, or between the HIV clinic and the laboratory or pharmacy);
- support external linkages between health facilities and community-based resources (e.g., assisting patients enrolled in HIV clinics to access nutrition support services in the community, or assisting individuals in the community to identify which health-care facilities provide HIV services); and
- encourage healthy behaviors and positive living, including secondary prevention of HIV transmission (i.e., “prevention with positives”).

Peer education can bring many additional benefits to treatment programs, such as reduced stigma and discrimination in the community, mobilization of community resources to support people living with HIV (e.g., food resources, social grants), and strengthened links between treatment programs and the communities they serve.

PEER EDUCATORS’ ACTIVITIES

Peer educators in HIV care and treatment programs generally perform a variety of tasks related to patient care and support. These may include:

- organizing and facilitating one-on-one and/or group sessions to educate patients, family members, and caretakers about aspects of care and treatment such as medications, adherence techniques, and side effects;
• providing patients with information and practical tips for “system navigation” and optimal use of program resources;
• providing specialized support to pregnant women and new mothers enrolled in prevention of mother-to-child transmission (PMTCT) and/or care and treatment services;
• organizing and facilitating patient support groups;
• providing education regarding treatment options for substance abuse and alcohol abuse;
• conducting home visits to support patients, or when patients miss appointments;
• conducting community outreach activities to raise awareness about the treatment program and mobilize community resources in support of the program;
• referring clients to psychosocial support services; and
• fostering dialogue between patients and treatment site staff by maintaining regular communication with both.

PEER EDUCATION PROGRAM MODELS
Treatment peer education programs generally fall into one of three design categories: facility-based, community-based, and combination models.

Facility-based: The peer education program is based at the clinic, health center, or hospital where the treatment is provided. This is where the program supervisor and peer educators work and carry out their activities.

Community-based: The peer education program is based at a site in the community other than the treatment site, such as a nongovernmental organization (NGO), community-based organization (CBO), or faith-based organization (FBO) meeting hall or other location. Patients from the treatment site are referred to this location.

Combination: The peer educators are based at the treatment site but spend a great deal of time on home visits or community-based work, such as leading support groups or advocacy efforts in the community.

As a rule, the peer education program design will reflect the particular needs, priorities, and resources of each treatment program. The following section reviews ways in which program planners may choose to select peer education models.

DESIGNING A PEER EDUCATION PROGRAM
Designing a peer education program generally involves five steps: (1) assessing stakeholder needs and priorities, (2) defining program goals and objectives, (3) determining what peer educators will do and how they will be supervised, (4) identifying program resources, and (5) finalizing the program design. Through these steps, the treatment program will gather the information it needs to determine what peer education model is most appropriate.

Assessing Needs
As with any other type of program, the first step is to assess needs. This will ensure that the program is designed to meet the real needs of its stakeholders, as identified by the stakeholders themselves. There are generally three key stakeholders in treatment peer education programs, in addition to the peer educators: patients enrolled in HIV care and treatment (sometimes called “clients”) and their families or caretakers, treatment site staff, and the surrounding community. The goal of the needs assessment is to find out how the program can best serve each group. Needs that can be addressed by a peer education program include the following:
• Patients (clients) and their families or caretakers may have a need for
  – improved understanding of HIV care and treatment, including the need for prophylaxis for opportunistic infections (OIs), regular clinical and laboratory monitoring, and ARV treatment when eligible (treatment literacy);
  – improved understanding of clinic protocols (system navigation);
  – adherence skills, techniques, and role models;
  – someone to talk to who understands what they are going through; and
  – information on where to go for services such as counseling, home-based care, and food assistance and/or social grants, when these are available.
• Program (treatment site) staff may have a need for
  – liaisons between staff and patients;
  – help in promoting attendance at scheduled appointments;
  – people to conduct home visits to follow up on facility-based care;
  – laypeople who can participate in or lead support groups; and
  – experienced patients who understand HIV and its treatment and can explain it to others.
• The community around the treatment site may have a need for
  – more information about HIV treatment;
  – more information about the HIV services being provided at the treatment site;
  – people to be open about their HIV status and speak out against stigma and discrimination;
  – assistance with integrating issues of traditional medicines and cultural beliefs about HIV/AIDS with new information regarding prevention, care, and treatment; and
  – advocates for more treatment-related resources.

Needs assessment tools include surveys, interviews, and focus group meetings with stakeholders. Each program must determine the type of needs assessment most appropriate to its setting. For some programs, this process will be relatively brief and informal. For others, especially for larger initiatives, this process may be quite lengthy. Periodic reassessments are strongly recommended, as needs evolve over time.

Defining Goals and Objectives
After the needs assessment is complete, the next step is to define the program's specific goals and objectives. This will ensure that staff and participants understand exactly what the program is trying to accomplish, and will help clarify expectations and focus planning.

By definition, the patients receiving support from peer education initiatives linked to HIV care and treatment sites are all HIV-positive. The emphasis of these programs, therefore, is generally on care and treatment and on ensuring that patients get the most from their participation by supporting treatment literacy and adherence. Another focus is on secondary prevention of HIV infection—that is, preventing the transmission of infection from clients to their sexual partners or, in the case of pregnant and breastfeeding women, to their children. Peer educators also promote healthy behaviors and “positive living” as well as family and community involvement and support.

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*Care and treatment services include but are not limited to counseling; education; adherence support; regular clinical and immunologic staging; prophylaxis of OIs; preventive measures such as the provision of insecticide-treated bed nets and clean water; early diagnosis and treatment of OIs, including tuberculosis; nutritional counseling and support; palliative care; and ART when indicated.*
The reason to carefully define goals and objectives is that these will directly inform program monitoring and evaluation. For more information on how to evaluate a peer education program, see the “Monitoring and Evaluation” section later in this chapter.

Determining Peer Educator Activities
The specific activities carried out by peer educators will vary from program to program and will be based on the needs assessment and objectives of the individual program and on the resources available. For example, if the program finds that patients need treatment education, the peer educators may organize individual and/or group educational sessions. If the needs assessment finds that many patients are missing appointments, the peer educators’ activities might include home visits to remind patients of upcoming appointments or to follow up on missed appointments. Although a detailed plan is not required at this stage, a general idea of peer educator activities is required prior to finalizing the program design.

Identifying Resources
The fourth step in designing a program model is to review the resources available for a peer education initiative. In addition to direct financial support, programs should inventory staff time, as well as physical space and community assets. Existing patient support groups, advocacy programs for people living with HIV, home-based care programs, and organizations providing support to people living with HIV can all be important building blocks for a peer education program.

Useful questions about resources for a program planner to consider include the following:

• What funds are available to support the project?
• Is there a member of your staff with the skills needed to manage a peer education program and supervise the peers (see the “Supervision” section later in the chapter)?
• If so, can a significant amount of his or her time be dedicated to the initiative? If not, how will you recruit and support such an individual?
• Are the staff members at your site interested in starting a peer education program?
• Does your clinic or hospital have sufficient physical space for the peer educators and their clients to hold peer education activities?
• Are other organizations or groups in your community working on HIV/AIDS care and treatment issues? Are they already conducting peer education activities that could be built upon?
• If so, are any of these organizations better equipped to house the peer education program (e.g., do they have more staff time, physical space, active counselors and peers, etc.)? Are they potential partners?

These questions will help the treatment site determine what resources are available and which program model is most appropriate (clinic-based, community-based, or combination).

Finalizing the Program Design
When finalizing the program design, it can be helpful to ask the following questions:

• What are the main needs identified by stakeholders?
• What are the goals and objectives of the program?
• Who will supervise the program?
• Where will the peer educators be based?
• What will the peer educators do? How often?
• How will the peer educators be incorporated into the larger treatment program? What will their role be?
• How many peer educators are needed?
• How will treatment site staff (other than the supervisor) be involved in the peer education program?
My personal experience was what prompted me to start working in the field of HIV/AIDS and to later become a peer counselor. I lost my baby boy, Ovie, in the year 2000 to HIV. He was six months old. He had been ill and was tested for HIV without my prior consent. The result was disclosed to my boss, who fired me soon after. The stigma level was very high at that time, mainly due to a lack of information. I found myself in the situation many young people living with HIV have found themselves in shortly after they have been diagnosed with HIV: with very little support and sometimes without a job or a home. There was also little access to antiretroviral therapy (ART) in Nigeria. Much of the misinformation available was that antiretrovirals (ARVs) did not work, and that people died soon after starting treatment. When I saw how well I was doing on treatment, despite a very difficult emotional period, and also knowing that many people were receiving the same negative information I had when I was first made aware of my diagnosis, I decided to give a positive face to HIV.

I began by joining a support group for people living with HIV (AIDS Alliance in Nigeria), and then began to volunteer within the group in 2001. After participating in a counseling workshop organized by Family Health International (FHI) in August 2002, I became much more confident about offering peer education and support. I provided group counseling at a nearby maternity home as well as at the Lagos University Teaching Hospital (LUTH), where I also received care and treatment.

I have been an active member of the Treatment Access Movement (TAM) in Nigeria since 2002. It is a coalition of people living with HIV and members of civil society and the media who have fought for free access to ART in Nigeria—and achieved this in principle in December 2005. Since January 2006, there has been access to free care and treatment in almost all the states in Nigeria.

I joined the Nigerian Community of Women Living with HIV/AIDS (NCW+) in 2002, which provides group counseling for pregnant women attending the antenatal clinic at the Nigerian naval hospital at Ojo Barracks in Lagos state. In January 2003, with funding from the Center for Development and Population Activities (CEDPA), we started a peer counseling and support group for women and vulnerable children. As the field supervisor / counseling coordinator for this project, I met with vulnerable women of different backgrounds. Some were widowed and at the mercy of their husbands’ relatives and feared losing their homes due to stigma and discrimination. Many were afraid to disclose their status to their spouses for fear of being thrown out of their marital homes, and...
so would not access prevention of mother-to-child transmission (PMTCT) services, resulting in their babies becoming infected, getting sick, and even dying.

These experiences have contributed significantly to my growth and development as a peer health educator/counselor, supporter, and HIV/AIDS advocate. I worked with Médecins Sans Frontières (MSF) for three years as a peer educator and adherence counselor. Currently, I work with Columbia University’s International Center for AIDS Care and Treatment Programs (ICAP) as the central adherence adviser in Nigeria.

As the central adherence adviser, with technical support from my supervisors, I have developed and implemented the adherence counseling and peer education services for all the ICAP-supported sites in Nigeria. I continue to provide comprehensive adherence counseling, mentoring, supervision, and technical assistance to the health teams at the facilities where we work; included in this is periodic training and continuous mentoring of site adherence supervisors who report regularly to me. My other key responsibilities include the initiation and facilitation of support groups for mothers and children, in addition to the provision of psychosocial support to HIV-positive mothers through their support groups. My job also involves recognizing and managing obstacles to the provision of adherence counseling within the systems that operate at sites, and implementing a framework that addresses these problems so advisers can problem solve on their own.

Recently, I received the Workplace HIV/AIDS Best Practice Award for workplace HIV/AIDS stigma reduction from the National Action Committee on AIDS (NACA). It is a national award that has practically impacted how HIV/AIDS is viewed in the workplace. Through the recipients of this award, organizations all over the country have now come to provide peer health education in the workplace and encourage counseling and testing among workers. They have also ensured implementation of policies on HIV in the workplace, including, for example, the prevention of termination of employment when a worker is determined to be HIV positive. I continue to advocate for organizations to amend employment policies to include noncompulsory screening for new employees, with the option not to disclose the results to the employer, while accessing care and treatment when necessary. I have been able to achieve all this because I received peer support from my support group and met other people living with HIV.

- What funds will be used to support the program?
- Will the treatment site collaborate with any other community organizations? If so, how?

MANAGING A PEER EDUCATION PROGRAM
This section provides a very brief overview of some things to consider when preparing to manage a peer education program. It is intended to give program developers a sense of what types of challenges may arise, what measures can be taken to avoid and mitigate these challenges, and what activities can be undertaken to ensure that the programs implemented are of the highest quality. The information is based on experience and lessons learned from peer education programs.
Supervision

Ongoing supportive supervision of peer educators is critical to program success. Although peers are often effective proponents of behavior change, it is important to remember that they are laypeople, not professional counselors or clinicians. As a result, good supervision is beneficial to both the peer educators and the program as a whole, and lack of supervision is one of the most common reasons that peer education initiatives fail.

It is not sufficient to appoint someone who already has a full-time workload to supervise the peer education program in addition to his or her other work. The supervisor must have dedicated time for the peer education program. Experience has shown that it is preferable to have at least one staff person from the supervising organization (either the treatment program or NGO/CBO) who can dedicate at least half of his or her working hours to supervising the program.

In many programs, the supervisor is a nurse or counselor, but advanced training is not required to be an effective supervisor. Qualities that program developers may want to look for in a supervisor, in addition to knowledge of HIV care and treatment, are enthusiasm, patience, flexibility, resourcefulness, training skills, knowledge of community resources, a belief in the importance of involving people living with HIV, and the ability to communicate well with both peer educators and multidisciplinary team members.

Supervisory duties in peer education programs may include some or all of the following:

- managing budgets and finances and overseeing peer educator reimbursement and stipends;
- supervising peer educators’ work, providing feedback, and meeting regularly with peer educators, both individually and as a group;
- answering questions and providing practical and emotional support to peer educators;
- scheduling and facilitating meetings between peer educators and the multidisciplinary team;
- collecting and compiling monitoring and evaluation data; and
- corresponding with donors and partners.

Recruitment and Retention of Staff

Prior to recruiting patients to work as peer educators, it is important to be clear about what their activities and scope of work will be. One recommended approach is to detail roles and responsibilities in a simple “terms of reference” (TOR) document. This TOR can then inform a description of preferred and required qualifications, which will vary depending on the needs of individual peer education programs. The qualifications of peer educators should include being HIV-positive and enrolled in the care and treatment program. Many programs specifically recruit individuals who are on and adherent to ARV treatment. Individual programs will have varying needs—some sample criteria are listed in Box 2—but most attempt to develop a varied team of peer educators, recruiting both men and women and attending to issues of race/ethnicity, language skills, and age.

Since enrollment in care and treatment is a prerequisite, recruitment activities will often take place at the clinic itself and at affiliated CBOs. Counselors and staff can generally recommend patients who are articulate and involved proponents of the program. Clinic receptionists can systematically inform patients of the opportunity, and written job postings may also be useful in some settings.
Setting Realistic Expectations
When starting any new program, it is important to ensure that participants clearly understand their intended roles and tasks (Box 3). Peer educators have an unusual position in treatment programs, in that they are both clients and service providers but are generally not clinic staff. Educators and program staff alike will benefit from clear and very specific descriptions of the intended activities and responsibilities of peer educators and their supervisors. It will be important to address the following issues:
- tasks (i.e., what exactly the peer educators will be expected to do, where, and how often);
- scheduling (i.e., who will be responsible for arranging meetings and visits);
- compensation (i.e., stipends, salary, transportation allowance—see “Compensation” section);
- number of hours of work expected or required;
- supervision (i.e., role of the supervisor, availability, responsibility);
- peer educator monitoring, evaluation, and feedback;
- role of peer educators in making decisions about the peer education program; and
- peer educators’ role in the larger treatment program.

The key to setting expectations is communicating early and often with peer educators. It is best to begin this communication during recruitment and training and to continue it throughout the duration of the program.

Compensation
By definition, peer educators are laypeople, not formally trained health-care professionals. There is no reason to assume, however, that peer educators are volunteers, or that they should work without appropriate compensation. Decisions regarding peer educator compensation can be difficult and are best made at the local program level. In some settings, peer educators receive a stipend based on hours worked or tasks completed. In others, transportation allowances, uniforms, training, meals, and/or other benefits are all that can be offered.

While it is important to keep long-term program sustainability in mind, we recommend that programs make every effort to pay peer educators for their work. Peer educators can have a significant impact on treatment programs and should be rewarded for their contributions. Peer educators are also less likely to drop out of the program if they are compensated. Conversely, peer educators are more likely to feel exploited and unhappy if they are not compensated for their work.

Decisions regarding peer educator compensation should be consistent, clearly communicated to participants, and periodically reassessed.
Training and Staff Development

Because peer educators are laypeople who play a unique role in treatment programs, peer educator training is an important factor in program success. Three main elements must be considered when developing a training program: content, design, and timing.

Content

Although peer educators are not meant to become or replace HIV treatment experts such as doctors, nurses, and counselors, it is important that they know the basics of HIV/AIDS and issues relating to treatment. It will be up to individual peer education programs to decide exactly which topics to address during training. Examples of training topics include:

- basic concepts of HIV transmission, prevention, and disease progression;
- using medications to prevent OIs (e.g., cotrimoxazole);
- using medications to delay HIV disease progression (e.g., ARV drugs);
- supporting patients’ ability to attend scheduled tests and appointments and to avoid loss to follow-up;
- supporting treatment adherence, and its importance;
- program “navigation” (e.g., how to make appointments, communicate with program staff, deal with problems, etc.);
- nutrition and food and water hygiene;
- condom use and secondary HIV prevention;
- communication skills (i.e., listening, asking questions, speaking to groups);
- organizing and running treatment support groups;
- the role of the peer educator; and
- processes for carrying out peer education activities.

Design

Several elements should be considered when designing a training program. These include how many days the training program will last, how the sessions will be structured, what kinds of activities will be included, and who will facilitate the sessions. There are several reasons to recommend against formal “didactic” training—that is, training structured around slide-based lectures or lengthy written materials. Counseling skills are best taught by role-playing, practice, and reflective observation, not PowerPoint! While each peer education program will design the training according to its own needs, experts recommend the use of interactive sessions rather than lectures, as well as the inclusion of activities such as case studies and role-playing, in which participants can practice using skills. The use of different facilitators for different sessions—such as nurses, doctors, social workers, nutritionists, counselors, pharmacists, and other peer workers—can provide an opportunity for participants to hear directly from the experts themselves. After classroom-based training, a supervised practicum can help peer educators transition into their “jobs” and continue to build skills. Finally, as with all training, regular (daily) opportunities for feedback and evaluation of the training methods and content ensure that adjustments can be made to improve the overall quality of training.

Timing

When planning recruitment and training strategies, it is important to remember that peer education programs generally have high turnover rates. Anticipating the need to train and initiate new educators is prudent, and may be required to ensure

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*These were adapted from Peer Support for HIV Treatment Adherence: A Manual for Program Managers and Supervisors of Peer Workers, produced in 2003 by the Harlem Adherence to Treatment Study at Harlem Hospital, New York.*
that the program has a steady supply of active peer educators. Some programs conduct training activities every three months, others every six months. While specific schedules will be program-specific, most programs will need to conduct repeat trainings in order to sustain the peer education program. Ongoing or “refresher” training courses can also be important tools to help peer educators reinforce their skills, add new or advanced skills, and maintain enthusiasm for the program.

Materials
Many programs use materials to support the work of the peer educators. Informational and behavior change communication materials can help reinforce knowledge and skills learned in training, and can also help peer educators transfer knowledge and skills to patients and their family members. Some examples include using posters or flip charts with drawings to inform and educate low-literacy audiences; handing out informational pamphlets or brochures in the clinic and/or community; showing videos to demonstrate certain skills to clients; distributing condoms for secondary prevention; and using pill boxes, treatment logs, and calendars to assist clients with adherence. Materials are most useful when they are developed or adapted within the local context, preferably with input from people within the target group—in this case, clients receiving HIV care and treatment services.

Staff Turnover
As mentioned above, one characteristic of many peer education programs is a high turnover rate. Peers leave the program for many reasons. Some transition to the formal economy. Others have competing priorities, including illness in the family or worsening personal health status. Inadequate supervision and/or a lack of consistent support may also result in frustration with the peer education program itself.

It is important for programs to be prepared for turnover among peer educators. Programs can do this by recruiting peer educator candidates regularly, offering the peer educator training course on a regular basis, communicating regularly with peer educators regarding their feelings about the program and future plans, and having alternate peer educators available to step in and help out if someone leaves the program or is temporarily absent.

Program features that can encourage peer educators’ ongoing involvement include adequate financial and other compensation, linkages to community resources, recognition of work performance and achievements through awards and prizes, flexible work schedules, opportunities to make meaningful contributions to the treatment program, and opportunities to interact with other staff members and other peer educators at the treatment site. When a peer educator does leave the program, it is important to document the date and reason he or she is leaving. This will give the program a formal record that the person is no longer a peer educator and help determine whether the reason for leaving is related to the program itself or to external circumstances.

Monitoring and Evaluation
The only way to determine whether the peer education program is achieving its goals and objectives is to monitor program indicators and evaluate program effects. Monitoring the program involves tracking and documenting what is being done. For example, programs generally monitor the number of peer educators receiving and successfully completing the training, the types of activities peer educators have carried out, the quantity and type of contacts educators have had with clients, the number of hours per week or month educators are working, and retention rates (i.e., how many educators have left the program).

Evaluation involves assessing whether the program has been successful in achieving the results it
aims for. For example, if one objective of the peer education program is to decrease the workload of the treatment site staff, an evaluation would seek to find out whether that actually happened by surveying the site staff. Two levels of evaluation are generally used in peer education programs: basic evaluation and intermediate evaluation.

**Basic evaluation** includes assessment of measures such as satisfaction with the program on the part of clients, peers, and program staff; the effectiveness of training in preparing peer educators to do their work; and the proportion of clients being reached by peer educators. Most peer education programs conduct this type of evaluation. Examples of specific measures that may be looked at include:

- proportion of clients reached by peer education services;
- peer educators’ satisfaction with their training (via interviews or questionnaires);
- peer educators’ knowledge (via written or oral examinations);
- peer educators’ skills (via observational checklists, interviews with clients, etc.); and
- client, peer educator, and/or staff satisfaction with the peer education program (via interviews or questionnaires).

**Intermediate evaluation** includes more complex evaluation techniques, such as those designed to determine whether the program impacted psychosocial measures such as perceived stigma, social isolation, and/or depression; whether clients were successfully referred to other services; whether the program increased clients’ knowledge and improved attitudes toward care and treatment; and whether the program had an impact on clients’ behaviors, such as adherence. Examples of specific measures that may be looked at include:

- client knowledge, attitudes, or self-reported behaviors before and after implementation of peer education services (via interviews, questionnaires, focus groups, etc.);
- client and/or peer educator utilization of HIV services before and after implementation of the peer education program (via interviews, questionnaires, appointment logs, registration records, and/or medical charts);
- client and/or peer educator adherence to medications (via interviews, pill counts, pharmacy records) before and after implementation of peer education services;
- client and/or peer educator self-efficacy before and after implementation of the peer education program (via interviews);
- impact on staff workloads (via interviews); and
- impact on stigma in the community (via focus groups, etc.).

**Rigorous evaluation** includes measures that can only be evaluated using scientifically rigorous methods, such as randomized controlled trials. Most peer education programs will not conduct evaluations at this level due to resource and time constraints.

Several tools can be used to monitor and evaluate peer education programs. These include surveys (written and oral), in-depth interviews, focus groups, supervision notes and checklists, clinic records, peer education logs/records, attendance records, and program entry/exit forms.

**Funding and Sustainability**

As with any program, securing funding to sustain a peer education program can be a challenge. Ongoing costs associated with peer education programs include training, peer educator stipends or salaries, supervisor salaries, travel, materials and uniforms as well as space and basic overhead costs.

There are several ways to raise funds and ensure that the peer education program is financially sustainable. These include:

- incorporating the peer education program into the clinic / treatment program budget;
• developing income-generating projects that directly support the peer education program;
• working with existing local NGOs, FBOs, and CBOs that are likely to have a sustained community presence and low operating costs; and
• securing funding from private foundations, other donors, local businesses, or other community support channels.

One creative approach to promoting program sustainability is to provide skills training and seed money to peer educators and their clients, enabling the creation of income-generating projects such as sales of beadwork and other crafts.

Formal partnerships with CBOs can also be beneficial to all involved.

CONCLUSION

Peer education initiatives can enhance HIV care and treatment programs by providing valuable input, perspective, and services. Clearly identifying specific program goals and objectives; designing programs to achieve these outcomes; and ensuring careful attention to training, supervision, compensation, and support will maximize outcomes for programs, peer educators, and clients.
As massive antiretroviral therapy (ART) scale-up efforts continue, so too will the associated challenges. For instance, millions of additional people will require HIV testing and counseling so that those in need of treatment can be identified. This first step alone necessitates large investments in infrastructure and human capacity in order to respond to the greater demand for services, stretching already overburdened national health systems. Among the main bottlenecks preventing effective scaling-up of ART are poor logistics, especially for efficient management of drugs and laboratory supplies, resulting in limited absorptive capacity of national health systems in many middle- and low-income countries. Another major obstacle is the shortage of human resources in the health sector, often referred to as human resources for health, which exists across the entire spectrum of care providers including doctors, nurses, pharmacists, laboratory technologists, counselors and support staff. These shortages continually prove to be a formidable obstacle to providing effective ART services in resource-limited settings.

Despite these shortages, many donors prefer not to support human resource costs, especially salaries to assist national health systems in retaining staff and increasing manpower, as part of their overall funding packages. Additionally, many donors fail to encourage and support governments to invest adequately in the health sector, and do not encourage changes to national policies that restrict critical activities (e.g., dispensing, prescribing, laboratory analyses) to specific cadres of health personnel, so as to allow task shifting to lower cadres of staff or laypeople. For instance, Malawi has only 2 doctors and 56.4 nurses per 100,000 inhabitants.\(^2\) The ratio recommended by the World Health Organization (WHO) is 20 doctors and 100 nurses per 100,000. With such severe shortages of trained health staff, even a massive scale-up of efforts over the next few years will still fall short of what is needed to save millions of people from dying a preventable death.

Brain drain of health-care providers from Africa and other less developed regions to wealthier nations has been a recognized problem for decades. However, a new form of internal brain drain has evolved more recently, as multiple donor-assisted programs compete for the few remaining in-country and regionally trained professionals. Adding to this problem is the naturally occurring, unequal geographical distribution of health staff within provinces or districts (rural versus urban).
HIV-related stigma has also, in some cases, resulted in reluctance on the part of health professionals to care for people living with HIV.3

Because of these difficulties, task shifting is not only urgently needed but is an absolute necessity if the timely scale-up of quality services is to be achieved. Prevention and treatment in the era of ART implies lifelong case management, which requires a new set of support services, such as ongoing behavioral and adherence counseling. Most health-care systems will have to shift away from an acute-care model, in which many of the tasks are currently performed by nurses and other paramedical staff, to a chronic-care model, in which laypeople play a significant role. Elements of this shift to chronic care have already been implemented in some countries, including Malawi, where the government has created a new cadre of staff called health surveillance assistants (HSAs), who after only 10 weeks of training are responsible for counseling and testing, as well as other routine health activities including immunization. Formal assessors agreed that these HSAs could also be trained to dispense antiretrovirals (ARVs) to ease the burden on the formal health-care system, but a national policy permitting such activities has thus far not been established.4 In addition to training laypeople to perform some forms of care, there is a growing realization of the critical need to develop innovative ways to educate, prepare, and engage communities in HIV prevention and treatment, especially to provide long-term adherence counseling and other forms of support necessary for life-long ART.

ADDRESSING HUMAN RESOURCE CONSTRAINTS IN SCALING UP HIV CARE

Efforts to address human resources and service delivery in scaling up ART should not be focused only on the formal health-care delivery system. Because resources are too scarce to reach all in need, it is therefore necessary to go beyond a focus on health professionals and established service providers and beyond facility-based service provision to include laypeople, families, people living with HIV, and community organizations in treatment services.5

For example, WHO recommends deployment of people with a wide variety of skills ranging from psychology, social sciences, nursing, and other health sciences, as well as lay health workers with relevant training, for the provision of HIV counseling. Many sites in Africa choose to enlist nurses to perform counseling, although in developed countries, trained psychologists usually undertake this task. Unfortunately, trained psychologists are not available in sufficient numbers in most countries to meet the counseling needs of people living with HIV. More commonly, social workers, even those with no medical background, or individuals trained in community service are trained to undertake counseling. One successful training model developed by The AIDS Support Organization (TASO) in Uganda trains people from diverse backgrounds, with or without any clinical training, as HIV counselors and treatment supporters during a six-month training program.6

Another significant shift in tasks can be observed in the growing role of lay counselors and adherence support workers. Traditionally, nurses have provided the bulk of psychosocial counseling, patient education, and adherence support. However, nurses take longer to train and are not available in sufficient numbers. A growing number of programs have begun using or are preparing to use lay counselors trained in patient education and adherence promotion, as well as other skills, to provide these time-intensive services. At most stages of HIV/AIDS disease, counseling takes more time than direct clinical activities, so reassigning these duties to nonclinical staff can significantly free up limited nursing resources. For example, the government of Tanzania estimated that treatment
and lifestyle counselors will spend an average of 630 minutes in year one for an individual on ART with a CD4 count of less than 200 cells/mm³, and 620 minutes in year two; but prescribing and evaluating clinicians spend 90 and 150 minutes, respectively, in year one, and only 40 minutes each in year two. Therefore, the number of patients started on ART could be increased dramatically by shifting scarce nurses away from counseling to patient evaluation and prescribing, while lay counselors could perform the bulk of the counseling.

A number of programs have already reassigned nurses to evaluate patients for ART and prescribe ARVs and other drugs in uncomplicated cases. In so doing, they have shifted counseling and education from nurses to lay counselors and trained peer support workers. It is important to note that the transfer of responsibilities needs to be accompanied by thorough training and supervision of all involved, as well as ongoing monitoring and evaluation to inform continuous program improvement. Countries like Malawi and Rwanda have begun to develop a certification process for some of these tasks to help ensure standards, quality of treatment, and sustainability. It is important to keep in mind that any system with a heavy reliance on nonprofessionals needs to be supported by higher-level personnel, such as physicians, for routine supervision, consultation, and management of complicated cases.

**HIV TESTING**

HIV counseling and testing (CT) is a crucial component of effective strategies for HIV/AIDS prevention and care. As the entry point for ART, CT is a critical step for a range of other interventions in HIV/AIDS prevention, care, and support. Gradually, CT is being integrated into other existing health services in order to increase uptake. For instance, some countries have introduced routine antenatal testing or opt-out testing. These developments have increased the demand for services, yet available manpower has by and large remained constant, and in some cases even declined. Perhaps owing to this trend, the available data suggest that the global coverage of HIV CT remains unsatisfactorily low. Demographic and health surveys in 2005 in 12 high-burden countries (accounting for 47% of adults and children living with HIV/AIDS worldwide) in sub-Saharan Africa showed that among the general population, the median percentages of men and women who had been tested for HIV and received their results were 12% and 10%, respectively. Although these figures have since improved, there is still an urgent need to scale up testing.

A wide spectrum of CT program models and approaches have been piloted and successfully implemented in resource-limited countries. However, in light of the current health-care worker shortages, these approaches cannot be sufficiently scaled up unless many routine tasks are shifted to laypeople who have undergone short-term training. Some strategies for pretest counseling that have utilized laypeople have included group counseling and hotline services that provide detailed HIV/AIDS information along with relevant referrals. Community outreach methods, including home-based voluntary counseling and testing (VCT), have successfully employed lay counselors, expert patients, and individual or groups of trained people living with HIV for peer counseling. This has proven to be a successful strategy, especially for providing counseling services to hard-to-reach populations. Various nongovernmental organizations (NGOs) and institutions, like TASO in Uganda, have developed simple, practical curricula for the training of lay counselors while ensuring rigorous follow-up training and peer support.

Included is a brief summary of the different models of CT service provision, along with a table highlighting the potential role for lay counselors in each model.
Free-Standing VCT Services

Free-standing VCT services were the first CT model to be introduced in many countries before the widespread availability of ART. In this model, CT services are offered apart from other health services but involve frequent referrals of patients to additional care and support services. They have the advantage of having focused staff, flexible hours of operation, and strong community linkages. However, this stand-alone, specialized approach to VCT has challenges of accessibility and availability, since the centers are usually situated in urban areas. In addition, they do not always offer clients quick and smooth referrals to the treatment centers, a situation that may lead to loss of follow-up or delay in accessing other health services or ART for those who need it. The centers may also be associated with stigma, which may limit attendance.13

Integrated VCT

CT services are usually integrated into existing health-care settings, such as general in- and outpatient departments, sexually transmitted infection (STI) clinics, TB clinics, and family planning and mother and child health services. Integrated VCT offers the advantage of ease of cross-referrals and is less costly to operate. However, this model may not appeal to certain groups such as young people and men, who normally do not routinely visit health facilities.

Routine or Opt-Out CT

In this model, HIV testing is offered as part of routine medical tests that are requested during the patient’s clinical visit. Pretest counseling is offered in groups, with more emphasis put on posttest counseling. Patients who refuse the test are considered to have opted out. This model has been implemented in many countries as part of other, related health activities, such as those for prevention of mother-to-child transmission (PMTCT), TB, and STIs, as well as within general medical wards.14 Routine testing has been recently recommended by the Centers for Disease Control and Prevention as one of the ways of increasing early diagnosis of HIV.15 Botswana has initiated routine testing at clinics and hospitals nationwide. With routine testing of inpatients in pilot projects in Uganda, acceptance rates were as high as 96%. Overall prevalence rates among family members were 30%, far above national seroprevalence rates, indicating that this model was efficient in reaching and identifying HIV-positive individuals.16

Diagnostic CT

In this model, a health worker initiates HIV CT as part of the diagnostic workup for patients who present with symptoms or signs that could be attributable to HIV disease. CT is indicated whenever a person shows signs or symptoms that are consistent with or suggestive of HIV-related diseases. This is particularly important in TB clinics, where up to 60% of new cases may also be coinfected with HIV. In fact, HIV and TB services should be integrated or closely linked whenever possible due to the associated high risk of mortality if coinfections are not promptly and effectively treated.17

Mobile or Community Outreach

CT may be offered from a van, motorcycle, bicycle, or other mobile means like a donkey, which may be used to access hard-to-reach populations. Mobile CT improves access and can link identified patients to care and treatment services. Extensive community mobilization is required to ensure uptake on the designated service date.

Home-Based VCT

CT is a powerful tool for providing information, education, and communication (IEC) on HIV/AIDS and serves as an entry point to treatment. For this reason, various ways to maximize the
Many organizations have found that offering home-based VCT and treatment support programs is not only an effective preventive strategy but also a way to increase access to treatment and adherence. Home-based VCT addresses the needs of the entire family at once so that discussions on prevention and behavior change may be more effective in the context of the family and the home. Other reported advantages include a reduction in perceived stigma; low operating costs, especially if lay counselors and/or CHWs are utilized; and ease of couples counseling and disclosure. Home-based VCT services could also be a promising strategy for encouraging disclosure, especially in cases of discordant couples and children, as well as reaching disempowered individuals, especially women.

### Table 1. Key Features of Different Counseling and Testing Models and Suggested Roles for Laypeople

<table>
<thead>
<tr>
<th>Counseling and Testing (CT) Model</th>
<th>Characteristics</th>
<th>Potential Role(s) for Laypeople</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free-standing voluntary counseling and testing (VCT)</td>
<td>Stand-alone, not part of formal health facilities Attractive to clients who find public-sector services inconvenient Relies upon high level of public awareness of benefits of VCT Depends on referrals for enrollment in treatment and other medical services</td>
<td>Advocacy and community mobilization Pre- and posttest counseling Ongoing counseling in posttest clubs Adherence and other follow-up treatment support</td>
</tr>
<tr>
<td>Integrated VCT</td>
<td>Services are integrated into existing health-care settings, such as general in- and outpatient departments</td>
<td>Pre- and posttest counseling Adherence and other treatment support</td>
</tr>
<tr>
<td>Routine CT</td>
<td>Testing is offered as part of routine medical tests during patient’s clinical visit Counseling is offered in groups, with more emphasis on posttest counseling</td>
<td>Pre- and posttest counseling</td>
</tr>
<tr>
<td>Diagnostic CT</td>
<td>A health worker administers or refers to CT as part of the diagnostic workup for patients who present with symptoms or signs suggestive of HIV</td>
<td>Pre- and posttest counseling Adherence and other treatment support</td>
</tr>
<tr>
<td>Mobile or community outreach (e.g., home-based CT)</td>
<td>Health workers travel to communities or individual homes to offer on-site CT to hard-to-reach populations</td>
<td>Community mobilization Pre- and posttest counseling Ongoing counseling and psychosocial support</td>
</tr>
</tbody>
</table>
INCREASING ACCESS TO ART THROUGH THE USE OF LAYPEOPLE

In addition to CT, laypeople also need to be mobilized to provide support for other crucial elements of HIV/AIDS care, such as treatment adherence, monitoring, and psychosocial support. The same counseling facilities established in the communities for CT services can also be used to expand access to care and treatment services.

Included is a brief summary of various models of service delivery, including descriptions and examples of how laypeople can play a key role in each.

Home-Based Care

Home-based care, which has been used for primary health-care promotion and VCT, may also be extended to include delivery of ART and monitoring of treatment adherence and toxicities. Outreach or home-based HIV care may have advantages over facility-based care, particularly for patients in settings where transport to clinic-based programs is a major barrier to accessing care. Home-based services also can help to lessen the patient load of already overburdened treatment facilities. In the home-based model of care, patients may make fewer trips to facilities, only going when specialized care is needed such as monitoring for side effects and treatment regimen changes. Health professionals such as doctors and nurses are then primarily in a supervisory and quality assurance role, while the outreach programs rely primarily on laypeople’s services.

One example of this model, the Home-Based AIDS Care project, was piloted in the Tororo and Busia districts in rural Uganda using trained laypeople to regularly visit patients at home, deliver medications, and collect information about adherence to ART and possible toxic side effects. Only patients identified as needing evaluation by a physician or a care review were referred to the clinic. In a majority of cases, laypeople were able to correctly diagnose problems needing referral and assisted in improving adherence and treatment effectiveness. 21

Facility-Based Care

To address the human resource gap in clinics, the AIDS Healthcare Foundation, working in Uganda and Zambia, has developed an intensive three-month course to train adolescents who have finished high school as “HIV medics.” The HIV medics are trained as lay providers to assist clinicians in the provision of ART. After training, they are able to provide ongoing adherence support, take medical histories, appropriately triage, provide knowledge on HIV and ART, refer sick patients, and perform physical examinations. They are also orientated on follow-up of clients. The HIV medics relieve physicians, clinical officers, and nurses of simple assessments and tasks and free them up to see more patients in a given clinic day and focus on more complex cases.

The Uganda Ministry of Health, in collaboration with WHO, has trained clients receiving ART to fill the great need for HIV counselors. These people, called “expert patients,” are mainly tasked with preparing, monitoring, and supporting patients in the comprehensive care of HIV/AIDS, specifically for those receiving ART. The types of support offered through the expert patients includes post-test and ongoing counseling, education of patients and their families, disclosure assistance, and guidance on prevention and positive living in the context of clinical care. 22

The network model is a type of facility-based delivery system developed by the Joint Clinical Research Centre (JCRC) in Uganda and currently operates successfully in over 60 ART clinics covering all regions of Uganda. ART clinics are located in both public- and private-sector hospitals and clinics, including faith-based facilities. To ensure the quality of the national ART program and to provide
services to rural areas, mainly through referrals, JCRC established a network of seven regional laboratories with the capacity to perform advanced tests including CD4, RNA polymerase chain reaction (PCR) for ART monitoring, and DNA PCR for infant diagnosis for the national PMTCT program.

Community-Based Care
Laypeople are utilized in the JCRC model to provide treatment support through the established positions of “volunteer community liaisons” and “support officers.” A five-day training curriculum was developed to ensure that laypeople have the essential skills and knowledge to effectively promote and monitor adherence within their communities. Many programs have also successfully used “buddies,” family members, or community volunteers who promote and support patients’ adherence to their ARV medicines.21

People living with HIV who serve as expert patients for others on ART have been powerful advocates for and educators of those starting on therapy. They lead by example and are a living testimony that HIV infection, although chronic, can be treated and managed and can allow patients to move on with their lives. Model patients have been incorporated in the JCRC and other ART programs in Uganda and have actively participated in health education talks, live testimonies, and music and drama performances. Prominent musicians and artists willing to speak out on HIV/AIDS can draw large crowds and help to sensitize people about ART and adherence. JCRC has also established patients clubs, called ART clubs, for different categories of patients including children, adolescents, and adults. These clubs provide psychosocial support and can serve to mobilize members to speak openly in their communities about services such as positive prevention programs and promotion of adherence.

There are other programs in Uganda that have piloted an integrated approach to community involvement in ART provision. They include Mbuya Outreach program in the suburbs of Kampala, which has established a support group called Community ARV and TB Treatment Supporters (CATTS). The CATTS are people from the community receiving ART who help to monitor the health of other clients in their area by conducting home visits. The CATTS help to promote adherence to ART and TB therapy and provide counseling and advice to clients on how to access other forms of social support. Clients are instructed to report to the clinic immediately if any serious problems arise.24

Another model initiative established by the Elizabeth Glaser Pediatric AIDS Foundation involves family support groups.15 These groups are comprised of HIV-positive antenatal and postnatal mothers and their families who come together to support each other to follow through with PMTCT interventions.

ADHERENCE
Adherence is the key to successful ART treatment outcomes. Sustaining adherence to life-long treatment through positive prevention methods (e.g., condom use) and reduction of HIV/AIDS-related stigma requires much more than proper selection and consistent supply of ARV drugs and treatment monitoring. There is a need for effective community and individual education about ARV treatment on topics including how to take and adhere to drugs, when to seek help for treatment of side effects, how to prevent HIV transmission, and how to access supportive care. Communities also need information on issues such as equity of access and criteria for enrollment into ARV treatment programs. The number of additional personnel required to provide adherence support in facility- and home-based models varies widely, and should include both medical and nonmedical personnel.
THE CREATIVITY INITIATIVE: EMPOWERING PEOPLE LIVING WITH HIV TO BECOME “CHANGE AGENTS”
Keith PWj McAdam, Andrew Kambugu, Leah Thayer, Penny AS McAdam, and Caleb Twijukye
Infectious Diseases Institute, Makerere University, Uganda

At the Infectious Diseases Institute (IDI), a tertiary care facility in Kampala, Uganda, some 12,000 people living with HIV (more than half on ART) are now called mikwano jaffe (our friends) instead of patients or clients. This shift represents a small change in language but a huge change in attitude. The word patients connotes problems, but friends implies solutions. Our friends, mikwano jaffe, need not be viewed as unfortunate victims, but rather as a key overlooked resource. Many are strong and committed individuals whose creative potential, if effectively harnessed and channeled to support prevention, could produce substantial, low-cost benefits for their communities. Such an approach to those receiving care is unusual at a tertiary care facility, particularly one that is part of a government hospital that must provide free care to everyone who requests it.

This “friend-led” initiative cuts across religion, linguistic group, age, gender, and income level. Friends join with other volunteers to sing, dance, and do drama; draw and paint; facilitate interactive board games; impart entrepreneurial and life skills; share testimonies; and provide spiritual and social support. The initiative is enabling dramatic changes in clients’ abilities to care for and encourage others receiving treatment at IDI. Through this approach, clients are gaining the courage and confidence to tell their poignant stories, and they are taking responsibility for the care and support of new clients.

DESCRIPTION OF THE INTERVENTION
It is 5:00 p.m. on a Friday afternoon. IDI doctors, nurses, and counselors are exhausted from the past nine hours, during which they have served over 300 people. The clients remaining in the clinic have been waiting for several hours to receive care, and some have just endured laborious medical procedures. Everyone is exhausted.

Suddenly a group of people begin drumming. Singers and dancers wearing brightly colored fabric begin moving around the clinic, inciting others to participate. Within minutes, almost everyone in the room is singing, dancing, smiling, and sharing their personal stories.

This event is part of a program called The Creativity Initiative, which aims to build the courage of IDI friends to share their life stories and to support other HIV-positive people in adhering to treatment. This is an initiative by and for people living with HIV, in which positive living is the emphasis. Through this exciting endeavor, IDI friends join with volunteers to develop creative communities within the clinic setting.

One year ago, before The Creativity Initiative began, the clinic waiting room resembled a morgue rather than a place of
treatment and hope. People sat quietly in a queue and moved up one space at a time. They didn’t talk to each other. They were private, silent, alone, and hoping that nobody would recognize them. The Creativity Initiative is now facilitating a dramatic change in the clinic’s atmosphere, as well as in friends’ abilities to care for and encourage others receiving treatment at IDI.

The Creativity Initiative builds community, enlivens the IDI waiting room, and aims to promote disclosure and adherence. The more relaxed atmosphere leads to conversation and builds peoples’ self-confidence. A number of interactive, supportive, and educational activities occur on a daily basis as part of this intervention. The following is a brief description of some of these activities:

- **On most days, between 15 and 20 friends gather in the clinic to express their feelings through drawing and painting. Beautiful pieces have been created that express a wide range of emotions.** Recently, there has been an effort to engage participation of a larger portion of those waiting in the clinic. The resulting collage project has become known as “fun art,” a participatory exercise whereby people can see how their small contribution can be represented in a beautiful outcome. Artists in residence facilitate this participatory exercise, and their creations now adorn the IDI walls.

- **Every morning, a few friends share their stories through impromptu testimony. Sometimes these are spoken and sometimes they are sung; they are always incredibly moving. People talk about how they became infected with HIV, how they are coping with having a chronic disease, and how they deal with the difficult challenges of taking medications every day for the rest of their lives.** These morning sessions encourage friends to share and build supportive relationships with one another. Experienced friends are great teachers for newcomers and feel better about themselves because of being able to serve others.

- **A singing and dancing group has been formed called Kalibobbo (strength).** Several times a week, a group of shy and quiet-looking women come to life and brighten the clinic with their songs about healthy living.

- **More than 50% of IDI friends are unemployed, and most are scratching out a living at less than one U.S. dollar per day.** Workshops have been organized on how to start small businesses, and friends have led programs on mushroom growing, fruit preserving, bead making, oven making, baking, bookkeeping, business planning, basket weaving, and making of local crafts. Small support groups have been formed, and they are looking for microfinancing so that friends can begin income-generating groups.

- **Interactive board games are set up in the waiting room. This gives friends something to do while they wait and also facilitates opportunities for interaction.**

- **For those feeling sick, there is a quiet area with a mat for resting.**

As a result of the confidence built through this initiative, friends have expressed a strong interest in beginning to provide support to HIV-positive people outside the IDI clinic. A participatory program is being designed to train interested friends and to provide them with the tools to support people living with HIV in an urban context.
community environment. The intention of this effort will be to encourage improved prevention (including family HIV testing), safe disclosure, better adherence, and reduced stigma.

OUTCOMES
The Creativity Initiative has been designed as a flexible program that is not too heavily managed; we feel this is important since it is by and for people, and peoples’ needs change over time. Empowering friends to have control of the waiting room has led to a real sense of ownership and responsibility among those who attend the clinic. We have received extensive informal feedback, both from IDI staff who work closely with friends and also from the friends themselves. We have also conducted customer satisfaction surveys before and one year after the program began—surveys were designed to measure changes during the program implementation period. The following improvements have been noted through these two sources of feedback:

• There is a strong sense that the waiting room environment has improved dramatically. There is also a sense among friends that they are being treated better than before the initiative, which indicates that the initiative has also had a positive impact on IDI staff. For example, friends report that they are experiencing less stigmatizing messages, are made to feel more welcome, and more frequently have an occasion to smile while they are attending the clinic. This reinforces the importance of staff training, particularly at reception and waiting areas, since staff are normally very stressed in busy clinics.

• There is a notably improved sense of confidence among friends who participate; in the customer satisfaction survey, 74% of friends said that they would be interested in helping to provide support at the community level to people living with HIV.

• According to the survey, there has been an increase in the percentage of friends who have disclosed their HIV status to a spouse, family member, relative, or friend.

LESSONS LEARNED
Implementation of this initiative has been a process of watching and learning how to support most effectively our friends’ efforts to help themselves. Observations to date include the following:

• A change in language—from patients to friends—has had a huge impact on the willingness of friends to be active partners in their own care, and on staff participation in the initiative.

• People living with HIV should be recognized as a cost-effective resource for promoting disclosure, prevention, adherence, and stigma reduction. However, it is important that they feel that they are actually in charge of efforts, and that they have some flexibility with regard to decision making, including how to spend the available budget. The decisions that they make might not always be the decisions that staff would make, but their decisions are most likely based on participants’ needs and therefore should be respected.

• In situations where those giving care and those receiving care are separated by culture, class, educational level, and/or economic difference, there may be significant disconnects in expectations about goals and means of meeting goals. It is important
to have people who can serve as “bridges” between the two worlds.

- It is important to find mechanisms for ensuring that the program is as inclusive as possible. This must include monitoring activities to ensure that subtle methods of exclusion are not being implemented. For example, if spiritual support is part of the program, it is important to ensure that all relevant religions are honored. In a situation where the vast majority of clients like to express their faith, there has to be sensitivity to differences.

- Creativity cuts across barriers (e.g., tribe, religion, age, sex) and is therefore a good way to bring people together.

- Routinely monitoring change (with the help of independent social science groups) can be a helpful way of seeing what is working and what needs to be modified.

- Monthly meetings that bring together volunteers and friends invigorate everyone involved and are a good way to bring in new potential sources of support.

- In a situation where every family is affected by HIV, it is constructive to engage creative volunteers as well as friends, as equal partners, with each bringing valuable qualities and working together to banish stigma.

- A queuing system that allows people to move around while waiting opens up the possibility for a range of activities that might not otherwise be possible in the clinic.

- Entrepreneurial skills training requires money at the outset; music creates “instant smiles”; musicians and artists in residence are a great way of stimulating new learning; people love to see their creative work displayed.

- The reception/waiting area is a critical target for staff training, as it sets the tone for the entire clinic.

**RECOMMENDATIONS**

There are a number of lessons that might be applicable to similar programs in different settings.

- **Improving the clinical environment**
  - Providing a means of engaging people in creative activities is a nondiscriminating way to engage people during long waits and cuts across faith, age, sex, and economic status.
  - Establishing a queuing system that allows people mobility during waiting times is important. For example, we found that using an electronic numbering system, rather than making people wait in a physical line, made it easier for them to tolerate the long waits because they were able to move around and engage in other activities. The numbering system also allowed clinic personnel to avoid calling out peoples’ names in public, which sometimes made people feel too exposed.

- **Building the confidence of those receiving care**
  - Providing people with opportunities to tell their stories in a nonstigmatizing environment is the single most important goal.
  - Build the program with the assumption that people feel better if they are engaged in, and critical to, a set of activities.
  - Aim to provide opportunities for people to help each other, as that will both give them something to do and also
provide them a chance to receive positive feedback.
- Focusing on peoples’ strengths and assets is enabling for everyone.

- **Enabling people living with HIV to lead programs that encourage prevention, adherence, disclosure, and stigma reduction**
  - Recognize that there needs to be a balance between the wisdom of those living with the virus, and experts’ opinions about what might work.
  - Leave extensive time for program development. If sufficient time is not given, a large degree of consultation and trial and error will be impossible and the program is unlikely to work.

- **General guidelines**
  - Provide for independent monitoring of progress on a fairly regular basis.
  - Involve community volunteers to invigorate everyone. This can be done through monthly meetings to review progress and opportunities, and through partnerships with businesses that want to express their corporate responsibility.
  - Building entrepreneurialism will help participants in the long run. This can be done through skills workshops and, if possible, microfinance.
  - An appreciation board is a public way to enable acknowledgment of others.
  - Relinquish control of the planning process for this type of program. Even if friends do not develop things as you would, they will develop a situation that works for them and their peers.
  - Provide space where participants can publicly express themselves—for example, through their own notice boards or through opportunities to display their creative works in public.

**CONCLUSION**

There are many efforts worldwide to develop peer support in communities affected by HIV, bringing together those who share a common cause or identity, for example, women, children, occupational groups such as sex workers, or factory employees. Peer education is widely adopted, and “buddies” provide individuals with care and treatment support. The Creativity Initiative has effectively cut across some of the most common barriers to communication: age, sex, religion, economic, tribal, and language differences. Empowering those living with HIV to take more control of their situations in the clinic, sharing their stories with others, and helping others to deal with difficult social situations has given many the vision and courage to contemplate becoming change agents in their own homes and communities. The medical paradigm for control of the HIV epidemic (which has been so effective in affluent countries) is being stretched to the limit in Africa, where institutional and human resources are inadequate for the large numbers seeking care. Those living with HIV can be part of the solution to the workforce needs. There are thousands of busy clinics in Africa where people wait patiently for hours to see health-care workers. Our experience of enlivening the clinic with creative activities and building “hope through friendship” could not only improve the ambience of HIV clinics but also empower their clients to become societal change agents.
The JCRC in Uganda has developed a countrywide network of volunteer “ART adherence monitors” consisting mainly of laypeople supervised by trained counselors/adherence supervisors. These monitors are selected from within the community and do their work among the patients accessing therapy within their neighborhood. The volunteers include those already involved in ART support activities, including people living with HIV, members of ART clubs, expert patients, and lay counselors. Active participation of patients in their own treatment as members of an adherence team encourages closer cooperation with health-care workers and better feedback on the effects of treatment.

Another strategy that has been adopted by many providers is a process whereby patients must nominate “treatment assistants” before they initiate therapy. Assistants serve as confidants and/or companions to help the patient adhere to their medications. Laypeople who fill this role may be family members, community counselors, friends, or others. They support adherence at the family level by supervising drug taking and can also offer moral support. Ensuring adherence using treatment assistants has been shown to yield excellent treatment outcomes, even in the absence of sophisticated laboratory monitoring.23

Peer counseling and other interpersonal communication by peers, in some cases using text messages via mobile phones, have also been utilized to encourage ART adherence.25

COLLABORATIONS WITH NGOS AND COMMUNITY-BASED ORGANIZATIONS

Community participation is increasingly considered to be a crucial factor in the fight against HIV/AIDS. Community-based programs commonly using laypeople and CHWs have been particularly effective in HIV/AIDS prevention, care, support, and treatment programs in sub-Saharan Africa.26-28 Organizations like Catholic Relief Services, World Vision, and the Salvation Army established the first anonymous CT services as early as 1987 in many resource-limited settings.29 They have initiated, supported, and organized a range of HIV/AIDS activities including VCT services and provision of ART using trained community volunteers. NGOs and faith-based organizations (FBOs) have established AIDS committees at the grassroots level using community lay volunteers and have trained them to support community-based VCT and care activities including advocacy, access, and referral for ART services. In addition, they have funded community-based organizations (CBOs) comprised of laypeople to implement VCT and ART services in the communities where they operate.30

There is increasing evidence from Uganda, Thailand, Senegal, and other countries with successful HIV/AIDS prevention programs that a diverse spectrum of public-private partnerships that include laypeople in CBOs, projects, and NGOs, in conjunction with high-level political commitment, is the most effective approach to controlling the epidemic.30-32 Most of the work in these initiatives involves full participation of laypeople who are trained to deliver some key services and work under experienced health professionals. NGOs, including FBOs and CBOs, are often the major providers of care and support services to people living with HIV. Indeed, FBOs are often the only true NGOs in many rural areas. FBOs can be better equipped to mobilize people and resources and to reach rural or isolated areas because of organizational networks that reach even the most remote villages. FBOs and CBOs also tend to have a good understanding of local social and cultural norms and are therefore appropriate, effective, and necessary vehicles in HIV prevention and patient care and support programs. Around the world, FBOs often have the influence to mobilize large
numbers of lay volunteers to work for the success of health delivery services.32

NGOs have also played a significant role in sensitizing their governments to HIV/AIDS issues and as a result, have found ways of working collaboratively with like-minded groups to ensure that VCT and other services are provided either directly or through referrals from the NGO and government and private sectors. Some NGOs that do not have the capacity to carry out testing themselves can still provide much-needed counseling services, thus easing the burden on the public sector.

Innovative and effective health promotion and education strategies include social marketing to help raise community awareness of HIV/AIDS and VCT. These campaigns have played a large part in normalizing and destigmatizing VCT and ensuring that communities continually demand and use services. NGOs have played a crucial role in such communication efforts, as well as in the identification and training of community members to lead the process as community volunteers, peer educators, or advisors.

Governments recognize the major role that NGOs and communities play in HIV/AIDS care and prevention. The Ugandan government, for example, has supported the role of communities through an initiative of the Uganda AIDS Commission called the Community-led HIV/AIDS Initiative (CHAI). The objective of CHAI was to empower communities to develop, implement, and manage HIV/AIDS interventions through a participatory process. The initiative focused on promoting community understanding of the gravity of the problem and community ownership of HIV/AIDS efforts. In so doing, the initiative positioned community needs at the forefront of service provision, promoting delivery of demand-driven services while demystifying the belief that the fight against HIV/AIDS is the sole responsibility of health and community workers.33

COMMUNITY INVOLVEMENT IN HIV TESTING AND ART DELIVERY

Community Mobilization and Ownership
In the context of high HIV prevalence in many countries, usually coupled with high levels of stigma and discrimination, an ongoing process of general awareness and community sensitization around HIV/AIDS is fundamental to the development of any client-centered, quality HIV/AIDS program. Accordingly, a pilot study on ART in a community clinic conducted in South Africa found community involvement to be a very valuable, untapped resource in ART delivery.34 There is also a basic requirement for individuals to be consistently informed about available VCT, treatment facilities, nearby HIV/AIDS services, and options available to them by CHWs or community groups and community-accessible media. Continuous but regularly appraised and up-to-date community IEC will go a long way in ensuring optimum use of care and prevention facilities.

Genuine community involvement and participation at all levels, from needs assessments and the design of programs to implementation and monitoring of services, is an essential strategy, primarily to ensure community ownership but also to contribute toward sustainability.

Stigma Reduction
Stigma remains one of the greatest challenges for people living with HIV. Even in communities where services are available and accessible, these are often not used optimally as a result of the stigma associated with HIV/AIDS. Community-based IEC can be an effective strategy to promote prevention and stigma reduction and is most effective with the full participation of community leaders, health-care providers, CBOs, and FBOs. The strategic use of mass media, especially radio, in IEC campaigns can often add greatly to the
success of IEC. Another strategy involves use of people living with HIV. In a survey conducted in Ethiopia, it was found that the recent trend of community involvement and active roles of people living with HIV in awareness and outreach campaigns has successfully established the idea that people living with HIV are not an immediate danger to society but rather a great resource. Through these programs, people living with HIV reach out to one another to provide needed care and support. This has been noted as a landmark step in breaking the stigma associated with HIV/AIDS in Ethiopia. Involvement of expert patients successfully using services, especially ART, is a powerful tool for combating stigma and subsequently encourages more people to come forward for HIV testing, counseling, and treatment. However, exclusive use of people living with HIV can in itself promote stigma unless the community as a whole is involved. For this reason, involvement of laypeople in the provision of health services will help improve health-seeking behavior and acceptance of ARV treatment, and reduce barriers to care and treatment.

**LESSONS LEARNED**

The experience of responding to the HIV pandemic over the past 20 years has shown that there are a number of effective approaches that utilize laypeople in support of HIV prevention and treatment. The challenge now is to move from successful, small-scale projects that reach relatively few individuals to effective strategies that can make a larger impact and contribute to reaching the goal of universal access to HIV prevention, care, and treatment. Laypeople have played key roles in different aspects of HIV service delivery, and their contributions and examples of successful projects need to be scaled up to benefit more individuals and programs for greater impact.

Key lessons learned are summarized as follows:

- **Use of lay counselors, CHWs, and people living with HIV improves VCT service uptake.** Laypeople have been especially effective when incorporated as part of home-based care teams and facility-based programs, especially where group information sessions and opt-in individual pretest counseling models of VCT are used.
- **When training lay counselors, it is important to ensure that they are made aware of their limitations.** While providing HIV counseling services, they must be supervised by senior counselors and learn to refer problematic cases and to undergo continuous education. The programs should make sure that counseling services are not left as the sole responsibility of laypeople without professional support.
- **It is important to ensure that training of laypeople is based on a well-developed, proven curriculum that offers opportunities for continuous training and support.**
education and provides standardized tools to assist laypeople in their work.

- It is clear that VCT and ART cannot be optimally scaled up without strong community mobilization from the start of implementation. This can be achieved with the involvement of NGOs and CBOs that utilize lay workers, including people living with HIV. Laypeople within the community are key for community sensitization, motivation, advocacy for services, stigma reduction, and ongoing support counseling. Ongoing programs have found that posttest care and treatment access are also greatly augmented by CBOs.

- Incorporation of people living with HIV as expert patients in facility-based ART clinics relieves the limited professional health personnel from time-consuming tasks. By delegating certain tasks to lay workers, the efficiency and effectiveness of clinics to handle a large number of patients can be maximized.

- Trained laypeople deployed as field officers can efficiently perform several follow-up tasks in the home related to ART, including ART delivery, adherence monitoring, ART failure or toxicity detection, detection of opportunistic infections, referral for medical treatment, and offering of VCT to household members. This eliminates much of the need for follow-up by health professionals, freeing up more of their time for clinical care.

- People living with HIV receiving ART, when trained and assisted to form ART clubs, are an invaluable resource for mobilizing communities and increasing awareness of VCT and ART, decreasing stigma, supporting adherence, and consequently increasing uptake of services.

- Home-based VCT using laypeople is not only an effective preventive strategy but also a way to increase access to treatment and adherence.

**RECOMMENDATIONS**

For making the scale-up of VCT and ART possible in countries with severe human resource constraints, it is imperative to incorporate laypeople within the communities including people living with HIV, NGOs, CBOs, and FBOs in public-private partnerships in order to urgently scale up ART to millions of people in need of treatment.

To achieve this goal there is a need for task shifting, especially for time-consuming, repetitive tasks that may easily be performed by nonprofessional staff. The development of national laypeople’s programs in various forms needs to be supported by governments at the policy level and coordinated with established medical and paramedical interest groups. This may require additional legislation or special authorization through ministries of health to change the current work practices that by and large rely on professional staff. Most current health-care systems rely on an acute-care model where many of the tasks are performed by the doctors, clinical officers, and nurses. This will need to change to a chronic-care model to address the current health worker shortages.

Task shifting should not be implemented at the expense of compromising standards of care and accountability. On the contrary, it should represent an improvement in the overall quality of care. Whether or not this occurs will depend on the level of training and supervision of the laypeople involved. Although a wide variety of training materials for these tasks exist, quality and good patient outcomes must be ensured through systematized training from carefully developed modules that are tailored to the education levels and understanding of laypeople. The training should be competence based and include refresher courses and in-service training.

To maintain a quality ART program, there is a need to mentor the laypeople who have undergone
training using more experienced health-care workers for an adequate period of time. Internship in established ART centers would quickly enhance the skills of these lay workers as well. Regular support supervision that is essential for any ART program would also apply to lay workers performing in their respective roles. Monitoring and evaluation of programs that use laypeople is absolutely essential to inform national programs and policymakers on how effective these workers are. Although evaluation using the common indicators of treatment outcome and quality of program would be used, it may be necessary to incorporate operational research to identify additional indicators to more appropriately evaluate performance of laypeople.

As both prevention and treatment are brought to scale, these initiatives should be carefully integrated to create a single continuum of services. Resources to make this transition possible and to sustain it over time need to be factored in to the long-term planning of ongoing programs.

**CONCLUSION**

Global consensus has been reached on the need for full involvement and participation of communities, including people living with HIV, young people, and civil society in HIV/AIDS programs. For this reason, efforts to address human resources and service delivery issues for the scaling up of ART should not be limited to a focus on the formal health-care delivery system. In order to ensure that the millions in need of ART gain timely access to treatment, it is important to go beyond a focus on professional service providers and beyond facility-based service provision to facilitate greater involvement of laypeople for a variety of health-related tasks.
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The Use of Midwives and Traditional Birth Attendants in HIV Care

Freddy Perez and Tih Pius Muffih

In 2000, the member countries of the United Nations agreed to reduce the mortality rate for children younger than five years of age by two-thirds and maternal mortality by three-quarters by 2015 as part of the Millennium Development Goals (MDGs). However, these goals are unlikely to be achieved due to the inability of current maternal and child health (MCH) programs to reach the poorest households. Achieving the health MDGs will be a major challenge in the years ahead, yet these goals must be achieved if we are to succeed in reversing the global HIV pandemic.

Of the estimated total 536,000 maternal deaths worldwide in 2005, developing countries accounted for 99%. More than half of maternal deaths occurred in the sub-Saharan African region alone, followed by Asia (45%). The rate of maternal mortality in sub-Saharan African countries is estimated to be around 900 deaths per 100,000 live births. Overall, the progress in reducing maternal mortality has been modest, with a decline of 5.4% between 1990 and 2005, while the regions of sub-Saharan Africa, western Asia, and south Asia have shown little progress.

The five major causes of maternal mortality are postpartum hemorrhage, obstructed labor, hypertensive disease of pregnancy, postpartum infection, and complication from unsafe abortion. HIV/AIDS has become an important underlying factor in direct maternal deaths and an indirect cause of maternal deaths in sub-Saharan Africa.

Women accounted for nearly half of the 40 million people living with HIV in 2006. In sub-Saharan Africa, females constitute 59% of those infected with HIV, and 76% of infected individuals are between the ages of 15 and 24. Thus, high levels of maternal mortality coexist with high levels of HIV prevalence among women of childbearing age.

There are important disparities with respect to access to health systems for women. Data from the World Bank show that in the poorest 20% of households in most developing countries, more than 90% of deliveries take place at home.

The International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), defines a maternal death as “a death of a women while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.”
Consequently, each year more than 60 million women worldwide deliver without the assistance of skilled care.\textsuperscript{16}

**THE SAFE MOTHERHOOD INITIATIVE**

Since the 1980s, the prevention of maternal mortality in resource-limited settings has received widespread attention from international health organizations and the scientific community.\textsuperscript{17} The Safe Motherhood Initiative was launched at the Nairobi Safe Motherhood Conference in 1987. This is a global initiative to reduce maternal mortality in developing countries through a collaborative effort of international agencies, national governments, and nongovernmental organizations.\textsuperscript{18,19}

This public-health strategy emphasizes safe delivery through the provision of skilled birth attendants, improved basic obstetric services in health facilities, development of prenatal care that includes screening for at-risk pregnancies, access to emergency obstetric care in hospitals, and family planning as key interventions to reduce neonatal and maternal mortality.\textsuperscript{20}

Unfortunately, 20 years have now passed since the Safe Motherhood Initiative was launched, and little progress has been reported.\textsuperscript{7,21} Accomplishments have been made in terms of greater awareness of the issue and of what works and what does not, but without achieving substantial decreases in maternal mortality.\textsuperscript{22,23} The stated reasons for not achieving the primary goal of the initiative, which was to reduce maternal mortality, included the absence of a clear focus, strategic errors such as focusing only on mothers’ risk of complications through screening at antenatal consultations, and an overreliance on traditional birth attendants (TBAs).\textsuperscript{24,25}

Despite these failures, a strong consensus exists about appropriate strategies to reduce rates of maternal mortality.\textsuperscript{26-28} Industrialized countries succeeded in halving their maternal mortality rates during the 19th century through the provision of professional skilled care at birth.\textsuperscript{29} Recent evidence from other regions of the world has shown promising achievements as well.\textsuperscript{30-32} However, in many developing countries, where lack of attended deliveries is considered one of the largest health inequities, there is still a long way to go to achieve goals for skilled attendance. Populations with the highest maternal mortality rates, many of which are in sub-Saharan Africa, are confronted with various barriers to achieving these attendance goals, such as geographical isolation, long distances from health facilities,\textsuperscript{33} inability to pay for services, and health facilities that cannot properly function due to the migration (“brain drain”) of health workers and frequent shortages of essential drugs.

There is no doubt that delivery with the assistance of a skilled attendant in a health facility should be a woman’s right if she so chooses. However, in many countries where maternal mortality is high and where professional birth attendants are in short supply or unavailable, universal access for all women to a skilled birth attendant is not achievable.

In this chapter, we provide an overview of maternal health services in the context of the HIV pandemic and outline the role of health professionals in maternal health and HIV prevention, care, and treatment. Particular attention will be paid to the potential role of TBAs in expanding access to quality care. We conclude by considering policy implications and highlighting areas where further research is needed.

**MCH SERVICES IN THE CONTEXT OF THE HIV PANDEMIC IN SUB-SAHARAN AFRICA**

Antenatal care (ANC) is a complex set of activities aimed at reducing maternal and fetal morbidity and mortality. This is achieved by decreasing the
likelihood that a pregnant woman will experience serious complications during pregnancy and by improving the maternal death and prelabor fetal outcomes of women with complications. ANC is one of the four pillars (along with family planning, clean and safe delivery, and essential obstetric care) of the Safe Motherhood Initiative promulgated by the United Nations Population Fund (UNFPA), the World Bank, and the World Health Organization (WHO).

Use of ANC Services
The level of uptake of ANC services is determined by several factors, including patient needs, demand for services, availability of services, and whether or not such care is offered during pregnancy. In the 1990s, a 20% increase in the use of ANC services worldwide was reported, and currently nearly 70% of women have at least one ANC visit with a health professional during their pregnancy.26,34 Despite these increases, important disparities exist between developed countries, where 98% of women use ANC services, and developing countries, where the rate is closer to 68%.21,35 WHO and the United Nations Children’s Fund (UNICEF) have shown a significant correlation in developing countries between having had at least one ANC visit during pregnancy and having delivered with the assistance of a qualified health professional. It has also been suggested that the likelihood of using skilled delivery services is mediated by the wealth of the household in which the woman lives and urban-rural differences in access to health facilities.36,37 Educational level has also been proven to be a determinant of the use of ANC services.38 Women who have at least a minimum level of formal education have better financial standing and, more importantly, more autonomy in decision making within the household.39,40

Perceptions also play an important role in whether or not a woman accesses ANC services, and, in turn, skilled attendance, in places where such services are available. In South Africa, a study of the perception of ANC services showed that the quality of interactions between women accessing ANC services and the health staff was poor and that, as a result, women accessing ANC services expected to be inadequately received by the midwife.41 Likewise, the use of ANC services can be determined by a woman’s perceptions of the risks associated with pregnancy. A number of reports from developing countries have also shown the importance of sociocultural determinants linked to the use of ANC services, such as the absence of women’s decision-making power and barriers grounded in traditional belief systems, among others.42,43

ANC is widely used as a strategy for improving maternal health through the prevention and treatment of pregnancy-related conditions and the detection of risk factors that could lead to complications during pregnancy and delivery.44 However, there is still insufficient evidence to link ANC interventions with a reduction in maternal mortality.45,46 Bloom and colleagues showed a strong association between the level of care obtained during pregnancy and the use of safe delivery care.47 Previous research concerning ANC attendance and maternal mortality has been inconsistent, with some studies showing a reduction in maternal mortality associated with improved nutrition and screening for high risk and presumptive treatment of infection during pregnancy,48,49 while other reports have found no such relationships.50 Graham and Hussein rightly point out that increased use of health care is a necessary but insufficient condition for the reduction of maternal and perinatal mortality at the population level, particularly if the quality of care is not ensured.51
Routine ANC Models
Since the 1980s, there has been a trend in favor of reducing the number of routine antenatal attendances in low-risk pregnancies. Recommendations have been made concerning the need to review the total number of ANC visits for women with uncomplicated pregnancies in view of the available evidence, which has suggested that reduced ANC packages or prenatal care for low-risk women can be as effective as standard models of ANC. The new “goal-orientated” model of ANC emphasizes fewer but more objectively oriented visits and fewer procedures per visit.

There has been a lack of evidence that ANC, as currently recommended (i.e., in terms of frequency, timing of visits, and content), is effective. Several trials have shown that for women without previous or current complications, a reduction in the number of ANC visits, including goal-orientated effective and evidence-based practice, is not associated with increased risk to women or their babies, nor does it have adverse effects on the major intermediate pregnancy outcomes as compared to a standard model of ANC.

Despite these findings on the questionable effectiveness of early and routine ANC visits, we should not overlook the value of ANC in the detection and treatment of pregnancy-related complications. This intervention still constitutes a first essential link to the management of pregnancy. It is during these visits that the health worker can educate women on the risks associated with pregnancy and childbirth, and discuss the various delivery options. ANC is also an entry point to the general health system, thus improving access to complementary services such as MCH care, family planning, and postnatal care. It is also the main entry point to care for pregnant women living with HIV and their unborn children.

Community-Based Interventions for Maternal and Neonatal Health
In the ideal scenario, every woman would give birth in a health facility in the presence of a professional health worker. This does not mean that community-based interventions have no place. Maternal health must be considered as a public-health issue, with community interventions being complementary to care received in health facilities such as health centers or district hospitals. In this sense, community participation has been advocated to build linkages between primary health services and their users and to improve the quality of these services.

Health promotion via women’s groups, where maternal and newborn care issues are traditionally discussed, is one community-based activity that has been shown to increase the use of ANC. This method of promotion has also been shown to improve linkages between the community and primary care services, increase the number of deliveries taking place at a health facility, and encourage better hygiene practices. In a study in Nepal, these changes in behavior resulted in a 30% reduction in neonatal mortality and a significant reduction in maternal mortality. Likewise, it has been reported that women in rural settings are aware of maternal health problems and can be motivated to address them through participatory research.

Postpartum hemorrhage (PPH) is a major cause of maternal mortality in low-income countries. In settings where the provision of skilled care at delivery is limited and could likely remain so, there is a need for community-based treatment for this condition. Recent reports have suggested that oral misoprostol, a prostaglandin analogue with uterotonic effect (i.e., ability to stimulate muscular tone in the uterus), could be a suitable treatment for PPH where access to skilled health workers during labor and delivery is limited. This low-cost treatment can
be administrated orally and does not require cold storage.\textsuperscript{60,61} It has been shown that misoprostol is a promising drug to prevent life-threatening PPH when administered via community-based treatment by trained TBAs.\textsuperscript{62} Many deaths related to hemorrhage could potentially be prevented at the community level if oral misoprostol were provided to trained community health workers.\textsuperscript{53,64} However, additional research is still needed on the best drug combinations, routes of delivery, and doses of uterotonic for the treatment of PPH.

Likewise, a recent study in Uganda showed how community health workers can safely provide contraceptive injections in rural settings when training and logistical support systems are provided.\textsuperscript{65}

The success of community-based interventions that emphasize the participation of TBAs depends on the role and status of TBAs in a given community. Community members’ perceptions of TBAs can greatly influence the capacity of TBAs to serve as health agents.\textsuperscript{66} In India, a 62\% reduction in neonatal mortality was achieved through a community-based approach that included training TBAs and local women to treat sick newborns at home.\textsuperscript{67} Furthermore, a trial in Pakistan reported substantial reductions in perinatal mortality and maternal mortality as a result of training and integrating TBAs into the health system.\textsuperscript{68}

A recent meta-analysis of 60 studies indicated that training TBAs was associated with significant improvements in their level of knowledge and the quality of advice they gave on family and child health. A reduction was also seen in rates of perinatal mortality, but there was no effect on maternal mortality. Notably, the authors of this meta-analysis were not able to address the question of causality and highlighted that training TBAs cannot be used as an isolated intervention, but should rather be implemented as a component of an overall MCH strategy.\textsuperscript{69} Thus, any interventions involving the use of TBAs should be “context-specific and community-based” so as to complement health center-based maternal care in countries with high maternal mortality rates.\textsuperscript{70}

Overall, studies have confirmed the possibility of improving perinatal and maternal health through community-level interventions. Complementary approaches, in which community-based interventions are paired with the strengthening and/or expansion of services at the health facility level, also have the potential to address a variety of other health challenges, such as uptake of HIV testing and compliance with prevention of mother-to-child transmission (PMTCT) regimens.\textsuperscript{71}

**MOTHER AND CHILD HEALTH SERVICES AND THE ROLE OF TBAs**

**Mother and Child Care by TBAs: What Is the Evidence?**

With such high maternal mortality rates in many countries, priority interventions for “safe motherhood” have been proposed and implemented in many resource-limited settings. Skilled attendance at birth is a key indicator for measuring progress toward improved women’s health.\textsuperscript{*} Available data from developing countries show an important increase in skilled attendance at birth, from 45\% to 54\%, between 1990 and 2000, except for the sub-Saharan African region, where coverage has stagnated at approximately 40\%.\textsuperscript{71} Additionally, a recent report confirms that worldwide, an estimated 63\% of all births were attended by a skilled health-care professional (midwife, doctor, or nurse) who has been educated and trained to proficiency in the skills needed to manage normal (uncomplicated) pregnancies, childbirth, and the immediate postnatal period and in the identification, management, or referral of complications in women and newborns.\textsuperscript{72}

\textsuperscript{*}A skilled attendant is defined as a health professional (midwife, doctor, or nurse) who has been educated and trained to proficiency in the skills needed to manage normal (uncomplicated) pregnancies, childbirth, and the immediate postnatal period and in the identification, management, or referral of complications in women and newborns.\textsuperscript{72}
worker, with considerable variations between developed regions (99%) and developing countries (59%). Therefore, only slightly more than half of the world’s mothers deliver with a skilled attendant, leaving more than 60 million women giving birth without skilled care every year, mostly at home.

TBAs are still the main obstetric care providers for most women. In developing countries, between 60% and 90% of deliveries in rural areas are assisted by TBAs. ANC, as well as deliveries in an institutional setting with skilled health workers, for all women remains a distant reality. Additionally, preference for home births is associated with cultural norms. TBAs speak the local language, have the trust of community members, and can provide psychosocial support at a birth, with important benefits for the mother and the newborn child.

WHO defines a TBA as “a person (usually a woman) who assists the mother at childbirth in her home, often having minimal or no formal education and who initially acquired her skills delivering babies by herself, or through apprenticeship from other TBAs in the family or neighborhood.” A trained TBA is a TBA or family TBA who has received a short course of training through the modern health-care sector to upgrade her skills. The period of training is normally not more than one month, although this may be spread over a longer time period. In addition to assisting at childbirth, a TBA’s responsibilities include care during pregnancy and assistance with family affairs. TBAs describe themselves as counselors, community teachers, and advisers of women in general and pregnant women in particular.

Interventions aimed at enhancing the participation of TBAs in mother-child services date from the late 1980s. Overall, the goal of these interventions has been to decrease the number of maternal deaths through the universal accessibility of maternal care during pregnancy and childbirth. The roles and responsibilities of TBAs were defined as (1) provision of health information and education, (2) sensitization of the population, (3) provision of safe home deliveries, and (4) referral of complicated cases. These roles and responsibilities are summarized in Table 1.

Over the last 15 years, many TBAs have received midwifery training as part of the United Nations (UN) Safe Motherhood Initiative. Even though the inclusion of these community workers in MCH programs has been high on the agenda, it has also brought controversies with regard to the impact this has had and could have on the reduction of maternal and infant mortality. A notable area of debate has been whether to invest health resources into the training of TBAs. Various studies undertaken in the 1980s and 1990s showed contrasting results from this strategy. There is still no definite consensus that TBA training as a single intervention can have a significant impact on maternal mortality. Lack of evidence has limited the widespread implementation of such training.

Recent analyses have come to the conclusion that the impact on maternal mortality of training TBAs is low. As such, international agencies and policymakers have moved away from further consideration of the role of TBAs in favor of advocating skilled birth attendants for all, and governments have been advised to stop training TBAs. Although TBAs cannot be a substitute for skilled health workers, and training programs have not contributed directly to reductions in maternal mortality, TBAs remain a significant workforce in maternity care in many developing countries. Various individual reports have shown improvements in the effectiveness of TBAs in reducing perinatal mortality and increasing timely referrals for complications, as well as increasing the use and provision of ANC through the identification of early signs of complications during labor and delivery, delivery of oral iron prophylaxis integrated into a primary health-care program, and...
On the whole, coverage is far below what is required to meet the UN target of reducing the proportion of children infected with HIV by 50% by 2010. The attainment of these figures necessitates that 80% of all pregnant women accessing ANC receive services for PMTCT of HIV. This will require strengthening MCH services as well as the health systems and the development of new interventions to improve the uptake of PMTCT services.

In conjunction with the Safe Motherhood Initiative, some countries are seeking to enhance the role of TBAs by encouraging their participation in PMTCT programs. Given TBAs’ potential coverage of underserved populations, participation of TBAs has been piloted to help improve the coverage and quality of services offered to rural populations, with participation being defined by a package of activities that TBAs are allowed to carry out.

The first reported PMTCT program worldwide to use TBAs to provide confidential HIV counseling and testing (using an oral fluid HIV rapid test) improving pregnancy outcomes. A recent systematic review showed that TBA training appears to increase ANC attendance rates by 38%.85

**TBAs in the Provision of HIV/AIDS Prevention and Care: Potential Role and Controversies**

Recent data show that, in low-and middle-income countries, the proportion of HIV-positive pregnant women receiving antiretroviral prophylaxis for PMTCT in 2006 was 23%. Current PMTCT programs do not reach many of the women who need them due to sociocultural, economic, systemic, and programmatic issues. Among the factors affecting the coverage of PMTCT interventions are insufficient sensitization among the general population; deteriorating health-care infrastructure, low quality of services, and a lack of available trained staff; fear of violence, discrimination, and stigma; and insufficient utilization of MCH services, with a significant proportion of mothers delivering outside health facilities.

### Table 1. Potential Impact of Participation of TBAs on Safe Motherhood Initiative Targets

<table>
<thead>
<tr>
<th>Roles and Responsibilities of TBAs</th>
<th>Anticipated Outcomes</th>
<th>Expected Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitize communities, especially women of reproductive age, about the importance of ANC, good infant nutrition, immunization, and family planning</td>
<td>Increased utilization of ANC services (e.g., clinic visits, iron supplements)</td>
<td>Improved maternal and infant health</td>
</tr>
<tr>
<td>Refer women presenting with complications during pregnancy or labor</td>
<td>Increased utilization of child health services (e.g., vitamin A supplementation, safe feeding practices)</td>
<td>Reduction of maternal and infant mortality</td>
</tr>
<tr>
<td>Provide safe delivery at home for women who are not using health facilities</td>
<td>Increased immunization coverage</td>
<td></td>
</tr>
<tr>
<td>Provide ANC or refer for immunization Establish communication with rural health centers</td>
<td>Improved TBA participation in primary health-care activities</td>
<td></td>
</tr>
</tbody>
</table>

ANC = antenatal care; TBA = traditional birth attendant
was in Cameroon. Here, TBAs also dispense nevirapine (NVP) to HIV-positive women and ensure that the newborn receives postpartum NVP prophylaxis as an integrated strategy in the PMTCT program. This approach has been implemented through community participation and training and is complemented by supervisory nurses who visit women in the villages on a monthly basis. The authors of the report stated that there was no evidence of confidentiality breaches, a common concern in community-based care. Focus group discussions with community members showed that the participation of TBAs in the PMTCT program has contributed significantly to community awareness of HIV/AIDS and has increased their confidence in TBAs overall.

The level of PMTCT program effectiveness among a selection of sites showed nearly 100% HIV testing uptake among those attending their first ANC visit if a specific cascade of steps was followed. The cascade of steps implemented by these programs comprise the following: (1) A pregnant woman receives ANC at a center offering HIV testing; if she consents to the test, she must receive the test results and, if she is found to be HIV-positive, she receives appropriate prophylaxis. (2) She must then take the prophylaxis during labor, and her infant must receive prophylaxis after delivery. (3) Finally, the mother and infant must receive follow-up care. Program challenges included maintaining adequate supplies of HIV test kits and ARV medications, as well as the provision of continuous support and supervision.

In Tanzania, it has been shown that TBAs, if they acquire additional skills and are sufficiently motivated, can be used effectively in program implementation and can contribute to delivering PMTCT interventions (from counseling to providing single-dose nevirapine [sdNVP]) to women who deliver outside health facilities. In Uganda, after careful selection, training, and sustained and regular supervision, TBAs played an important role in supporting and referring pregnant mothers for facility-based PMTCT services. Manzi and colleagues report on the need to use TBA networks in decentralized PMTCT strategies in Malawi so as to be able to improve coverage.

Table 2 contains a comprehensive summary of activities related to PMTCT that could potentially be performed by TBAs, based on different experiences reported in the literature (though not all activities are being implemented in all initiatives). These activities include identifying pregnant women in the community and facilitating the use of available antenatal and delivery services; reinforcing health messages, including the importance of nutrition during pregnancy; providing information and communication on basic PMTCT concepts and the importance of HIV testing (i.e., community mobilization); and making sure that pregnant women and their partners have free access to HIV counseling and testing services.

The provision of sdNVP to women at the onset of labor and to newborns within 72 hours of birth has been shown to reduce mother-to-child transmission of HIV by 47%. Women receive the maternal dose during pregnancy to ensure that the medication is available for self-administration at the onset of labor. TBAs could have a role in the direct supervision of the PMTCT treatment regimen with sdNVP for the mother and/or child, as advocated in Malawi. For example, Kagaayi et al have reported encouraging results of maternal self-medication and provision of NVP to the newborns in Uganda. Finally, provision of counseling for women and their partners on the reduction of HIV transmission, especially during the postnatal period (including the importance of exclusive breastfeeding if HIV-positive), could also be part of TBA activities.
Table 2. Proposed TBA Activities in Support of PMTCT Programs

<table>
<thead>
<tr>
<th>Activities</th>
<th>Potential Outcomes</th>
</tr>
</thead>
</table>
| Community sensitization focused on a family-centered approach to PMTCT     | • Increase in couples counseling and HIV testing in ANC  
• Increase in number of reproductive-aged women tested for HIV  
• Decrease in unwanted pregnancies among HIV-positive women |
| Community-based HIV counseling and testing                                 | • Increase in number of reproductive-aged women tested for HIV                                                                                           |
| Provision of support and adherence follow-up for PMTCT                     | • Increased dispensation of sdNVP or ART to mother and child  
• Directly observed ingestion of ARVs  
• Early referral of infant for sdNVP or ART dosage if not made directly available to TBAs  
• Greater opportunities to provide or refer exposed infants for sdNVP or ART within 72 hours of birth  
• Improved adherence of mother-child pair to complex PMTCT regimens |
| Appropriate referral of mother and/or infant                               | • Decreased maternal mortality  
• Improved immunization coverage  
• Increased coverage of VCT and PMTCT                                                                 |
| Provision of care and support to affected families                         | • Improved observance of exclusive breastfeeding practices and decreased rate of postnatal HIV transmission  
• Improved follow-up of HIV-exposed infants and adequate referral for early diagnosis, care, and treatment  
• Increased referrals for HIV prevention and care services, including ART |

ANC = antenatal care; ART = antiretroviral therapy; ARV = antiretroviral; sdNVP = single-dose nevirapine; TBA = traditional birth attendant; VCT = voluntary counseling and testing

TBAs can also play an important role in ensuring that HIV-positive pregnant women who require cotrimoxazole prophylaxis take their medication daily and in educating women on the importance of medication adherence, even after they give birth. A recent study reported that out of an estimated four million (HIV-exposed and HIV-infected) children in need of cotrimoxazole prophylaxis, only 4% are currently receiving this intervention.\textsuperscript{126} TBAs can also educate women in the PMTCT program on needed follow-up for the baby and proper administration of infant cotrimoxazole prophylaxis, which needs to be taken from six weeks of age.

For instance, mobilization of TBAs in Uganda has been advised in regions where they carry out the bulk of child delivery in order to expand access to PMTCT services. In this way, they can assist in persuading pregnant women to go for voluntary counseling and testing (VCT) and can mobilize community support for PMTCT.\textsuperscript{116}

As described previously, increasing numbers of pregnant women are resorting to home deliveries
due to conditions of extreme poverty affecting both urban and rural populations in many developing countries. When health professionals are not available, TBAs are usually the only caregivers present at the time of delivery in high-HIV-burden countries. In such settings, encouraging the participation of TBAs in public-health programs could help increase the coverage of MCH care, including PMTCT.

It should be noted that doubts have been raised as to the potential significance of the health improvements that would be gained by involving TBAs in HIV prevention and care tasks during home deliveries in developing countries. In this sense, the use of traditional medicine can also be stigmatized and be associated with nonadherence to antiretroviral therapy (ART) regimens, as has been reported recently in Zambia.

Zimbabwe has one of the greatest HIV burdens in the world, with an average antenatal HIV prevalence rate of 18.1%. PMTCT is among the key HIV prevention strategies in the country’s national HIV/AIDS response. A decrease in the use of ANC services with an increase in home deliveries is affecting the coverage of PMTCT interventions in a context of an accelerated economic crisis. According to the 1999 Zimbabwe Demographic Health Survey, 23% of all deliveries nationally were home deliveries. In 2003, this number had increased twofold, to 46.4%.

A study was undertaken to evaluate the acceptability and feasibility of reinforcing the role of TBAs in family and child health services through their participation in the country’s PMTCT program. TBAs were found to be willing to expand their scope of work regarding MCH activities (e.g., referrals, follow-up) related to PMTCT (see Table 3). Although the long-term delivery of ANC services in Zimbabwe remains in the hands of skilled delivery attendants, PMTCT programs would benefit from complementary approaches led by TBAs to prevent missed opportunities.

**HIV/AIDS Training Programs for TBAs: The Cameroon Experience**

Trained TBAs in Cameroon are indigenous village women who are chosen and supported by their communities. Cameroon Baptist Health Services, a nonprofit health-care organization, offers TBAs a three-week basic training course in theory and practice and one month of observed practical experience. TBAs then practice in their village health center, with periodic support and supervision from a field supervisor (a qualified nurse) for a period of at least six months. A minimum of 10 deliveries are conducted by each TBA under the supervision of the nurse-midwife in charge, or until it is believed that the TBA will perform satisfactorily. Continuing education is carried out annually, and TBA certificates are updated upon successful completion of the refresher course. Provided TBAs have reached a satisfactory standard and their community is prepared for the next stage, they then take part in a one-week intensive PMTCT training.

The training package includes basic etiology of HIV/AIDS, basic counseling skills, principles of ethics and confidentiality, and applied anatomy and physiology. In addition, the “six components of care” are taught, which include planned pregnancy, family health, ANC (including the application of risk scores), safe delivery, postnatal follow-up and infant monitoring, and the use of rapid HIV tests (i.e., testing skills, use of reagents, and reading results). This training package is conducted by a TBA supervisor, health staff directly involved in the program, experienced counselors, obstetrician consultants, midwives, and laboratory technicians. The program is followed up by regular supervisory visits, field-orientated seminars, and refresher courses at the district level. TBAs are usually female, but if a community requests training for a male promoter whom they trust and who is known to have all the attributes of a good village health worker, then he is accepted and trained.
Community-based care

Evidence-based guidelines on HIV/AIDS care and treatment protocols specific to the level of each health facility have been designed to facilitate expanded access, yet in many developing countries, these protocols cannot be fully applied due to the lack of human resources. Doctors constitute a majority of the decision makers responsible for the development of health policies. However, effective leadership without the necessary institutional capacity, midwives and TBAs as part of the health-care team in the provision of maternal health services and HIV/AIDS care.

The Role of Doctors and Nurses in Defining HIV/AIDS Health Policy

Expanding access to ART to treat HIV in resource-limited settings has demonstrated benefits to the health and survival of women and their newborn children.\textsuperscript{134,135} Evidence-based guidelines on HIV/AIDS care and treatment protocols specific to the level of each health facility have been designed to facilitate expanded access, yet in many developing countries, these protocols cannot be fully applied due to the lack of human resources. Doctors constitute a majority of the decision makers responsible for the development of health policies. However, effective leadership without the necessary institutional capacity,

<table>
<thead>
<tr>
<th>Mothers</th>
<th>% Who Agreed to Perform Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raise awareness</td>
<td>14%</td>
</tr>
<tr>
<td>Inform women and men of benefits of HIV testing</td>
<td></td>
</tr>
<tr>
<td>Refer women for HIV testing</td>
<td></td>
</tr>
<tr>
<td>Perform blood tests</td>
<td></td>
</tr>
<tr>
<td>Dispense medication to women</td>
<td></td>
</tr>
<tr>
<td>Directly observe women ingesting their medication during labor</td>
<td></td>
</tr>
<tr>
<td>Inform women of appropriate breastfeeding measures</td>
<td></td>
</tr>
<tr>
<td>Provide psychological support to HIV-positive women</td>
<td></td>
</tr>
<tr>
<td>Provide continuum-of-care services to HIV-positive women and their children</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children</th>
<th>% Who Agreed to Perform Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refer infants to health center for medication</td>
<td></td>
</tr>
<tr>
<td>Accompany infants to health center for medication</td>
<td></td>
</tr>
<tr>
<td>Administer medication to infants</td>
<td></td>
</tr>
<tr>
<td>Assist health center in the documentation of ANC services</td>
<td>16%</td>
</tr>
</tbody>
</table>

\textsuperscript{*All comparisons between trained (n=30) and untrained (n=42) TBAs are not statistically significant.}
resources, or effective policy will not be able to mount effective responses to HIV/AIDS.136

Physicians have a key role to play as reference health staff, particularly in making care and treatment decisions (e.g., initiating or switching therapy, managing serious conditions) as well as in providing supervision and defining HIV/AIDS policies and their implementation. In most countries, HIV/AIDS policies are conceived and developed at the national level by senior health staff and then decentralized to the peripheral levels. Frontline physicians and allied health professionals need to be a part of policymaking and major decision making in all countries. They spend a significant amount of time with patients and, as such, have much to offer in helping to formulate or reform policies. For instance, physicians are acutely aware of the shortage of trained personnel and are likely to support policies that promote the use of complementary staff such as TBAs and lay counselors.

Senior nurses interface with doctors at the regional level to offer technical interpretation and provide support for effective implementation of HIV/AIDS policies at the regional and local levels. They offer the bulk of care to patients and thus play an important leading role in implementing appropriate prevention, care, and treatment services as well as in the routine follow-up of HIV-infected and affected individuals in referral hospitals and rural health centers. As such, nurses should also be consulted concerning decisions on whether or not to use TBAs and lay counselors, since they will be responsible for supervising these community health workers.

Collaboration of TBAs with Nurses and Midwives in Scaling Up Comprehensive HIV/AIDS Care

Nurses and midwives are the primary health-care providers for the majority of populations in resource-limited settings. Their roles are complemented by the use of TBAs, particularly in rural areas. There are simply not enough midwives and nurses to provide PMTCT services and HIV/AIDS care, treatment, and support to all those in need of services. In practice, lay counselors and TBAs have stepped in to fill this gap, with supervision from nurses and midwives.113,115 Due to the absence of nurses and midwives in most villages, TBAs have played this complementary role for many years, and their role has increased significantly with the emergence of the HIV epidemic.

The public-health approach to HIV/AIDS treatment advocated by WHO includes strategies to reduce dependence on trained physicians for the scale-up of ART.137 For this reason, there is a need to devise sustainable human resource solutions, such as the use of nonclinical staff, for the provision and monitoring of ART. One strategy that has been advocated to make better use of the available human resources is to shift routine tasks to less-specialized workers.138 Such an approach involves nurses in prescribing and dispensing ART while community health workers, including TBAs, undertake a wide range of HIV-related activities, thus freeing up the time of nurses for more advanced levels of care. In Cameroon, nurses perform screening, diagnosis, and treatment of people living with HIV, according to standardized protocols, due to an acute shortage of physicians. TBAs are also successfully providing care to people living with HIV in rural areas (T. Pius Muffih, oral communication, 2007). In South Africa, a community-based ART program successfully used nurses to diagnose and treat opportunistic infections and provide follow-up care in line with standard protocols.139 Furthermore, experience from the Botswana ART programs has shown that better utilization of nurses has the potential to increase access to ART, reduce congestion at centralized ART centers, reduce unnecessary travel by patients, and allow for improved adherence and education.140
Training, support, supervision, and the integration of HIV/AIDS care topics into the curricula of national nursing schools as well as national legislation and policy are necessary to guarantee that essential standards of care are provided by nursing professionals. Short-term training has been shown to be successful in increasing the ARV-related knowledge base of midwives. 

In Zambia, to meet the human resource needs for PMTCT programs, employment of off-duty health personnel was shown to maximize the utilization of existing health-care workers. Such investments in human resources can be expected to contribute significantly to the achievements of the MDGs.

The Role of Lay Counselors in HIV/AIDS Programs

Proper, adequate, and appropriate counseling is an essential component of successful HIV/AIDS prevention, care, and treatment programs. Clinics and hospitals in developing countries are severely understaffed, with nurses serving as the primary caregivers. In some settings, this acute shortage of trained personnel has compelled caregivers to increase the use of lay counselors. These experiences have been successful, thanks to the short and intensive counseling training given to these community volunteers. This innovative approach is geared toward increasing access and uptake of VCT, especially in rural settings.

The training of lay counselors (i.e., community volunteers with basic training in counseling skills) who work alongside health professionals is meant not only to enhance care for people living with HIV but also to reduce associated health costs in developing countries. In addition, community-based services have been reported to promote greater access to HIV counseling, as compared to facility-based services, through the use of lay counselors.

In Cameroon, lay counselors double as trained birth attendants and have functioned effectively in rural communities to provide care to people living with HIV. Training for lay counselors may last two to six months, with emphasis on actual practice as well as theory. At the conclusion of training, lay counselors are adequately prepared to provide pre- and posttest counseling, as well as ongoing counseling, psychosocial support, and referrals to community-based health facilities. In most rural areas, the role of lay counselors extends to the provision of ANC and the provision of support in post-obstetric wards and well-baby clinics.

The feasibility, effectiveness, and acceptability (by both staff and clients) of using community volunteers in operational HIV/AIDS programs in sub-Saharan Africa has been demonstrated. This strategy needs to be complemented by community mobilization and education programs to promote VCT, as well as supervision of the quality of training and adherence to confidentiality policies at the community level.

HUMAN RESOURCE SHORTAGES FOR MCH AND HIV/AIDS PREVENTION, CARE, AND TREATMENT

The lack of human resources for health care is considered to be one of the most serious obstacles in providing MCH services. While the bulk of bedside care does not depend on highly trained health personnel, skilled health-care providers are critical in ensuring high-quality antenatal, delivery, and emergency obstetric and postnatal services. Their role includes the supervision of less-skilled care providers who can help deliver needed services, including bedside care and community follow-up and education.

Only half the world’s women receive care from a skilled health-care professional when giving birth, despite the fact that low densities of doctors,
nurses, and midwives have been linked to higher maternal mortality rates. There are examples of innovative approaches in which safe and effective maternal services have been provided by other trained health personnel in settings with few, if any, physicians. These findings support the idea that nonphysician medical staff and even trained community counselors can fill some of the gaps created by the lack of physicians and/or nurses.

Ill health due to HIV/AIDS and the emigration of health workers to foreign countries have been cited as the two major factors depleting the number of health workers in sub-Saharan Africa. In areas where there is a high prevalence of HIV, shortages often result from the illness and death of the health workers themselves. Estimates show that Botswana lost 17% of its health workforce to HIV/AIDS between 1999 and 2005. In Malawi, AIDS-related death is the largest cause of health workforce attrition.

The importance of greater use of TBAs and lay counselors is reinforced by the fact that more and more countries are falling short of the WHO-recommended minimum ratios for doctors and nurses. In fact, South Africa is the only country in sub-Saharan Africa that has the minimum of 20 doctors, 100 nurses, and 228 health providers per 100,000 population as recommended (see Table 4). It is common practice for a single medical assistant to see close to 200 patients a day in districts in Malawi and Mozambique. Patients are forced to wait for up to two months to begin treatment because of the lack of doctors and nurse clinicians. This is an indication of the acute shortage of health professionals for MCH and HIV/AIDS prevention, care, and treatment in sub-Saharan Africa. This shortage is not limited to the countries cited above. In effect, there is an urgent need to develop simple, sustainable models of health service delivery, including the provision of ART, that can maximize the potential of existing health-care staff and increase the value of health resources in resource-limited settings.

CONCLUSION

To achieve the stated goals for MCH in resource-limited settings, it is essential to link safe motherhood initiatives with other health services, such as HIV/AIDS and family planning, through an integrated approach. Ensuring that local healthcare systems have the capacity to provide a comprehensive package of ANC services should be considered a priority. PMTCT programs should be used as an opportunity to strengthen these services.

A major challenge for health policymakers is to make the best use of available human resources, including TBAs, but also to plan and implement a definite public-health strategy based on essential obstetric care provided by skilled attendants. Professionalization of maternity care must remain a top priority. For this reason, skilled attendance at birth must be made more accessible through political leadership and the identification of models to deploy and retain health workers. Identifying roles for community workers, such as TBAs and lay counselors, can facilitate the improvement of MCH when simultaneous efforts such as the upgrading of existing lower-level facilities, improving referral systems, training, and supervision are undertaken. Where this strategy is pursued, it will be necessary to adopt health policies that do not coerce but rather legitimize and acknowledge the practice of TBAs and integrate them into specific health programs. There is very limited evidence-based data on community interventions and the impact of community health workers on improving maternal health, including their role in HIV/AIDS interventions. Operational research in this field is still needed, since it is likely that TBAs and midwives will
Glaser Pediatric AIDS Foundation for the continuous support, which has enabled us to implement PMTCT programs in Zimbabwe (grant number 26-01) and Cameroon (grant number uu-0-9-1055-0-0), and to Conseil Régional d’Aquitaine-France (for ISPED-Zimbabwe) and Bread for the World Germany (for Cameroon Baptist Convention Health Board) for additional funding to undertake the community surveys and activities.

**Acknowledgments**

The authors would like to thank the ISPED-Zimbabwe (now OPHID Trust) and the Cameroon Baptist Convention Health Board staff for their dedicated work. Special thanks to the Elizabeth Glaser Pediatric AIDS Foundation for the continuous support, which has enabled us to implement PMTCT programs in Zimbabwe (grant number 26-01) and Cameroon (grant number uu-0-9-1055-0-0), and to Conseil Régional d’Aquitaine-France (for ISPED-Zimbabwe) and Bread for the World Germany (for Cameroon Baptist Convention Health Board) for additional funding to undertake the community surveys and activities.

### Table 4. Number of Health-Care Providers per 100,000 Inhabitants in Selected Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Doctors per 100,000 Inhabitants</th>
<th>Number of Nurses per 100,000 Inhabitants</th>
<th>Number of Health-Care Providers per 100,000 Inhabitants</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-recommended minimum</td>
<td>20</td>
<td>100</td>
<td>228</td>
</tr>
<tr>
<td>Lesotho</td>
<td>5</td>
<td>62.6</td>
<td>68.2</td>
</tr>
<tr>
<td>Malawi</td>
<td>2</td>
<td>56.4</td>
<td>58</td>
</tr>
<tr>
<td>Mozambique</td>
<td>2.6</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>South Africa</td>
<td>74.3</td>
<td>393</td>
<td>468</td>
</tr>
<tr>
<td>United States</td>
<td>247</td>
<td>901</td>
<td>1,147</td>
</tr>
<tr>
<td>UK</td>
<td>222</td>
<td>1,170</td>
<td>1,552</td>
</tr>
</tbody>
</table>
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The Role of Traditional Healers in Comprehensive HIV/AIDS Prevention and Care in Africa: Untapped Opportunities

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b Traditional and Modern Health Practitioners Together against AIDS (THETA), Uganda  
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The practice of traditional medicine (TM) has served the health-care needs of African populations for countless generations, well before the introduction of biomedical (sometimes referred to as “Western” or “conventional”) medicine on the continent.1,2 Today, TM continues to be the primary, and sometimes the only, accessible health-care option for the vast majority of people living in sub-Saharan Africa.3 The greater integration of TM with modern biomedical practice has recently taken on a renewed importance,4 as more comprehensive models of HIV care are being actively sought in response to the devastating impact that HIV and AIDS have had across the African continent.

African TM consists of a combination of healing techniques, labeled by the first visiting social scientists and health professionals as “herbalism,” “spiritualism,” “sorcery,” “divining,” and “bone setting,” to name but a few.1,5 During the period of African colonial rule, various forms of traditional medicine were perceived to be a threat to the spread of colonial power and Western religious belief systems, and these practices were actively discouraged and in many cases repressed through violence and other means of coercion.6 The historically negative association of African TM with terms such as “witchcraft” that stem from these early experiences continue to influence modern perceptions of African TM.1,3

As a result of these historically negative attitudes, modern African traditional healers (THs) tend to describe and demonstrate their practices to outsiders in a way that keeps the validity of their methods from being called into question—namely, by avoiding discussion of the spiritual aspects of their practices. Yet in reality, most African TM practices that have been described in the literature are comprised of a variety of different methods shaped by the cultural contexts and geographic settings in which they are practiced. The TM practitioners referred to in this chapter generally employ a complex, holistic system of care that as of yet has been only partially captured and understood through outside observation.

As the predominance of biomedical medicine on the African continent began to grow in the latter part of the 20th century, it became increasingly
important to bridge the language and value divide between biomedical practices and African TM, since many people continued to use both systems. This need became acutely clear with the arrival of HIV, which continues to cause disproportionate suffering and loss of life through the deadly combination of widespread infection and severely limited health resources (human, financial, and infrastructure). To meet the enormous need for health services that currently exists in Africa, health-care providers have a moral and medical responsibility to ensure that people have access to the best of both the traditional and the biomedical systems of care. To achieve this goal, decision makers and program managers at government, civil society, and community levels should be armed with the necessary information and tools to successfully integrate these systems. This chapter discusses some of the strategies that have been successful in integrating African TM with biomedical medicine and points the way forward for establishing and expanding collaboration with African TM practitioners as part of a broader and more efficient approach to community-based HIV prevention and care.

AFRICAN TRADITIONAL MEDICINE AND HIV/AIDS

Well before the discovery of HIV, biomedical medicine was responsible for major technological advances that dramatically changed the health status and life expectancy of people around the world. The introduction of sophisticated, laboratory-based diagnostic capabilities, surgical techniques, and synthetic pharmaceuticals, including vaccines, has made a profound difference in the lives of those who have had access to these services. In the context of HIV/AIDS, even though a cure or effective vaccine is not yet available, the recent advent of antiretroviral therapy (ART) has considerably increased the life expectancy and the quality of life of people living with HIV. However, to date only a small proportion of those in need and who are eligible for these services have benefited from them. Despite the increasing availability of ART, the vast majority of African people continue to use TM for the treatment of HIV-related conditions and other common diseases, and TM remains the sole culturally accepted, holistic health-care service available and accessible to all Africans.

The link between African TM and HIV/AIDS was first made by people living with HIV throughout sub-Saharan Africa. Since the beginning of the AIDS pandemic, access to comprehensive HIV/AIDS care in rural settings has remained a challenge due to limited health infrastructure and human resource shortages. Thus, like the rest of the population, a large proportion of people living with HIV have consulted both biomedical doctors and traditional healers. These people often receive palliative care from traditional healers for signs and symptoms that, to the healers, do not look any different from the fevers, diarrhea, respiratory diseases, sexually transmitted infections (STIs), and other infections they were caring for before the arrival of HIV. In some cases, TM has been shown to relieve or successfully treat HIV-associated symptoms or minor opportunistic infections.

Formal calls for the integration of biomedical and traditional health care for people living with HIV have been made since at least the early 1990s, when the World Health Organization (WHO) recommended that traditional medicine be included in national responses to HIV. Early efforts to combine the best of both systems included a number of projects that looked at the usefulness of traditional herbal remedies for the treatment of illnesses associated with AIDS. Studies looking at TH perceptions of STIs and HIV were also conducted as early as the late 1980s. Using information from these studies, collaborative projects began to train THs as educators and counselors to disseminate information on HIV and other
STIs within their communities and among their peers.\textsuperscript{15,17,21} Available evidence indicated that when THs are equipped with referral, counseling, and communication skills, coupled with timely and accurate information on HIV, they can greatly contribute to HIV prevention, care, and support.\textsuperscript{5}

**Areas of Collaboration with Traditional Healers for HIV Prevention and Care**

Advocacy for wider use of TM and attempts to involve THs in primary health care began in several African countries well before the arrival of HIV. Yet by 2000, more than 15 years into the AIDS pandemic, there were still few collaborative efforts between THs and biomedical health practitioners (BHPs) for HIV prevention or care (see Table 1 at the end of this chapter).\textsuperscript{15,22} Most collaborations used a strategy in which a core group of THs were trained as trainers and were then mobilized to educate communities and/or train their peers.\textsuperscript{5} Some projects also involved THs in the development of health education materials,\textsuperscript{23} social marketing of condoms,\textsuperscript{24} or the provision of basic HIV counseling.\textsuperscript{21,24,25} Yet only a few of these projects reported on the effectiveness of training THs to provide counseling for STIs and HIV.\textsuperscript{16,26,27} Moreover, evaluations were infrequent, spaced over long periods, and relied too often on healers’ surveys alone. Since then, the number of studies on TM and HIV/AIDS and the number of collaborations between THs and BHPs have not increased significantly, despite the growing needs and opportunities for collaboration. The following section discusses some of the key interventions undertaken between 2000 and 2007.

**Prevention**

Since 2000, only a few programs designed to bring together THs and BHPs for HIV prevention have been described in the literature (see Table 2 at the end of this chapter). One such program took place in Nigeria, where a three-year prospective study was conducted to evaluate the possible role of THs in the spread of HIV.\textsuperscript{28} In this study, 69 patients and 20 THs were randomly selected and interviewed to assess their HIV knowledge. Results showed that patient HIV knowledge was poor and that there was an HIV-related risk associated with TH practices due to the use of unsterilized instruments and possible cross-contamination with infected blood.\textsuperscript{28}

In addition to assessing patient knowledge, other studies have reviewed indigenous representations of illness in sub-Saharan Africa and how these have changed with the emergence of AIDS.\textsuperscript{29,30} In one study, Liddell et al found that strong beliefs in traditional concepts of illness were associated with more positive attitudes toward AIDS risk-reduction behaviors.\textsuperscript{29}

In contrast, a more comprehensive approach has been designed in Tanzania by the Tanga AIDS Working Group (TAWG), which was formed in 1992 by a group of health-care professionals with a primary aim of collaborating with traditional healers and enabling early referrals of HIV-positive patients with treatable conditions.\textsuperscript{12,17,31} This original aim led to the creation of an indigenous knowledge program with the following objectives:

- Raise awareness among THs to protect both THs and clients from HIV transmission
- Build TH capacity in providing community AIDS education and care
- Conduct research on promising herbal remedies in collaboration with TH and scientific institutions
- Ensure a sustainable supply of medicinal plants through conservation and cultivation
- Build and strengthen collaborative bridges between traditional and modern health systems

Since the program began, TAWG has trained 429 THs, including 87 traditional birth attendants (TBAs). Moreover, 4,500 patients with HIV-associated conditions have been treated with
herbal medicines in six treatment centers, and 468 patients have been referred to health facilities for HIV testing and care.\(^\text{12}\)

At the peak of the HIV epidemic in Uganda in 1992, health workers, families, and communities were feeling overwhelmed and powerless against an enormous tide of health-related challenges. This crisis sparked a flood of new ideas, including the creation of Traditional and Modern Health Practitioners against AIDS (THETA), a Ugandan nongovernmental organization (NGO) aimed at fostering collaboration between modern health workers and traditional healers. THETA was formed in 1992 as a collaboration between The AIDS Support Organization (TASO) of Uganda, a national NGO providing care and support to people living with HIV, and the international humanitarian NGO Doctors without Borders, with the support of Uganda’s National AIDS Control Programme and the Uganda AIDS Commission. One of THETA’s projects, which tested the effect of training traditional healers as STI/HIV educators and counselors, showed that THs could successfully provide preventive services, such as community AIDS education that focuses on care and prevention, condom promotion and distribution, positive prevention, STI prevention education, and prevention of mother-to-child transmission (PMTCT) education.\(^\text{4,31-36}\)

**Care and Support**

Between 2000 and 2007, a number of projects were initiated to assess health-seeking behavior for HIV-associated conditions. One study in Gabon among people living with HIV found that healers were consulted for treatment of disease in 90\% of cases (N=150 HIV-positive patients).\(^\text{37}\) Traditional medicine was used concurrently by 17\% of those who had started biomedical care. The authors concluded that a multitude of factors related to the patients, the health system, and culture or society (including TH consultation) contributed to the diagnosis of HIV infection in Gabon.\(^\text{37}\)

In Malawi, health seeking was reported to take place in three stages: (1) traditional care and treatment by families, followed by (2) treatment by traditional healers, and, when TM fails, (3) biomedical care from hospitals or clinics.\(^\text{38}\) TH consultation, together with home herbal remedies, was reported in a South African cohort, in which 84\% (n=44) of study participants reported having ever used traditional medicine.\(^\text{39}\)

Another category of studies on TM have assessed the knowledge and attitudes of TM practitioners about HIV and about collaboration between health sectors. Peltzer et al in South Africa found that most THs had correct knowledge of HIV transmission, prevention, and ART, but 21\% of the 233 THs interviewed believed there was a cure for HIV.\(^\text{19}\)

**Integration of Prevention, Care and Treatment, and Collaboration among Health Sectors**

Although the burden of caring for people living with HIV is expected to increase into the foreseeable future, health-care systems in the most affected regions of Africa remain inadequately prepared to meet the increasing demand for services.\(^\text{40}\) In response, the importance of involving THs in efforts to scale up HIV/AIDS care has recently been reemphasized.\(^\text{4}\)

Despite calls for further collaboration between THs and BHPs, relationships between these different practitioners are still often characterized by indifference, suspicion, and mutual rejection. Joint efforts to intensify HIV prevention and care cannot be sustained unless attitudes among these two groups are improved and their respective prejudices addressed. To establish a successful model for collaboration, a new approach to training has been called for that is based on a participatory approach to learning and that underscores the importance
EMPOWERING TRADITIONAL HEALERS TO SUPPORT HIV PREVENTION AND CARE: THE THETA EXPERIENCE

Traditional and Modern Health Practitioners against AIDS (THETA) was one of the first groups to demonstrate that traditional healers (THs) can be empowered to play a significant role in HIV/AIDS prevention and care. In Uganda, 80% of the population lives in rural areas, and less than 25% of the sexually active population has been tested for HIV. Yet despite low levels of testing, demand for these services is high. The formal health sector in rural communities is severely overstretched and, in many cases, is not adequately equipped to respond to the health needs of rural communities. As a result, a majority of the rural poor turn to informal community-based health-care providers, including THs and traditional birth attendants, as well as to family members and other community caregivers and resource people.

Over the past 15 years, THETA’s work has focused on empowering and tapping existing informal community care structures and linking them to the formal health and social sectors. This work has contributed to improved access to quality HIV prevention and care services and has mitigated the impact of the country’s HIV epidemic.

Between 2003 and 2007, THETA trained and mobilized 1,321 THs and built a collaborative network between them and the biomedical health practitioners to provide comprehensive sexually transmitted infection (STI) and HIV/AIDS prevention and care services in 12 rural districts of Uganda. To contextualize the situation in Uganda, there is one doctor for every 12,000 people. A referral network was developed among THs, health facilities, and community health workers that included the development and use of TH referral and client care forms, as well as a monitoring system. Over a period of four years, the number of documented referrals from THs to conventional health facilities for HIV counseling and testing, prevention of mother-to-child transmission (PMTCT) of HIV, TB, and opportunistic infections treatment increased from 132 to 4,832; the cumulative number of community members who received HIV/AIDS prevention messages and supportive counseling from THs was 85,584. The success of this experience prompted THETA to develop a model for collaboration between traditional and conventional health and social services for HIV/AIDS prevention, care, support, and referrals in rural settings. This model is aimed at supporting national efforts to scale up prevention strategies, counseling and testing, PMTCT, and support for orphans and other vulnerable children (OVC).

After acquiring HIV/AIDS knowledge and skills, many THs trained by THETA started their own HIV/AIDS initiatives in their respective communities. These initiatives have developed through the engagement of community members and utilization of existing community resources, such as land and labor, to provide for those in need of assistance, including widows and OVC. THETA has supported 38 such initiatives through capacity building and the provision of seed grants. These initiatives have helped provide education, nutritional support, and psychosocial care to 3,700 orphans through the work of 1,635 caretakers, of which 1,175 (71%) are women who are mostly widows or grandmothers.
of mutual respect and the value of learning from one another. This model is in contrast to previous approaches to training, which often used BHPs to train THs but not the other way around; such one-sided approaches can be perceived as asserting the superiority of BHPs over THs, leading to alienation of the latter group.

LES SONS LEARNED AND IMPLICATIONS FOR FUTURE PRACTICE

The continuous spread of HIV and the typically poor state of health-care systems in most of sub-Saharan Africa are compelling reasons to further involve THs in the fight against HIV. To achieve this goal, deeper commitments and sustained efforts are needed on the part of policymakers and advocacy groups in order to tackle existing prejudices and systemic obstacles that lay in the way of successful collaborations between THs and BHPs.

The lessons highlighted in this chapter speak to the need for changes in the approach to African health systems as a whole. We must move away from the singular focus on biomedical, curative approaches in order to build more comprehensive and holistic programs. The provision of HIV care can be viewed as a shared responsibility between patients (and their families and communities), BHPs, and THs. Sustainable coverage and enhancement of the quality of HIV care requires simultaneous improvement in all areas of care, including palliative care, care for orphans and other vulnerable children (OVC), and social and economic support. These dimensions cannot be addressed by the formal health-care sector alone.

Collaborative projects have demonstrated that encouraging greater dialogue between THs and BHPs is feasible but complex. Bringing about change in individual attitudes or perceptions is not always straightforward. Changes in practice require more than short-term interventions. The development of intersectoral collaboration requires long-term coordination among all relevant stakeholders at the community level. The transformation of relationships between THs and BHPs also needs to be supported by a number of policy shifts on issues such as mutual referrals, recognition of traditional medicine, and protection of related intellectual property rights. Effective linkages with community groups and support for the emergence of organized bodies of THs will also help bring about needed changes. All such efforts require the support of enlightened health policymakers who understand the importance of greater collaboration among health providers.

Greater involvement of THs in the fight against HIV/AIDS represents a unique opportunity to effectively increase community access to HIV services, such as prevention education, counseling and testing, PMTCT, palliative care, and OVC support in a culturally appropriate, economically sustainable way. THs work in the community and will continue to do so without additional incentives. For this reason, they represent a low-cost, sustainable community health resource once they are provided with appropriate information and training.

Limitations

One of the major shortcomings in the assessment of interventions involving THs has been the lack of systematic and controlled evaluations. Even when traditional or biomedical health concepts are translated in an attempt to bridge the gap between the two medical worlds, the lack of thorough evaluations, together with a persistent, pervasive skepticism among BHPs regarding “unscientific” approaches, leads to a vicious cycle in which lack of data on the effectiveness of collaborations and African TM in general justify the lack of funding; that lack of funding, in turn, limits the ability to perform evaluations.
Bridging Gaps, a multisite project, was initiated in 2002 in Zambia and Uganda with the aim of developing a model for greater dialogue between traditional healers (THs) and biomedical health practitioners (BHPs) in order to improve quality and increase uptake of sexually transmitted infection (STI) and HIV/AIDS care services. To achieve this goal, a study was conducted among community members, TH clients, and groups of THs and BHPs from two Zambian cities and two Ugandan districts. At the outset of the study, the level of collaboration between BHPs and THs was assessed through focus group discussions and semistructured interviews with THs, BHPs, and community members. Quality of care was assessed through semistructured interviews with patients from each sector, as well as through direct observation of provider-patient interactions and care areas and through “simulated client” patient visits.

The survey confirmed fairly low levels of collaboration between BHPs and THs prior to the study (24% of BHPs and 13% of THs in Zambia and 11% of BHPs and 57% of THs in Uganda stated that they had ever worked with the other sector) and showed that the rare interactions that did occur had been limited to instances where BHPs had trained THs (usually traditional birth attendants). However, there was a willingness to collaborate on both sides and to learn from one another; this willingness was in addition to general community support for collaboration between the two sectors. Unclear national policy guidelines, mainly concerning referrals between BHPs and THs, were identified as a major obstacle to smooth collaboration.

In terms of perceptions of quality of care at baseline for patients living with HIV or other STIs, the two groups of providers both recognized their limitations with respect to the provision of community health education and the lack of joint palliative care initiatives and home-based care services. Both groups also recognized skill deficiencies and highlighted the need for training.

Based on these initial study findings, an intervention was designed by Bridging Gaps. The intervention was similar in both Zambia and Uganda and comprised peer group discussions, interactive group discussions, training or information exchange sessions, and peer-influenced networking of THs and BHPs in the study areas. For 13 months during 2004 and 2005, participants (82 THs and 42 BHPs)
were brought together for interactive group discussions and training sessions and were encouraged to network with other participants and colleagues in order to apply newly acquired skills and attitudes to their practice.49

At the completion of the intervention, collaboration and quality of care were again measured in the intervention and control districts. Providers and community members reported greater awareness of collaborative efforts, with many more BHPs and THs acknowledging the value of their counterparts’ contribution to care for HIV and other STIs and expressing a greater interest in collaboration. These changes in attitude were clearly translated into significantly improved practices of collaboration; after the intervention, 39% of BHPs and 66% of THs in Uganda (22% for each of the two sectors in Zambia) stated that they currently worked with providers from the other sector.

By the end of the study period, referrals and cross-visits between BHPs and THs increased significantly in Bridging Gaps intervention districts as compared with the control districts. For example, THs in the Uganda intervention district reported receiving about twice as many visits from BHPs, as compared with the control district.42,55 Referral numbers also increased in intervention areas, particularly from THs to BHPs, both as reported by providers and as documented with referral forms generated collaboratively by those who participated in the intervention.52

The study also found significant improvements in the intervention districts in terms of quality of care provided by THs, particularly in Uganda, as reported by community members and as observed through simulated client patient visits and through checklist audits of care areas.42,56 Significant improvements (P<.05) were demonstrated among THs in the intervention districts in both Uganda and Zambia with regard to hand washing, proper disposal of sharps used in patient care, condom availability, record keeping, and the presence of health education materials in care areas (measured only in the Ugandan follow-up survey).53 Other improvements included the use of gloves and the correct packaging of herbal medications. (It should be noted that in the Zambia intervention district, many of the significant improvements observed were seen in both the intervention and control districts, thus making it impossible to attribute these improvements solely to the intervention.)

Counseling about and provision of condoms by THs improved in the intervention districts in both countries, with intervention THs giving more correct and less negative information about condoms than those in the control districts. THs were documented to correctly counsel appropriate patients about condoms and were 5.5 (Uganda) to 17 (Zambia) times more likely to have condoms to provide to clients than did THs in the control districts. The intervention THs often provided condoms free of charge to patients who had STI- or HIV-related concerns.

In both countries, THs who participated in the intervention were significantly less likely to claim that they could cure or prevent AIDS through traditional medicines or tattooing. In fact, it was documented that no TH in the Ugandan intervention district made such claims to simulated patients seeking care for HIV- and STI-related scenarios.56

In addition to the documented improvements in collaboration and care quality found
in the study intervention districts, another outcome in the Ugandan intervention district included the spontaneous formation of joint community associations of THs and BHPs (three local and one umbrella association for the district). This effort was spearheaded by intervention participants in order to continue collaboration between the sectors beyond the intervention period. These associations have continued to meet, with the support of district health structures, and have, on their own initiative, conducted joint trainings for community members on topics of HIV, STIs, and TB.

These results provide evidence that together with BHPs, THs can be engaged in collaborative intervention projects to improve counseling, education, condom promotion, and referral practices, thereby improving the quality of HIV and STI care in resource-limited settings.49,50

The lack of advocacy and leadership at the policy level and blanket application of the biomedical model also leads to a dearth of comprehensive, well-assessed, and documented models of collaboration. WHO Regional Office for Africa (WHO/AFRO) has developed a series of tools for use by African policymakers,57-60 but countries are generally slow to adapt those tools for their own use. Yet despite these difficulties, the projects discussed in this chapter all demonstrate that once a common language is established, it is indeed possible to design, plan, implement, and evaluate collaborative projects, as long as the views of THs and the fundamental concepts that inform their practice are acknowledged.

Potential Areas for Future Expansion
Potential areas of collaboration between BHPs and THs include HIV prevention education, male circumcision, PMTCT, ART literacy and adherence support, and reproductive health (with an emphasis on family planning, STIs, and sexual health).

PMTCT
The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that less than 20% of pregnant women in sub-Saharan Africa know their HIV status and that in a number of countries with generalized epidemics, mother-to-child transmission (MTCT) is responsible for a large proportion of new HIV infections.7 Given that a majority of women in many African settings deliver their babies at home, often with the help of a relative, TBA, or private midwife, there is a need to train and equip these providers with basic PMTCT knowledge and skills. This training will help maximize uptake of HIV testing among pregnant women, assess their eligibility for ART, and provide access to care for themselves and their families. Promising preliminary results of projects that involve THs and TBAs in PMTCT activities have shown that these providers could play an important role in building effective community support systems that complement facility-based PMTCT services by helping to increase uptake and follow-up of HIV-positive mothers and their HIV-exposed babies.49,50

ART Literacy and Adherence Support
Although the number of people receiving ART in Africa has continuously grown since the advent of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), the President’s Emergency Plan for AIDS Relief (PEPFAR), and other similar efforts, there are still many HIV-positive Africans...
in need of urgent treatment. Moreover, evidence continues to accumulate regarding the importance of achieving high ART adherence rates in order to maximize treatment benefits and cost-effectiveness, as well as to minimize the risk of treatment failure and drug resistance.\(^6\) Even where HIV counseling and testing (CT) and ARVs are widely available and accessible, there is still a critical need to sensitize communities about ART and the importance of testing and to support those receiving ART to adhere to their treatment. For those not yet eligible for ART, they can be encouraged to adopt preventive behaviors and to regularly monitor their health status. THs are in a unique position to fulfill such roles because they already work in the community and are largely trusted and respected by community members. On the other hand, if THs continue to be marginalized and left untrained, they will serve as a barrier to the successful roll-out of ART, as any misconceptions they may have will confuse the public and further alienate THs from BHPs.

Reproductive Health

African THs and TBAs continue to play an important role in reproductive health. Historically, they were responsible for ensuring the fertility of their communities; to this day, they offer guidance and care to those who wish to have a baby or have other reproductive health concerns. THs are also regularly consulted regarding the treatment of diseases perceived to be sexually caused, related, or transmitted, independent of the availability of antibiotics.\(^4,32,33\) As a result, THs often serve as psychosocial counselors for sexual issues and are in an ideal position to influence community perceptions and behaviors in a number of areas related to reproductive health, including sex and gender issues; STI prevention, treatment, and care; and attitudes and practices regarding family planning. Yet where these activities are undertaken as part of a comprehensive HIV/AIDS strategy, THs have rarely been directly involved in planning or implementation.

Despite being underutilized, THs are well positioned to enhance the limited capacity and scope of government and other facility-based health-care services through the communication of important HIV-prevention messages to their communities. THs can also assist in integrating reproductive health and HIV services through the dispensation of health messages and additional information about reproductive health. So far, this goal has been widely promoted but rarely achieved in sub-Saharan Africa.\(^6\) In addition, although traditional beliefs are often seen as a barrier to health behavior change, experience has shown that THs can adapt and change their own traditional beliefs, as well as those of the community, in the face of extreme threats such as HIV. For example, THs have been successfully involved in promoting the use of condoms, which is, in principle, antithetical to their traditional role of ensuring fertility.\(^5,22,27\)

To further public health strategies in order to reduce the spread of HIV, THs should be equipped with up-to-date information about basic reproductive health issues and primary HIV prevention and care. They should also be confidently able to counsel clients about the relationships among sexual practices, STIs, family size, and HIV in their local context and should be empowered to educate and influence communities to adopt preventive and protective attitudes and behaviors. They can thus be leaders in demystifying common misconceptions in reproductive health and therefore promote uptake of reproductive health services.\(^6\)

Unfortunately, because the majority of HIV resources are externally sourced, indigenous solutions, such as TM, may not be prioritized by policymakers. Evidence shows that countries that fund their own national health programs are more likely to develop TM alongside biomedicine.\(^37,40\)
CONCLUSION

Traditional healers represent a largely untapped source of human capacity that can complement and strengthen existing HIV prevention and care services in sub-Saharan Africa. Yet despite the considerable lip service given to this concept, the amount of resources that have been allocated in support of this approach remains insignificant in relation to what can be and needs to be accomplished to achieve this goal. The paucity of data and evidence regarding the involvement of African TM and THs in HIV prevention and care attests to the need for additional resources. Yet the little available evidence supports the idea that THs are eager to collaborate with BHPs and can be a unique ally in expanding comprehensive HIV services to the most difficult-to-reach populations in a culturally appropriate and sustainable way. It is therefore the responsibility of policymakers, public health officials, international donors, and others to recognize that the conventional biomedical health-care system alone has not and will not (in the foreseeable future) be in a position to fulfill the ultimate goal of every national HIV/AIDS strategic plan—namely, to curb the spread of HIV—without engaging the help of all relevant stakeholders, including traditional healers.
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</table>
| Botswana             | Seminars for TH on AIDS, 1993                                                        | MOH                                    | To sensitize THs to AIDS  
To coordinate TH activities with district health teams                                                                 | No information                                                                                                                                                                                        | Seminars held sporadically with THs on various diseases, including AIDS                                                                                                                                               |
|                      | Botswana Dingaka AIDS Awareness and Training Program, 1991–1993                      | CIDA, WHO, MOH                         | To provide a forum for exchange of information and experiences between THs and BHPs  
To promote cooperation and collaboration for health services  
To create AIDS awareness among THs  
To train core trainers who will pass the information to other THs in selected pilot areas                                                | 2-week TOT on AIDS held with 12 THs from 6 districts  
Independent evaluation interviewed 32 THs, 19 nurses, and 20 medical doctors                                                   | Trained THs trained, on average 45 other THs per district in 2 years  
72% of THs said they had changed something in their practice in relation to AIDS training  
80% said they recommend condoms  
Educational video produced  
Flip chart addressing TH practices produced                                                                                                                                              |
| Cameroon             | KABP survey of TH, 1990                                                               | NACP; National TM Program               | To sensitize and introduce THs to AIDS control                                                                            | National seminar on TM and AIDS to be conducted                                                                                                                                                    | TH knowledge improved, except for their own risk practices  
Repetitive, rather than single, training model suggested                                                                                                                                                   |
| Central African Republic | ADERT, 1995                                                                         | MOH, University of Bangui, World AIDS Foundation, CDC, CIDA, University of Washington (USA) | To identify and reinforce aspects of TM believed to promote public health, while discouraging those that have negative health impact  
To enable THs to deliver preventive messages, support people living with HIV, and modify their own risk practices | Focus groups to identify training topics and methods  
Working group of TH and MOH staff to develop curriculum  
103 THs at 4 locations (urban and rural) completed 6-day training  
96 THs completed pre- and post-KABP questionnaires                                                                                     |  

Table 1. Summary of Documented Collaborations with Traditional Healers for Prevention of Sexually Transmitted Infections and HIV in Sub-Saharan Africa (1987–1999) (cont.)

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<tr>
<td>Ghana</td>
<td>Unit for TM established in MOH, 1990</td>
<td>WHO, MOH</td>
<td>To involve THs in primary health care.</td>
<td>Establishing a dialogue with THs</td>
<td>Recommendations for involving THs in management and treatment of AIDS</td>
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<td></td>
<td>Training manual for TH</td>
<td>Save the Children</td>
<td>To produce a document to systematically train THs for AIDS</td>
<td>Production of training manual</td>
<td>No information</td>
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<tr>
<td>Guinea</td>
<td>MOH, TM Unit: Integration of TH into health activities, 1985</td>
<td>MOH</td>
<td>To identify the factors within TM that can increase the effectiveness of the fight against AIDS in Guinea</td>
<td>Survey of STIs known to TH</td>
<td>THs are registered with MOH</td>
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<td></td>
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<td></td>
<td>To increase TH knowledge on modes of HIV transmission and prevention, clinical manifestations, care, and support</td>
<td>Research on traditional treatments for fertility, AIDS, and STIs</td>
<td>Research on 898 THs since the beginning of the program found that increasing numbers of THs refer to health centers (using referral forms), hospitals, and other THs for diagnosis and treatment; BHPs refer back</td>
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<td></td>
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<td>Baseline survey of TH knowledge on AIDS</td>
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<td>2 workshops organized for THs</td>
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<td></td>
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<td>Each district has a physician in charge of TM</td>
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<td>Liberia</td>
<td>Anthropological Research on STIs, 1988</td>
<td>SOMARC/USAID, Johns Hopkins University (USA)</td>
<td>To learn how to promote condoms to limit the spread of HIV</td>
<td>Focus group discussions with 53 participants</td>
<td>THs advise against prostitutes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conducted interviews with 103 THs</td>
<td>THs should be taught STI diagnosis and referral because people believe in TM for STIs</td>
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<tr>
<td>Malawi</td>
<td>Training on AIDS for TH, 1992</td>
<td>International Eye Foundation, Malawi International Center for Eye Health (UK)</td>
<td>■ To better understand the practices and roles of healers in their communities                                                                     ■ To promote greater communication between THs and the “formal” health-care sector                                                 ■ To educate THs about HIV/AIDS and STI transmission and prevention                                                                 ■ To encourage community-based AIDS prevention and care by THs</td>
<td>■ Series of orientations and focus group discussions were held with THs                                                                 ■ Eye-care program formed the initial base of contact and collaboration between project staff and THs ■ Baseline and follow-up (6 months posttraining) were conducted with 89 THs ■ One-day training sessions were held in 14 sites in one district (334 THs)</td>
<td>■ Increase in community education, condom distribution, and patient counseling activities 6 months posttraining</td>
</tr>
<tr>
<td>Mozambique</td>
<td>Anthropological research and training on AIDS and STIs for THs, 1991–1994</td>
<td>MOH, Swiss Cooperation</td>
<td>■ To improve intersectoral cooperation in the prevention and treatment of STIs                                                                  ■ To identify and reinforce aspects of TM believed to promote public health, while discouraging those believed to have negative health impact</td>
<td>■ Conducted interviews with 51 THs specializing in STIs to develop training strategy ■ 5 focus group discussions were held with 7 THs per group ■ 2 one-week workshops in 2 provinces</td>
<td>■ Developed culturally appropriate strategy for the NACP involving THs for STIs ■ 30 THs participated in workshop on STIs in 1991; in 1994 follow-up, 21 THs and 8 clients interviewed and showed increased knowledge on HIV transmission, condom use, and promotion</td>
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<td>Namibia</td>
<td>Anthropological Research on TM, 1995</td>
<td>PhD thesis fieldwork</td>
<td>■ To analyze TH patients, health-seeking behavior</td>
<td>■ Quantitative and qualitative methods</td>
<td>No information</td>
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</table>
| Rwanda    | AIDS research project (Project San Francisco), 1990 | University of California, San Francisco (USA); MOH         | ■ To analyze health-seeking behavior of women patients with regard to AIDS and traditional medicine  
■ To analyze knowledge, attitudes, practices surrounding AIDS and STIs | ■ Quantitative and qualitative methods, including questionnaires and in-depth interviews among 40 women involved in a prospective cohort study  
■ 25 THs interviewed on KABP on AIDS | ■ Majority of women used both biomedical and traditional systems and believed in greater effectiveness of TM for certain AIDS symptoms  
■ All THs had heard of AIDS, knew modes of transmission, signs, and symptoms, and knew that there was no treatment or vaccine |
| Senegal   | Promotion of Traditional Medicine (PROMETRA), 1981 | Center for Experimentation of Traditional Medicine (Senegal); Tulane School of Public Health (USA); Morehouse School of Medicine (USA) | ■ To promote traditional medicine                                         | ■ 383 healers organized into an association called PROMETRA  
■ Conducted training on diarrhea and family planning, but not yet on AIDS  
■ Needs assessment conducted prior to training | ■ 87% of interviewed patients were satisfied with TH services  
■ 67% of interviewed physicians stated they referred patients to THs |
| Sierra Leone | Counseling training for TH, 1992            | National STI/AIDS Control Program                          | ■ To train THs in HIV/AIDS counseling                                       | 1-day training held with 150 THs                                      | ■ 150 THs trained in HIV/AIDS counseling  
■ 80% of people with HIV/AIDS prefer TM treatment |
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| South Africa | TOT for healers, 1992                   | AIDSCAP (USA); AIDS.COM (USA); MOH (South Africa)                                      | ■ Initial goal was to determine the level of interest, knowledge, and skills of THs in HIV prevention and whether they could serve as effective agents of behavior change  
■ Ultimate goal was to engage THs in combating HIV/AIDS in South Africa through training other healers and incorporating HIV/AIDS prevention into their practices | ■ 1-year feasibility study  
■ Preliminary 5-day workshop (Nov. 1992) with 28 THs  
■ 3 follow-up workshops (July 1993, Nov. 1993, July 1994) | ■ 630 THs trained by 28 trained THs on basic AIDS facts  
■ 7-month follow-up: >80% retained correct STI/AIDS information and practiced counseling |
|              | Pilot survey of THs, 1992               | Center for Natural and Traditional Medicine (USA)                                      | ■ To assess TH potential for AIDS prevention and care                                                                                                                                                    | No information                                                                                                                                                                                     | THs had high knowledge about AIDS, were treating symptoms |
|              | Training program in KwaZulu-Natal, 1994 | AIDS Foundation of South Africa, National Traditional Healers Association of South Africa | ■ To increase AIDS prevention, education, and management in KwaZulu-Natal by providing training and resources to THs  
■ To help trained THs become accepted by the biomedical system in KwaZulu-Natal                                                                 | ■ Emphasize strengthening resources in disadvantaged communities | THs can identify signs and symptoms of AIDS after training  
■ THs identified need for rural AIDS hospices and trained home-care personnel to care for people living with HIV  
■ 75% of THs believed they could cure AIDS before training; none after |
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| South Africa     | Training of THs in HIV prevention and collaboration, 1998                            | Government of South Africa                                  | ■ To train THs in every province of South Africa on AIDS prevention  
 ■ To build collaboration between traditional and biomedical health systems | ■ 3-day workshop for THs in every province of South Africa, using participatory methods                   | ■ Prevention training was successful, but not collaboration  
 ■ Recommend using THs to train THs because THs respect their fellow members                                      |
| Uganda           | THETA, 1992 to present                                                               | Doctors without Borders, TASO, NACP, MOH, Uganda AIDS Commission, Rockefeller Foundation | ■ To provide training for THs in community counseling and HIV/AIDS education, basic clinical diagnosis, and patient management  
 ■ To provide a resource center for information sharing on TM and AIDS  
 ■ To advocate for TM among health professionals and other scientists to build a true collaboration | ■ Community mobilization;  
 ■ TH training in AIDS education and counseling in 7 districts with 40 THs per district since 1993  
 ■ TH training in patient management with 30 THs in Kampala in 1 year  
 ■ Resource center that collects and disseminates information on TM and AIDS  
 ■ Promoting collaboration between TM and biomedicine | ■ Increased counseling and AIDS education by trained THs and increased knowledge and condom use among clients of trained THs  
 ■ More than 120 THs trained with more than 96,000 people who benefited in 2 years  
 ■ Collection of a wide variety of materials on TM and AIDS  
 ■ Production of 2 videos in Luganda and English for educational and informational use |
|                  | Community-based home care, 1993                                                      | CONCERN, Ireland MOH, Uganda                                | ■ To train volunteers to provide care and support to the sick using a primary care herbal kit developed by the project  
 ■ To disseminate information on herbs and disease | ■ Workshops centered on skills and confidence building in giving out herbal medicine | ■ THs trained 68 volunteers involved in home care and distributed herbs for common AIDS-related symptoms |
Table 1. Summary of Documented Collaborations with Traditional Healers for Prevention of Sexually Transmitted Infections and HIV in Sub-Saharan Africa (1987–1999) (cont.)

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| United Republic of Tanzania | TAWG, 1990–present  | FHI, Shaman Pharmaceutical, Evangelische Zentralstelle fur Entwicklungshilfe, GTZ      | - Raise HIV/AIDS/STI awareness among THs in 3 districts to safeguard both THs and clients from HIV during practices  
- Train THs as HIV/AIDS/STI educators and home-care providers for people living with HIV and their families  
- Promotion of community-based condom distribution | - Series of sensitization meetings between local government, district PHC committees, village health committees, local communities, and THs  
- 2 participatory approaches identified and trained people  
- TAWG trained 120 THs in 1994  
- Health personnel were trained to support the program | - 160 THs have been trained in HIV/AIDS and health information  
- THs involved in collaborative clinical work, AIDS education, counseling, home visits, and village theater groups  
- Training manual produced |
| Zaire                    | Workshops with THs, 1989 | CONNAISSIDA, Zaire Traditional Healers Association                                        | No information                                                                 | Action research using 2 experimental risk reduction workshops with women in low-income area       | Demonstrated TH pragmatism and the role they can play in promoting behavior change for safer sex practices         |
| Zambia                   | AIDS workshop, 1987  | Traditional Practitioners Association of Zambia, MOH                                      | - To exchange ideas and experiences on AIDS and the gaining of TH support in fighting its spread | Dialogue between the MOH Health Education Unit and the secretariat of the Traditional Practitioners Association of Zambia  
- Workshop held with 40 THs | - 40 THs attended  
- Knowledge increased, misconceptions about HIV still strong |
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<td>Zambia</td>
<td>AIDS research, training and follow-up 1994–1996</td>
<td>MOH, USAID, Morehouse University School of Medicine (USA)</td>
<td>To educate THs about HIV/AIDS and STI transmission, prevention, and care</td>
<td>25–40 prominent THs selected to participate in 3-day workshops on AIDS between June 1994 and Nov. 1995</td>
<td>2,000 THs trained on AIDS facts and 120 THs trained in community education</td>
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<td>To enable THs to educate their patients about these issues and motivate them to avoid high-risk behavior</td>
<td>Trained THs attended monthly or alternate-month follow-up meetings led by health center staff</td>
<td>Knowledge increased; THs started selling condoms through a social marketing program</td>
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<td>Zimbabwe</td>
<td>AIDS workshops, 1988</td>
<td>ZINATHA, MOH</td>
<td>No information</td>
<td>No information</td>
<td>Workshops organized to train THs in AIDS and counseling</td>
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<td></td>
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<td></td>
<td>Pamphlet on AIDS in local language designed for THs</td>
</tr>
</tbody>
</table>

## Abbreviations

- **ADERT**: Action to Define, Broaden, and Strengthen the Role of Traditional Practitioners
- **AIDSCAP**: AIDS Control and Prevention Project
- **AIDSCOM**: AIDS Public Health Communication Project
- **BHP**: Biomedical health practitioners
- **CDC**: Centers for Disease Control and Prevention
- **CIDA**: Canada International Development Agency
- **FHI**: Family Health International
- **GTZ**: Deutsche Gesellschaft für Technische Zusammenarbeit (German Technical Organization)
- **KABP**: Knowledge, attitudes, beliefs, and practices
- **MOH**: Ministry of Health
- **NACP**: National AIDS Control Programme
- **PHC**: Primary health care
- **PROMETRA**: Promotion of Traditional Medicine
- **SOMARC**: Condom Social Marketing Program
- **STI**: Sexually transmitted infection
- **TASO**: The AIDS Support Organization Uganda
- **TAWG**: Tanga AIDS Working Group
- **TH**: Traditional healer
- **THETA**: Traditional Healers and Modern Practitioners Together Against AIDS
- **TM**: Traditional medicine
- **TOT**: Training of trainers
- **USAID**: United States Agency for International Development
- **WHO**: World Health Organization
- **ZINATHA**: Zimbabwe National TH Association

*Source: Adapted from King R*
<table>
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</table>
| Gabon           | (Okome-Nkoumou et al, 2005) | - To describe the use of TM as an alternative or complement to BM in people living with HIV  
                   - To describe the delay between presentation of HIV-related symptoms and diagnosis | People living with HIV consulted traditional healers for cure of disease in 90% of cases, initiation rites (23%), and sorcery (20%) (total N=150) | Better communication between BHPs and THs could improve care of HIV-infected people |
| Malawi          | (Hatchett et al, 2004)   | - To examine the health-seeking behavior of families affected by AIDS in rural Malawi | Health seeking was seen to progress in 3 stages: (1) traditional care and treatment, (2) remedies from TH, (3) BHP | Traditional practices can be integrated into interventions to improve the quality of care and treatment for people living with HIV |
| Nigeria         | (Peters et al, 2004)     | - To evaluate the role of THs in the spread of HIV in southeast Nigeria     | Clients’ HIV knowledge poor  
                   - HIV-related risk in the practices of Nigerian THs include the use of unsterilized instruments and cross-contamination with blood and body fluids | Basic HIV education should be given to THs, their patients, and the general public |
| South Africa    | (Babb et al, 2007)       | - To determine the prevalence of TM use, source, recommended products, and costs | 37 (84%) of clinic attendees reported ever using TM—25 from TH, 8 from own garden, 4 from pharmacy  
                   - Clients spent 4–27 UK pounds per month on TM | TM use is common among individuals with moderate and advanced HIV disease |
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<thead>
<tr>
<th>Country</th>
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</thead>
<tbody>
<tr>
<td>South Africa (Johnson et al, 2007)</td>
<td>Prevention</td>
<td>To conduct a pilot study of the safety of a common indigenous South African phyto-therapy (Sutherlandia) and its uses for HIV-associated conditions, TB, and cancer</td>
</tr>
<tr>
<td></td>
<td>Care and Support</td>
<td>To contribute to establishing methods for ethical and scientifically sound clinical trials of African TM</td>
</tr>
<tr>
<td></td>
<td>Other Objectives</td>
<td>Findings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant differences in general adverse events or physical, vital, blood, and biomarker indices between treatment and placebo groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group showed significantly improved appetite compared with placebo (p=&lt;.01)</td>
</tr>
<tr>
<td>South Africa (Liddell et al, 2005; Liddell et al, 2006)</td>
<td>Prevention</td>
<td>To test the theory that indigenous belief systems influence attitudes toward HIV prevention in southern Africa</td>
</tr>
<tr>
<td></td>
<td>Care and Support</td>
<td>To examine illness representations and how these representations have evolved in relation to AIDS</td>
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<tr>
<td></td>
<td>Other Objectives</td>
<td>Findings</td>
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<tr>
<td></td>
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<td>Biomedical and traditional views on HIV prevention were reported to be conflicting, with potentially harmful results</td>
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<td></td>
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<td>Consumption of 800 mg/day Sutherlandia leaf powder for 3 months was tolerated by healthy adults</td>
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<td>Sutherlandia is commonly given to people living with HIV for associated illnesses, such as nausea and lack of appetite</td>
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<td>Next phase would collect more data on how the probably active ingredients of Sutherlandia are absorbed and broken down to assess safety at different dosages</td>
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<td></td>
<td></td>
<td>Research on the influence of indigenous beliefs on sexual behavior and safer practices could offer helpful explanations for AIDS-prevention programs</td>
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<td></td>
<td></td>
<td>Indigenous beliefs have an association with attitudes to AIDS prevention, although these associations may be reducing across generations</td>
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</tbody>
</table>
Table 2. Summary of Documented Collaborations between Traditional Healers and Biomedical Health Practitioners for Prevention and Care of Sexually Transmitted Infections and HIV in Sub-Saharan Africa (2000–2007) (cont.)

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<td></td>
<td>Prevention</td>
<td>Care and Support</td>
<td>Other Objectives</td>
</tr>
<tr>
<td>South Africa</td>
<td>To investigate TH HIV/AIDS, STI, and TB KABP</td>
<td>Of 233 THs interviewed, most common conditions seen were STI, HIV, and TB</td>
<td>Authors call for randomized controlled trials to test the effectiveness of TM for HIV, STI, and TB</td>
</tr>
<tr>
<td>South Africa</td>
<td>To assess level of knowledge of 32 THs and 17 caregivers and their ability to recognize HIV-associated oral lesions</td>
<td>Recognition of defined common oral manifestations of AIDS increased dramatically after a 2-day workshop</td>
<td>THs and caregivers constitute an untapped resource with great potential</td>
</tr>
<tr>
<td>South Africa</td>
<td>To highlight the perceptions of BHPs about the strengths and weaknesses of TM for people living with HIV</td>
<td>Strength of the TM is sharing of belief system of users, being an alternative to an inefficient BM system, privacy and absence of time limitations, treating patients psychologically, and relief of the symptoms of specific illnesses</td>
<td>Recommended that THs be encouraged to change harmful practices in a nonjudgmental manner</td>
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<td></td>
<td>Joint workshops should be held with THs and BHPs to demystify traditional healing practices</td>
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</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>(THETA, 4, 15, 16, 21, 22, 23, 32, 36)</td>
<td>- To involve THs in HIV prevention through training and collaboration</td>
<td>- To build self-sustaining community support groups that can improve the</td>
<td>- To build respectful and lasting collaborations between THs and BHPs through</td>
<td>- Training of 1,321 THs in HIV/AIDS education, counseling, and care has allowed an estimated 85,584 people to access correct information, improved care, and referral for HIV in 12 districts over 10 years</td>
<td>- Trained THs provided increased counseling and AIDS education</td>
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<td>livelihoods of the underprivileged communities and empower them to mitigate the</td>
<td>advocacy, cross-referrals, and partnerships in service delivery and research</td>
<td>- TH referrals for HCT, PMTCT, TB, and OI treatment increased from 132 to 4,832 in 2006</td>
<td>- Clients of trained THs showed increased HIV knowledge and condom use</td>
</tr>
<tr>
<td></td>
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<td>effects of poverty, HIV/AIDS, and other health challenges</td>
<td></td>
<td>- To provide THs with information and to share resources on TM and AIDS</td>
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<td></td>
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<td></td>
<td>- To document the safety and effectiveness of traditional herbal medicine for</td>
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<td>the management of HIV-associated opportunistic illnesses</td>
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Community-based care
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<tr>
<td><strong>Uganda</strong>&lt;br&gt;(Tororo Hospital PMTCT Program and THETA)</td>
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<td></td>
<td><strong>Prevention</strong>&lt;br&gt;■ To involve TBAs in mobilizing, counseling, referring, and supporting pregnant women to access comprehensive PMTCT services</td>
<td>■ Trained TBAs were able to refer women for HCT and family planning</td>
<td>■ TBA can be an important part of a community support network to increase awareness of, access to, and adherence to PMTCT services</td>
</tr>
<tr>
<td></td>
<td><strong>Care and Support</strong>&lt;br&gt;■ To develop a model of community support for PMTCT</td>
<td>■ TH accompanied clients to deliver in hospital, supported them for drug adherence, and improved the hygiene and sanitation of their clinics or homes</td>
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<tr>
<td></td>
<td><strong>Other Objectives</strong>&lt;br&gt;■ Trained TBAs were able to refer women for HCT and family planning</td>
<td>TBA can be an important part of a community support network to increase awareness of, access to, and adherence to PMTCT services</td>
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<td><strong>Tanzania</strong>&lt;br&gt;(TAWG, 1992–2007; Mtullu, 2007&lt;sup&gt;12&lt;/sup&gt;)</td>
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<td></td>
<td><strong>Prevention</strong>&lt;br&gt;■ To promote community-based condom distribution</td>
<td>■ TAWG trained 429 THs</td>
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<td><strong>Care and Support</strong>&lt;br&gt;■ To build capacity of THs as community-based HIV/AIDS/STI educators and home-care providers for people living with HIV and their families</td>
<td>■ 4,500 HIV-positive patients treated</td>
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<tr>
<td></td>
<td><strong>Other Objectives</strong>&lt;br&gt;■ To conduct research on potential herbal treatment in collaboration with THs and scientific institutions</td>
<td>■ 1,618 educational sessions conducted</td>
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<td>■ Ensure sustainable supply of medicinal plants through conservation</td>
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<td>■ 9 TH initiatives on orphan care and community theater</td>
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<td>■ 468 referrals from TH to BHP for HIV testing and care</td>
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<td>■ HIV-positive individuals have greater access to low-cost treatment</td>
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<td>■ Plans to develop TOT of TH to scale up in the region</td>
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<td>■ Planned training on medicinal plant propagation for home gardens</td>
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<td>■ Integration of local healers into joint forestry management</td>
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<tr>
<td><strong>Tanzania</strong>&lt;br&gt;(Kayombo et al, 2007&lt;sup&gt;65&lt;/sup&gt;)</td>
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<tr>
<td>Tanzania</td>
<td>Kisangau et al, 2007</td>
<td>To document herbal remedies used in the management of HIV/AIDS OIs in rural Tanzania</td>
<td>TB and oral candidiasis were the most common manifestations of HIV/AIDS OIs affecting most of the population in the area</td>
</tr>
<tr>
<td>Tanzania</td>
<td>McMillen, 2004</td>
<td>To explore the shared relationships between THs and BHPs to describe some relevant possible adaptations of modern-day healers</td>
<td>Multiple factors, especially sociocultural changes, BM, AIDS, and other research or researchers can influence healer changes in relation to the environment and context</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Plummer et al, 2006</td>
<td>To examine STI and AIDS treatment-seeking behavior in rural Tanzania</td>
<td>Treatments were varied and opportunistic, usually beginning with home remedies (both biomedical and traditional), followed by visits to TH and/or BHP</td>
</tr>
</tbody>
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<td>Zambia</td>
<td>Prevention</td>
<td>To assess prevalence and predictors for TM use among pregnant women in Lusaka government health system</td>
<td>30% of 1,128 women reported use of TM in past; 54% of those surveyed believed that disclosing TM use would result in worse care</td>
</tr>
<tr>
<td></td>
<td>Care and Support</td>
<td>Use of TM during pregnancy is common, stigmatized, and may be associated with nonadherence to ART</td>
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<tr>
<td></td>
<td>Other Objectives</td>
<td>■ Health-care providers must open lines of communication with TH and pregnant women to maximize program success</td>
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"Banda et al, 2007"
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<td>Multi-country Projects</td>
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<tr>
<td><strong>UK, Uganda, Sweden, Zambia (Bridging Gaps 2002–2006)</strong></td>
<td>To improve HIV/STI care in the traditional and biomedical sectors through increased collaboration</td>
<td>Recognition of THS through TH/BHP partnership increases quality of care, particularly for THs, as THs can pass on correct health information to clients</td>
<td>Urgent need for policy development to enhance TH/BHP partnerships and to scale up coverage and quality of HIV/STI services at community level</td>
</tr>
<tr>
<td></td>
<td>To develop and evaluate innovative strategies to create mutual understanding, increased dialogue, and better collaboration between the public and TM</td>
<td>Official referrals from BHP to TH sector are difficult due to policy context, though they occur informally</td>
<td>THs have integrated new information about HIV testing, condom use, and HIV into services they provide at the community level after intervention</td>
</tr>
<tr>
<td></td>
<td>To improve HIV/STI care in TM and BM through increased collaboration</td>
<td>THs counsel on HIV testing, give advice on HIV medicine, and distribute or sell condoms</td>
<td>Information about PMTCT not adequately disseminated by TH, suggesting that targeted information be provided to THs</td>
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<td>This type of intervention could be scaled up to other areas of Uganda as well as to other countries in the region</td>
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<td>Multi-country Projects</td>
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<tr>
<td><strong>UK, Uganda, Sweden, Zambia</strong> (Kaboru et al, 2006&lt;sup&gt;49,50&lt;/sup&gt;)</td>
<td>To identify obstacles and opportunities for BHP and TH to collaborate for HIV and STI care</td>
<td>To explore BHP and TH experiences of and attitudes toward collaboration</td>
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<tr>
<td><strong>Abbreviations</strong></td>
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<tr>
<td>BHP</td>
<td>Biomedical health practitioners</td>
<td>TAWG</td>
</tr>
<tr>
<td>BM</td>
<td>Biomedicine</td>
<td>TBA</td>
</tr>
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<td>KABP</td>
<td>Knowledge, attitudes, beliefs, and practices</td>
<td>TH</td>
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<tr>
<td>HCT</td>
<td>HIV counseling and testing</td>
<td>THETA</td>
</tr>
<tr>
<td>OI</td>
<td>Opportunistic infection</td>
<td>TM</td>
</tr>
<tr>
<td>PMTCT</td>
<td>Prevention of mother-to-child transmission of HIV</td>
<td>TOT</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
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REFERENCE LIST


58. WHO. Seventh Meeting of the WHO Regional Expert Committee on Traditional Medicine; December 17-21, 2007; Brazzaville, Republic of Congo.


64. Summerton JV. Western health practitioners’ view about African traditional health practitioners’ treatment and care of people living with HIV/AIDS. Curationis. 2006;29(3):15-23.


Use of Laypeople to Scale Up HIV Testing and Antiretroviral Therapy in Uganda

Michael Etukoit, Christine Nabiryo, and Alex Coutinho

The AIDS Support Organization (TASO), Uganda

The AIDS Support Organization (TASO) was the first and is currently the largest nongovernmental organization (NGO) in Uganda providing prevention, care, and support services for people living with and affected by HIV in Uganda. TASO has been in existence for 20 years and in the last 5 years has been scaling up its core services, including HIV testing. In 2004, TASO also commenced and scaled up the provision of antiretroviral therapy (ART) services to its clients, and today 20,000 of its 60,000 clients are on ART.

Uganda is considered one of the HIV/AIDS success stories in Africa, particularly in regard to the reduction of the national HIV prevalence from a high of 18% in 2002 to the current level of just over 6%. This success was largely based on the grassroots mobilization of the entire population of Uganda, involving the top political leadership, the government of Uganda, community gatekeepers, laypeople, AIDS-related organizations, and people living with HIV. The key prevention messages were mainly the ABC strategy (i.e., abstinence, being faithful, and condom use).

Today, the government of Uganda, TASO, and other HIV/AIDS service organizations are faced with the challenges of scaling up HIV prevention, treatment, and care services in general and HIV testing and ART services in particular. These challenges are not unique to Uganda or to TASO, and the lessons described in this chapter on how to use laypeople to scale up HIV testing and ART at the community level can inform and assist other countries and organizations facing this formidable challenge.

EPIDEMIOLOGY OF HIV IN UGANDA

A 2006 report by the Uganda Bureau of Statistics indicated that the estimated population of Uganda in 2005/2006 was 27.2 million, with females constituting 51% of the population. The population of Uganda is dominated by children under 15 years of age. The country has experienced a rapid population growth rate of 3.4% per year from 1991 to 2002. This growth rate, if it continues, will result in a doubling of the population in just 21 years.

According to the same 2006 report, the prevalence of HIV in Uganda was estimated to be 6.4%, translating into 1.1 million people living with HIV (58% of whom were women). HIV prevalence was higher among the urban population. Only 12.7% of women and 10.8% of men between the ages 15 and 49 had been tested for HIV and received their results. As of 2006, it was estimated that 234,500 people were
in need of antiretroviral drugs (ARVs), but that less than 50% had accessed treatment.1

According to the World Health Organization (WHO) World Health Report 2006,4 there are 2,209 doctors in Uganda (0.08 doctors per 1,000 people); 16,221 nurses (0.61 per 1,000 people); and 688 pharmacists (0.03 per 1,000 people). Less than 30% of these health-care workers are based in rural areas, where the majority of the population resides.

**TASO UGANDA**

TASO is an indigenous organization operating in Uganda since 1987, with 11 clinics throughout the country. TASO provides a full continuum of comprehensive HIV prevention, care, and treatment services (see Box 1) for its 60,000 active clients targeted by President’s Emergency Plan for AIDS Relief funding, 66% of whom are female.

The largest proportion of the organization’s clients live in rural areas, and most are poor and cannot afford the transportation costs to visit a health facility on a regular basis. This is why most of TASO’s services are also offered in the home, including home-based delivery of ARVs. Over 30,000 family members have so far been tested for HIV at their homes through TASO.

TASO is a membership organization for individuals living with HIV and their families, and members have significant input into its operation. TASO provides a wide range of services, including counseling and testing, clinical care, spiritual and emotional support, aromatherapy, ART, and local and national advocacy, along with extensive training in all these areas. TASO has an innovative home-based ART program that is serving as a model for the region as a way to ensure drug adherence.

The TASO drama groups play an important role in advocacy, community sensitization, and mobilization, as do peer educators and care supporters for people living with HIV. All TASO activities are linked to the organization’s training and capacity building, which operate through one international training center and four national training centers. In combination, these centers train over 1,000 health workers annually.

TASO operates within or in close collaboration with Ministry of Health (MOH) facilities in order to support the MOH and to have access to referral services for clients (e.g., inpatient services). In addition, TASO has close linkages with the Uganda AIDS Commission and the leadership in the districts where it operates. This collaboration with the public health system ensures that the organization continues to serve the neediest people. Services are provided using a combination of facility-based and community-based approaches, with a particular emphasis on family-centered care. The facility-based approach is practiced at 11 stand-alone clinical facilities strategically located throughout Uganda. The home-based services are offered at clients’ homes. With both approaches, TASO encourages the entire family to participate in services, especially HIV testing and subsequent clinical management. TASO also links families to support structures within the community and/or peer groups for people living with HIV and their families. In addition, all the organization’s activities have the active and meaningful involvement of people living with HIV, especially through drama performances for community sensitization and education.
ROLE AND SIGNIFICANCE OF LAYPEOPLE IN HIV CARE DELIVERY

Laypeople have been used to support health-care delivery for many years. In major disasters, laypeople have been trained to offer emergency medical services. For routine health-care delivery, highly motivated individuals can be identified, trained, and oriented to offer medical services under the supervision of trained health workers. Until recently, nursing aides (lay workers) ran health-care services at lower-level public health facilities. The use of laypeople offers individuals an exciting opportunity to practice a previously exclusive trade, and there is an element of peer support, as in most cases they will be offering services to other laypeople with whom they have a shared perspective.

Other laypeople offering health-care services in Uganda include traditional healers, traditional midwives, village health workers, and laypeople who sell medicines and offer medical advice to their clients. Some of these people have been trained in basic health care by the MoH in collaboration with other partners.

A number of organizations and individuals have made the case for training laypeople to offer medical care, including the identification of life-threatening conditions. Husum and colleagues demonstrated that laypeople who are given first aid skills can effectively respond to emergencies in a community with a high trauma burden. In Ghana, Mock and colleagues demonstrated that commercial taxi and minibus drivers trained in first aid can provide effective prehospital care. The researchers observed that laypeople are likely to be successful where the burden of injuries and other emergencies is high and also noted that attrition of both the laypeople and their skills is a concern unless they are put to frequent use.

The majority (80%) of the population of Uganda is concentrated in rural areas. Consequently, up to 90% of TASo clients are also based in rural areas. The majority of these clients live below the poverty line, surviving on less than US$1 per day, and illiteracy levels are high. The majority of the clients, at the time of their registration with TASo, are very sick, have diminished income, or have lost their means of livelihood altogether. Others are widowed, separated, or divorced or have been abandoned by relatives. These circumstances can make it difficult for clients to access urban-based health facilities, due to lack of transportation or money to pay for services.

Community-based services using laypeople remain an important alternative for the appropriate delivery of HIV/AIDS prevention and care services. TASo rolled out a community- and family-based ART program model in 2004 designed to be the largest rural-based program of its kind in Africa. The program design incorporates a built-in set of adherence strategies to ensure that the highest possible level of adherence to ARVs and other drugs is attained (Box 2).

<table>
<thead>
<tr>
<th>Box 2. Antiretroviral Therapy Adherence Strategies Employed by TASO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective supply chain management</td>
</tr>
<tr>
<td>Proper management of opportunistic infections</td>
</tr>
<tr>
<td>Couples counseling</td>
</tr>
<tr>
<td>Music, dance, drama, and personal testimonies</td>
</tr>
<tr>
<td>Continuous counseling and education</td>
</tr>
<tr>
<td>Clinical and psychosocial evaluation and reevaluation</td>
</tr>
<tr>
<td>Medicine companions or “buddies”</td>
</tr>
<tr>
<td>Disclosure of serostatus to significant others</td>
</tr>
<tr>
<td>HIV testing of family members</td>
</tr>
<tr>
<td>Home- or community-based antiretroviral therapy (ART) delivery</td>
</tr>
<tr>
<td>Window for facility-based antiretroviral delivery</td>
</tr>
<tr>
<td>Field officers</td>
</tr>
<tr>
<td>Nutritional support as needed for clients on ART</td>
</tr>
<tr>
<td>Community ART support agents</td>
</tr>
<tr>
<td>Peer support groups</td>
</tr>
<tr>
<td>Pill boxes</td>
</tr>
<tr>
<td>Client tracking system</td>
</tr>
<tr>
<td>Information, education, and communication materials</td>
</tr>
<tr>
<td>Home visits</td>
</tr>
</tbody>
</table>
In most developing countries, the paucity of resources affects all spheres of social services provision, including the availability of skilled personnel to dispense lifesaving medications such as ARVs. The use of laypeople in scaling up HIV testing and ARV delivery was deemed necessary based on the limited availability of trained health workers in the country. For a program to be able to deliver a quality and comprehensive HIV/AIDS care package, success depends on ensuring a continuum of care. Given the need for quality care (e.g., ability to determine the accuracy of HIV test results) and the importance of multiple adherence support strategies for ART, Uganda needed a concise and high-quality training program for laypeople, with ongoing supervision and refresher training, to ensure adequate human resources for the scale-up of quality HIV/AIDS services.

Key Functions of Laypeople in HIV Care Provision

HIV Testing

HIV testing is a key entry point to accessing HIV/AIDS care services, including prevention. The availability of testing in Uganda has until recently been scarce for rural populations. However, a number of providers, including TASo, have now started to offer home-based rapid HIV testing conducted by laypeople.

HIV testing takes place in the community, giving people being tested the opportunity to observe the procedure and thus building confidence in the health-care system. Community-based testing can help reduce the denial period for people testing positive and can enhance strategies that help a person cope with a positive test result. During routine visits, laypeople can also administer rapid HIV tests to consenting family members. This approach is an example of task shifting, where the few qualified medical personnel are relieved from routine tasks such as HIV testing so that they may concentrate on specialized medical work, management, and training.

ARV Delivery

Laypeople can assist with the delivery of ARVs to clients in their homes and/or communities, identify complications, and offer advice on seeking further medical help.

Client Follow-Up

Another key function for laypeople is following up with people on ART to ensure that drugs are taken correctly and that any emerging side effects or drug failures are detected early and referred as needed.

Adherence Support

Laypeople offer direct adherence support through counseling and peer support. HIV-positive laypeople can also serve as ART adherence role models.

Categories of Laypeople

There are two main categories of laypeople trained by TASo to offer HIV testing and ART services in the communities: field officers and community ART support agents (CASAs).

Field Officers

Field officers are full-time trained lay staff who have at least 15 years of formal education and a diploma or degree in social sciences or education. Field officers receive five weeks of training in a field officers’ course designed by TASO. Training covers a variety of skills and topics, including basic HIV/AIDS information, counseling, home-based care, home-based voluntary counseling and testing, behavior change communication, community mobilization, principles and practices of ART, principles of adult learning, and universal precautions, among others. Field officers are also introduced to the TASO vision, mission, values, and organizational culture in order to motivate them and ensure adherence to the overall goals of TASO.
Box 3. Key Responsibilities of Field Officers

- Mapping of clients in designated geographical areas of assignment
- Counseling clients on ART and adherence
- Performing rapid HIV tests for family members of clients initiating ART
- Delivering ARVs to clients’ homes or at drug distribution points
- Visiting clients at home
- Liaising with community nurses and other volunteers in the community
- Facilitating the setting up of peer support groups in the community
- Supporting peer support groups and community ART support agents
- Participating in community meetings
- Writing reports
- Identifying ARV complications and liaising with facility-based home-care teams
- Advising clients on seeking professional medical help
- Referring complex counseling issues to qualified counselors

Box 4. Key Responsibilities of CASAs

- Sharing experiences of being on ART with other clients
- Checking on adherence through pill counts and self-reports
- Checking for antiretroviral side effects and reporting to TASO field officers or community nurses
- Checking for proper use of the basic care kit
- Mobilizing clients to pick up their refills from the community drug distribution points
- Sensitizing family members of the index clients on home-based HIV counseling and testing
- Educating family members on adherence support
- Distributing condoms and educating clients on correct condom use
- Participating in activities at the drug distribution points
- Advising on referrals when necessary and keeping records of work

Box 3 lists field officers’ key responsibilities, and Figure 1 depicts a field officer’s typical daily work routine.

**CASAs**

CASAs are expert HIV-positive TASO clients who provide positive prevention and general HIV prevention messages to family members and the wider community. CASAs usually have had minimal formal education and draw largely from their own experiences with HIV care and treatment, supplemented by knowledge gained from the community ART course. CASAs are a practical example of the principle of greater involvement of people living with HIV in ART delivery.

Expert clients are individuals who have successfully coped with their HIV infections and are open about their HIV status. The majority of CASAs are receiving ART. The selection of CASAs is a participatory process involving clients in a particular geographical area. Clients select from among their peers those people that they feel are well positioned to support others.

After the selection process, CASAs are taken through an intensive one-week training that includes information on TASO background and activities, including the community and ART programs; basic facts about ART and ART adherence; positive prevention and general prevention; behavior change relating to ART; roles and responsibilities of CASAs; and record keeping. Upon completion of the training, CASAs work in communities in and around where they reside. Their key responsibilities are listed in Box 4.

Incentives for CASAs are in the form of facilitation to enable them to perform their roles. Upon completion of training, each CASA is
given a bicycle to ease movement in the community and a stipend for maintaining the bicycle. CASAs are also provided with T-shirts and caps with messages to create awareness in the community. In addition, they each receive one pair of gum boots. Regular refresher training keeps the team motivated.

Key Processes in the Training and Deployment of Laypeople

1. **Develop a strategic plan.** The overall institutional strategic plan must be in line with national testing and ART plans.

2. **Define the operational strategy.** Clearly define the strategy for implementation while involving all key stakeholders and soliciting buy-in.

3. **Identify the magnitude of work to be done.** Determine the volume of work to be handled. Map the clients to determine the catchment area in order to determine the logistics required. Identify other players active in the catchment area.

4. **Determine the number of laypeople required.** Determine the number of patients to be looked after by each layperson, depending on how

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**Figure 1. Daily work routine for TASO field officers**

- Report to work
- Summarize previous day’s work
- Enter data
- Check motorcycle for readiness
- Liaise with medical and counseling teams for home-care visits

- Sign out drugs from pharmacy
- Sign up for home-based HIV test kits
- Review client directory and drug distribution point information
- Travel to community

- Refill client ARVs and offer adherence counseling
- Perform household assessment
- Map out new ART clients
- Conduct home-based HIV counseling and testing
- Assess psychosocial readiness of eligible new enrollees for ART
- Coordinate other community activities with community
  ART support agents and peer support groups

- Return from field
- Write reports
- Obtain list for next day’s refills
- Return unused test kits and drugs
- Debrief medical and counseling teams
many people currently are or are expected to be on ARVs. Each field officer can look after 100 clients on ARVs. Each CASA can take care of up to 20 people on ARVs.

5. **Design an appropriate curriculum.** Determine the skills and knowledge required and design the curriculum around them. Involve TASO clients, the potential trainers, and experts in curriculum design, if available, to develop the curriculum. Periodically review the curriculum to keep the training relevant and up-to-date.

6. **Recruit volunteers.** Widely disseminate information and solicit applications for lay volunteers. Then short-list candidates based on a preset scoring system and invite the highest-scoring applicants for interviews. For CASAs, the recruitment is restricted to expert clients, although in some circumstances competent community volunteers may be selected to serve as CASAs.

7. **Select qualified candidates.** Select the individuals who are willing to learn, are motivated, and have the right attitude and the required qualifications. In the case of CASAs, the individuals must have enough free time to volunteer, as it is not a full-time position.

8. **Conduct training.** The training is conducted based on a designed curriculum. If there are already other experienced laypeople in the community, involve them in training new team members in order to provide hands-on field experience. This activity motivates the senior team members, as their roles are being appreciated and the job is being enriched. The field officer training lasts five weeks. For CASAs, a selected group first undergoes a two-week training-of-trainers (TOT) course to prepare them to train fellow CASAs. Subsequent training of new team members lasts one week.

9. **Induct and orient the team.** Teams need to be inducted and oriented at their places of work.

10. **Geographically zone and allocate work areas.** Allocate workers’ operational areas based on geographical zones to prevent overlap and improve efficiency and avoid duplication. CASAs are selected by fellow clients in a particular geographical area after the clients are sensitized about the benefits of the community ART program, the quality of the individuals required, and their roles upon completion of training. A counselor and the field officer in charge of a particular geographical area support the selection process.

11. **Compile a client directory.** Each layperson compiles a detailed directory of clients under his or her care, indicating demographic information and details of addresses, including landmarks, neighborhoods, local leaders, and sketched diagrams indicating location.

12. **Work in groups that include senior staff.** Initially, the new laypeople should work hand in hand with experienced laypeople or counselors, who will introduce them to the clients and family and community members.

13. **Provide adequate supervision.** A field officer supervisor based at the center is immediately in charge of supervising the field officers on a day-to-day basis while they are in the field and reports to an ART team leader. A center manager takes overall responsibility at the facility level.

14. **Conduct program reviews.** Program reviews are performed on a quarterly basis by management. Reviews involving many stakeholders are conducted annually as well as at other times when the need arises. At the points of implementation, reviews on a daily, weekly, biweekly, or monthly basis can be performed.
Confirm status, and blood is taken for CD4 lymphocyte count testing. A clinical evaluation for ART is carried out, focusing on opportunistic infections, including TB. The client returns two weeks later for the test results. Clients who are eligible for ART receive a home visit that includes a psychosocial readiness assessment. During this visit by a team consisting of a field officer and a counselor, a medicine companion is identified and family members are offered the opportunity to have an HIV test performed at home. Clients who have not yet disclosed their status to family members are initiated into the process of assisted disclosure. The client is then given an appointment to come to the facility to receive the first dose of ARVs, along with counseling on adherence, sexual behavior change, and general ART issues.

All clients are started on drugs at the TASO facility and subsequently receive their refills on a monthly basis at home. Monthly refills are provided.
for the first three months to allow frequent contact with support staff, ensuring that monitoring for side effects and adherence take place before shifting to less frequent refills. After three months, a case conference is convened and the client’s adherence to drugs and other issues are reviewed. This review takes place with considerable input from the field officer in charge of the geographical area where the client resides. Clients whose adherence levels are above 95% are then graduated to refills once every two months. They may choose to receive their refills from the facility, at home, or from a community drug distribution point run by a field officer. Those whose adherence is below the 95% target continue to receive their ARV refills on a monthly basis. This information is passed on by the field officers to the CASA, who then takes up the issue with the client and his or her family members to offer additional adherence support.

### Challenges and Concerns Related to ART Delivery

#### Drug-Related

Patients receiving ART often have a number of concerns, including having to take their pills daily for life; possible side effects and drug interactions; the availability of adequate food; the availability of and access to ARV drugs throughout life; concerns about adherence; the possibility of graduating to second-line drugs that are expensive and “stronger”; and the pill burden, especially when on treatment for other chronic illnesses such as diabetes, hypertension, and cancer, or while on long-term treatments such as anti-TB drugs, cotrimoxazole, and fluconazole used for prophylaxis. Additional concerns include the efficacy of drugs from a different manufacturer, the efficacy of generics or brand-name drugs when a client is shifted from one category to the other, and changes in the interval between refills or doses.

#### Social

Once they have been initiated on ART and begin to see improvements in their health, clients often wish to reestablish previous failed relationships and/or start new relationships, have children, or return to work or school. Some clients must deal with relatives and friends with whom they had discontinued sharing property in the belief that they would soon die. They may also worry about availability of drugs for other HIV-positive family members. Some clients must deal with a return to normal life after previous openness about their positive status, having thought that death was imminent. In these cases, clients may revert back to non-openness about their status and may face moral dilemmas about disclosure.

#### Economic

Clients often need to find a job, return to a previous job, or obtain financial resources to start income-generating activities. The role of laypeople in addressing these concerns includes offering continuous counseling, delivering drugs, providing continuous education for clients and their family members, and linking clients to other support services.

### Positive Outcomes of Utilizing Laypeople

#### Increased Access to Free HIV Testing

Using laypeople to provide health services increases access to free HIV testing, especially for family members of index clients initiated on ART, including children. Most of the tests are performed at home by trained laypeople. It has been observed that the majority of family members reached through this method were taking an HIV test for the first time (Table 1). Many of them, including spouses, were surprised that they were either HIV negative or positive, contrary to their previously held conviction. This finding demonstrated the previously limited availability of
Reduced Loss to Follow-Up

A common challenge of facility-based ART programs in resource-limited settings is the difficulty of tracing people on ART when they are lost to follow-up. This is because most facility-based ART delivery programs do not have the logistics, human resources, and necessary community networks for tracing defaulters. To combat this problem, laypeople keep a client directory and personal information about each client gathered over time. From this information, it is often possible to find out where a client has relocated to, his or her health status, and/or whether the individual has been hospitalized or has died.

Hospitalized clients are followed up and continue to receive their ARVs. Support can also be provided to hospitalized clients through the provision of other required medications and care supplies. Clients on ARVs who end up in correctional facilities can be traced and can continue to receive their drugs, nursing care, and counseling while they are in prison.

The data in Table 3 show the high levels of client retention achieved by TASO at their site in Mbale, HIV testing and other HIV/AIDS services for rural populations. HIV testing serves as an access point to HIV/AIDS treatment, care, and prevention services. This activity provides access to comprehensive HIV/AIDS care for a wider population.

Sustained High Levels of Drug Adherence

Use of laypeople has led to sustained high levels of adherence, not only to ARVs but to other drugs such as cotrimoxazole that are refilled concurrently with ARVs (Table 2). This approach widens the social safety networks that help support and promote good adherence. The laypeople based in the communities, such as the CASAs, support adherence in general and also administer directly observed therapy (DOT) for those who have been identified as nonadherent to treatment. The lay workers are trained in measuring adherence and can identify individuals who are nonadherent using the three-day recall method, self-reports, reports from medicine companions, and pill counts conducted during scheduled and unscheduled home visits.

### Table 1. HIV Testing Uptake among Family Members of TASO Index Clients (2006)

<table>
<thead>
<tr>
<th>Ever had an HIV test?</th>
<th>Total tested</th>
<th>HIV positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No*</td>
<td>16,222</td>
<td>901 (5.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>2,566</td>
<td>316 (12.3)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>18,788</td>
<td>1,217 (6.5)**</td>
</tr>
</tbody>
</table>

*Over 86% of the family members were accessing an HIV test for the first time; 74% of those who tested HIV-positive were first-time testers.

**This figure tallies with the current 6.5% national HIV seroprevalence.

### Table 2. Comparison of Drug Adherence between Facility- and Home-Based Clients among 4,132 TASO clients (2006)

<table>
<thead>
<tr>
<th>Client Type</th>
<th>Poor adherence (&lt;95%) (%)</th>
<th>Good adherence (&gt;95%) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility-based</td>
<td>15.4</td>
<td>84.6</td>
</tr>
<tr>
<td>Home-based</td>
<td>9.8</td>
<td>90.2</td>
</tr>
</tbody>
</table>

A common challenge of facility-based ART programs in resource-limited settings is the difficulty of tracing people on ART when they are lost to follow-up. This is because most facility-based ART delivery programs do not have the logistics, human resources, and necessary community networks for tracing defaulters. To combat this problem, laypeople keep a client directory and personal information about each client gathered over time. From this information, it is often possible to find out where a client has relocated to, his or her health status, and/or whether the individual has been hospitalized or has died. Hospitalized clients are followed up and continue to receive their ARVs. Support can also be provided to hospitalized clients through the provision of other required medications and care supplies. Clients on ARVs who end up in correctional facilities can be traced and can continue to receive their drugs, nursing care, and counseling while they are in prison.

The data in Table 3 show the high levels of client retention achieved by TASO at their site in Mbale,
Increased Family and Community Support
Involving laypeople increases the level of disclosure and improves family and community support for those living with HIV. Caregivers in the family are educated on basic facts about HIV/AIDS, prevention, and home nursing care to allay their fears about caring for an HIV-positive person and to give them skills to protect themselves from infection. This education helps reduce stigma, leading to a healthier home-care environment.

Reduced Levels of Stigma
The presence in the community of field officers and CASAs, coupled with the improvement that community members observe in previously very sick people, helps reduce negative sociocultural constructs around HIV/AIDS that promote self- and external stigmatization of HIV-positive people.

Enhanced HIV Prevention at the Family Level
Family members who test positive are educated on issues of positive prevention. Those who test negative are provided with information on how to protect themselves from contracting HIV using enhanced risk perception and the development of personal risk-reduction strategies. Often a spouse whose partner is HIV-positive assumes he or she is also HIV-positive. Family testing and prevention education have enabled the identification of partly due to efficient follow-up systems supported by laypeople.

Meaningful Involvement of People Living with HIV
The involvement of lay providers who are expert clients, such as TASO CASAs, helps strengthen the partnership TASO has with its clients. Some expert clients are trained in a TOT course so that they can train others to support their peers on adherence to treatment. They are also involved in delivering positive prevention messages to HIV-positive people and general prevention messages to those who are HIV-negative.

Delay of ARV Drug Resistance
Suboptimal adherence to ARVs (adherence levels below 95%) is the most common cause of virologic failure among those receiving ART. The use of laypeople to improve adherence reduces the risk of an early shift to second-line ART or salvage therapy, which can be significantly more expensive than first-line therapy. This delay also increases the opportunity for others to access treatment. Of the 13,000 clients TASO has started directly on ART up to the end of 2006, only 0.3% were on second-line treatment. It is believed that this low proportion is due to TASO’s multipronged approach to ensuring adherence. The majority of the 0.3% on second-line treatment were transferred in from other programs.

Table 3. Patient Retention at TASO Mbale after One Year on ART

<table>
<thead>
<tr>
<th>Patient cohort</th>
<th># started on ART</th>
<th>Patient status after one year</th>
<th># still in cohort</th>
<th>Retention rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dead</td>
<td>Transferred out</td>
<td>Lost to follow-up</td>
<td></td>
</tr>
<tr>
<td>Nov 2004</td>
<td>376</td>
<td>13</td>
<td>2</td>
<td>361</td>
</tr>
<tr>
<td>Jun 2005</td>
<td>487</td>
<td>39</td>
<td>0</td>
<td>448</td>
</tr>
<tr>
<td>Jan 2006</td>
<td>301</td>
<td>23</td>
<td>0</td>
<td>278</td>
</tr>
</tbody>
</table>

*Each cohort was recruited during a one-month period.*
Reduced Mortality and Morbidity

A number of treatable causes of mortality and morbidity can be detected and immediately referred for treatment through a family- and community-based approach. Such conditions include anemia, lactic acidosis, drug-induced pancreatitis and hepatitis, Stevens-Johnson syndrome, treatable opportunistic infections, and other common illnesses.

Increased Community Involvement and Participation

Community participation in HIV/AIDS programs promotes support for those who are ill, combats stigma, and promotes HIV prevention and ownership of HIV/AIDS programs by communities, thus ensuring the sustainability of these programs.

Increased Demand for HIV/AIDS Services

In addition to actually taking services closer to the population, this community-based approach actually generates demand for HIV/AIDS services, including HIV counseling and testing. It also generates greater demand among patients who wish to receive their ARV refills at their homes or communities, thus helping them adhere to treatment.

Wider Availability of Services in Hard-to-Reach Areas

Thanks to the use of laypeople, care teams have been able to reach areas that had not been accessed before by HIV/AIDS services. Such areas include

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Table 4. HIV Serostatus among Sexual Partners of HIV-Positive TASO Clients (2006)

<table>
<thead>
<tr>
<th>Ever had an HIV test?</th>
<th>Negative (%)</th>
<th>Positive (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>209 (67.4)</td>
<td>101 (32.6)</td>
<td>310</td>
</tr>
<tr>
<td>No</td>
<td>169 (52.8)</td>
<td>151 (47.2)</td>
<td>320</td>
</tr>
<tr>
<td>TOTAL</td>
<td>378 (60.0)</td>
<td>252 (40.0)</td>
<td>630</td>
</tr>
</tbody>
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a large number of couples in discordant relationships and have provided HIV-negative spouses with the means to protect themselves from infection. Table 4 contains the HIV test results among the sexual partners of 630 HIV-positive TASO clients at the TASO Mbale site. The results indicate that in this cohort, 60% of couples were serodiscordant. The Uganda HIV/AIDS Sero-Behavioral Survey (2004-2005) estimated a national population-based serodiscordance of 5.4% among cohabiting couples.

Improved Ability to Monitor Deaths

Lay health workers can facilitate the tracking of mortality and the identification of possible causes. Laypeople can track clients who die while on treatment and can obtain verbal autopsies to try to ascertain probable causes of death.

Increased Monitoring of Drug Side Effects

Monitoring drug side effects in the community, which is often a challenge, can be carried out by laypeople. Most clinical manifestations of drug side effects can be detected at the community level, allowing timely remedial action to be taken. Hematological manifestations of side effects such as anemia are also monitored in the community using portable hemoglobinometers. Other parameters monitored in the community include anthropometric measurements such as weight and height (or length for children under 24 months).
remote geographical areas, mountainous regions, refugee camps, internally displaced persons camps in conflict and postconflict areas, areas isolated due to poor transport infrastructure, and very conservative communities.

Challenges Related to the Use of Laypeople

High Initial Cost
Initial costs of recruitment, selection, orientation, training, and provision of the necessary logistics for work are high.

Limited Resources
Because of limited resources, the work that can be performed is restricted in terms of both geographical areas and target groups. For example, although many community members express interest in receiving an HIV test, only family members of registered TASO clients are tested. In addition, home-based services are only offered within a 75 km radius from the facility.

Limited Supervision
Supervision in the community is a challenge, especially when there are many lay workers and operations are spread out over a wide area.

Pipeline Issues
Sometimes pipeline logistics fall short of what is required to implement activities. Shortages may be the result of planning bottlenecks or issues that may be beyond the control of local authorities.

Managing Increased Demand
Appropriate, quality service delivery generates increasing demand. More and more people seek out services, putting a huge strain on available resources. This strain, if not well managed, can negatively affect the quality of service provision.

Sustaining Motivation of Lay Workers
Maintaining motivation as the initial excitement wears down and the work starts to become monotonous and routine can be a challenge if a continuous process of job enrichment is not in place.

Worker Attrition
Because of the high demand for multiskilled lay workers who can play multiple roles in the communities, workers may soon leave for better-paying jobs. In a competitive job market, formally trained lay workers will have a comparative advantage over others seeking similar positions.

Coordination
Coordination, especially among multiple partners, can be very challenging. Many resources can be wasted through the duplication of work or the concentration of providers in a particular location.

Insecurity
Insecurity affects service provision in conflict and postconflict situations due to the mobility of both the civilian and the military populations and the threat posed to service providers by protagonists.

LESSONS LEARNED

Planning
Careful long-term planning of activities is needed to put the necessary logistics in place in time for the implementation of activities. The roles of laypeople should be well adapted to the sociocultural context in which they will be working. Their roles should not be in conflict with the values of the community, because such conflicts will gravely impact the success of the program.

Constant availability of drugs and supplies builds confidence in the system and helps ensure adherence to ARVs. For essential commodities
Training should include both didactic and practical work. Training sharpens skills, adds new knowledge, and motivates team members. It also enriches their capabilities, preparing them to take on higher-level health-care tasks.

National Policy Framework
A national policy framework that supports the participation of lay workers in the provision of health care is a necessary prerequisite. Outdated public-health policies that exclude laypeople from the provision of health care must be reviewed and appropriate changes incorporated. Policies should not exclude laypeople from directly providing health care.

At the institutional level, necessary measures should be put in place to create a conducive and safe working environment for health workers, including lay providers. There should be clear guidelines on how to deal with accidental occupational exposures, occupational infections, compensation, and the handling of clinical waste generated from the community. These guidelines should cover the topics of postexposure prophylaxis, universal precautions, and hazardous waste management.

Appropriate training curricula for lay providers should be in place and regularly reviewed so that workers are up-to-date on current information in the rapidly changing field of HIV/AIDS care.

Stewardship
Dynamic and responsive leadership must be crafted to steer the program at all levels of implementation. Laypeople should have a leadership structure that is well aligned with that of the parent institution or organization.

Strategy
A strategic framework to support and guide activities over an extended period of time should be put into place and should be concordant with the national or territorial strategic framework for HIV/AIDS.
A general client directory should be compiled, with each team member keeping a directory for the clients under his or her charge. The directory should capture demographic information and the location of the patient, using sketch diagrams that indicate routes, easily recognizable natural and artificial landmarks, and/or the names of widely known local area residents.

There is a need for a clear documentation plan using audio, visual, and print media in order to have a clear and representative picture of events. All processes, achievements, challenges, and lessons learned should be documented to preserve memories so that they can be shared to enhance the learning processes. Documentation also enables easy tracking and monitoring of progress.

Advocacy
Strong advocacy strategies must be in place to create awareness about the complementary role lay workers can play in the delivery of public health-care strategies, and primary care strategies in particular. Lobbying for resources and suitable policy changes is also an important activity.

Stakeholder Involvement
Key stakeholders must be involved at all levels of program implementation, from planning to evaluation. Mobilization, consultations, and sensitization of key stakeholders must take place from the community up to the highest possible level of policymakers (e.g., clients, family members, community members, staff, opinion leaders, civic and political leadership, and public servants working in relevant government departments).

Use of Appropriate Technologies
Equipment for use by lay workers must be simple and easy to operate and should be easy to service and repair. Equipment should be portable and resistant to damage by transportation or adverse weather conditions. Protocols must be written in simple language that is easy for laypeople to understand. Multiple-tier algorithms should be avoided whenever possible. Simple visual aids should be available to guide equipment usage.

Operations are more cost-effective when the team members are located in the targeted geographical areas. This helps localize the operations of the lay workers, as opposed to having to attend to clients dispersed over a wide area. Client assignments should be clearly indicated on enlarged maps of the geographical area.

Team members must be able to multitask because of the demands of the program and the expectations of community members. Lay workers should be able to offer basic counseling and basic medical care (i.e., home nursing care) and be knowledgeable about HIV/AIDS. Ideally, they will have skills in communication, community mobilization, record keeping, data collection, and basic research methods, and they should be comfortable using motorized or pedal cycles where these are available to the program.

Partnerships
To avoid duplication of efforts, resulting in wasted resources, strategic partnerships should be forged that offer opportunities for synergistic efforts in program implementation.

Communication
A robust form of transport must be provided to enable faster access to hard-to-reach areas and extensive coverage in a relatively short period of time. Such modes of transport will include motorized or pedal cycles, which are efficient and cost-effective. In addition, a 24-hour ART hotline should be available. The number should be made easily accessible to all clients on ART by posting it on clients’ notice boards or having it scripted on clients’ health cards or on the covers of personal record books kept by the clients. Health workers should regularly remind
clients of this number during health talks. The number should also be availed to medicine companions. The availability of an ART hotline enhances communication with clients and their families in the communities. This mode of communication relies on cell phone network coverage.

**Operational Research**

The use of laypeople offers many opportunities for operational research and the development of new and appropriate strategies for combating HIV/AIDS in the most affected regions of the world. Operational research in this area can inform policy, operational, and strategic decision-making processes.

**Integration**

For programs that are just starting, activities should be implemented according to well-defined needs, a strict time frame, specific outputs, specific inputs, and a budget. Activities should also be implemented in a well-defined geographical area. At the end of the planned time period (i.e., trial or pilot period), activities can be reorganized and integrated into the rest of the health-care system. A pilot area should be identified and a pilot project implemented before a new program is fully rolled out. A formative evaluation at this stage can save time and other scarce resources later on.

**CONCLUSION**

The use of laypeople in the provision of medical care has a pedigree dating back many years and was especially prominent during the advent of primary health care. Trained lay health workers have successfully filled the gap caused by the shortage of health workers and other needs unique to resource-limited settings. Laypeople continue to play a critical role in the provision of a continuum of care, especially for chronic conditions such as HIV/AIDS.

The use of lay health workers is a cost-effective strategy that supports a public-health approach to the control of the HIV/AIDS epidemic. A public-health approach facilitates broad coverage and enables the majority of the population to access HIV/AIDS care, including ART. It offers the opportunity to provide several useful interventions to a wider population, including routine HIV testing and counseling, simplified clinical management supported by clinical mentors and referral pathways for individual complications, and family-centered care for chronic disease management. Other benefits can include an uninterrupted supply of commodities and free care at the point of delivery. When care is offered within the community, points of contact with health service providers are increased, thereby increasing the opportunities to reinforce prevention messages for those living with and affected by HIV and AIDS.
REFERENCE LIST


The number of people and families living with and affected by HIV and AIDS who need care and support services is continuously increasing. This creates challenges for the formal health-care and community-based systems that are needed to respond to the pandemic. To improve comprehensive care for people living with HIV, it is important to provide acute clinical care based at health facilities, as well as care and support based at home. Due to limited resources, combined with increasing numbers of HIV-positive individuals and demand for services, home-based care (HBC) programs are an essential part of the continuum of care for people living with HIV. The goal is to provide hope and reassurance through high-quality, appropriate care that helps family caregivers and sick family members maintain their independence and achieve the best possible quality of life. This chapter will present a review of lessons learned from care approaches developed specifically for people living with HIV in Thailand, as well as discuss the significance of care, care models, partners and their roles, and human rights aspects of care.

Epidemiology of HIV/AIDS in Thailand

In Thailand, HIV/AIDS is a major problem because there has been a rapid increase in the number of those infected in the past 10 years. The first case of AIDS in Thailand was reported in September 1984, but it is believed that widespread transmission began in the late 1980s. Early cases were generally confined to Thai homosexual males. Among injecting drug users, HIV prevalence rose from nearly zero to 40% in a single year. A second wave of infection spread among sex workers; in 1989, 44% of sex workers in Chiang Mai in the north of the country were found to be infected with HIV. The rising infection level among sex workers launched subsequent waves of the epidemic in male clients of sex workers, their wives and partners, and their children. In September 2007, 321,650 AIDS cases from a total population of 65 million had been reported since the beginning of the epidemic; among these, 90,054 had died. It was found that 25.77% of people living with HIV were in the age group 20-39 years, and 23.93% were in the age...
group 25-29 years. Forty-four percent worked as laborers and 20.6% worked in agriculture.4

The main routes of HIV transmission have changed over time. During the 1990s, most HIV transmission occurred through commercial sex. Now, half of the newly identified infections occur among the wives and sexual partners of men who became infected several years ago. There are also signs that unsafe sexual behavior is increasing among young people in Thailand. It is estimated that 572,500 people are currently living with HIV in the country, of whom 55,000 could develop serious AIDS-related illnesses.4

Given these facts, it is clear that these people will continue to need care and treatment. In the late 1990s, care and treatment for people living with HIV consisted mostly of treatment for their various opportunistic infections. In 1992, antiretroviral therapy (ART) was introduced in Thailand. ART eventually became the standard regimen to achieve maximum viral suppression and has now become the main form of HIV treatment. The complexity of medication regimens renders ART especially difficult for many clients to manage and presents major challenges for care providers. As more people become ill, many will not be able to stay in hospitals, hospices, or other institutions. HBC is a realistic approach to cope with this situation.

HBC DEFINED
As cited in South Africa’s national guidelines on home- and community-based care, HBC is defined as “the provision of health services by formal and informal caregivers in the home in order to promote, restore and maintain a person’s maximum level of comfort, function and health including care toward a dignified death.”6 Care involves participation by family members in responding to the needs of their relative who is ill through the creation of specific roles and responsibilities for each family member.

HBC for people living with HIV is specifically defined as care and support given to people living with HIV and their families in their home environment by family caregivers, trained community volunteers, nongovernment organization (NGO) staff, religious organizations, and health-care workers to meet the client’s physical, psychological, and spiritual needs. HBC may involve self-care, clinical symptom management, health promotion, nutrition, counseling, and emotional support.7,8

HBC IN PRACTICE
HBC for people living with HIV covers physical, mental, emotional, and social aspects of care. Most people living with HIV can take care of their daily physical needs, such as eating, drinking, and bathing. Some may be able to only partially care for themselves, and others may require full-time assistance, especially if they are seriously ill or very young. Apart from the physical challenges associated with HIV/AIDS, mental and social disorders can cause deeper and more serious problems. Rejection by society, because AIDS is incurable, and the appearance of unsightly skin lesions are some of the additional challenges that can cause people living with HIV to become severely depressed and, in some instances, even suicidal. Communication campaigns have done a good job of giving society a better understanding of HIV/AIDS and encouraging acceptance. Still, many people cannot completely accept their HIV-positive status. To change these negative attitudes, people living with HIV must protect themselves from opportunistic infections and raise society’s level of understanding.

The most common problem in providing HBC to people living with HIV is financial.9-10 Many people living with HIV are poor and unemployed, sometimes as a direct result of discrimination due to their HIV-positive status. In some cases, the sick person is abandoned by his or her family and has
no one to care for him or her. For those who meet the necessary criteria, antiretroviral (ARV) treatment can improve the physical health of people living with HIV and can reduce the occurrence of opportunistic infections. Once health improves, it may be possible to go back to work, alleviating some of the financial strain associated with the person’s illness. Some people who have lost a spouse to HIV/AIDS may eventually decide to remarry. In such cases, it is essential that people living with HIV are counseled to disclose their HIV status to new partners and to use condoms during all sexual intercourse. Methods to prevent transmission of the virus, regardless of the partner’s HIV status, must be continuously emphasized.

SUCCESSFUL APPROACHES TO HBC

Experiences in Thailand have shown that in order for an HBC program to be effective, it should be guided by the following principles:

- **HBC is a joint effort of many players.** These include people living with HIV, family, community members, community-based organizations (CBOs), health-care facilities, and other organizations that work together to ensure that people living with HIV receive the best care possible with little or no duplication of activities. Within the community, a group of caregivers should be organized into a “care team.” This team can comprise volunteers from any of the participating partners as well as individuals, with each team member assigned a task that he or she is capable of performing.

- **Communication is essential.** A periodic discussion group or forum should be organized for people living with HIV to meet and exchange information. This activity can provide much-needed psychosocial support and foster a sense of supportive community.

- **HBC activities should not focus on HIV/AIDS alone but also address other problems of people living with HIV and their communities.** HIV/AIDS is a complex issue that affects one’s social, economic, and legal environment. Activities should address all these areas and encourage greater participation from the concerned organizations and people in the community, such as community leaders, health volunteers, local organization committees, and religious leaders.

- **Community members must be able to assess their problems and come up with an achievable set of solutions.** Solutions could include generating additional income through learning a new vocation or acquiring new skills, such as bookkeeping to document income and expenses.

- **Once people in the community have a better understanding of HIV/AIDS, they will be more accepting of people living with HIV.** Community health systems should encourage people to take care of one another and harness the power of local wisdom. One example of this would be using locally found safe and effective herbs as complementary treatment for those receiving ART.

- **Self-care is a learned skill.** The capacity of people living with HIV and family members to care for themselves and their relatives should be developed through health education about HIV/AIDS, opportunistic infections, and techniques of self-care.

- **Periodic forums for the exchange of knowledge and experiences should be held.** Local health personnel, organization committees, and community leaders can facilitate these discussions.

- **Health facilities must understand the common problems of people in the community and if possible participate in solving those problems.**

- **The government must address HIV/AIDS issues in its policies and convert those policies into action.** The government must also
allocate enough money to pursue such actions. Up to now, HIV/AIDS issues have not been well considered by the government (in the case of Thailand), nor has the government allocated enough funds to convert policy into action.

**IMPACTS OF HBC FOR PEOPLE LIVING WITH OR AFFECTED BY HIV AND AIDS**

According to a study conducted in Thailand, there are four types of impacts of HBC:

1. **Impact on patients.** HBC has had a positive impact on clients, making them feel happier and allowing them to be more at ease within the community. They generally have had more self-confidence and self-value and want to fight their illness so that they might live longer.

2. **Impact on nurses.** Nurses have felt proud of how they are helping their clients. They feel needed and have experienced a positive change in their attitudes toward people living with HIV. Their levels of depression associated with their jobs have also decreased.

3. **Impact on the health sector or health-related organizations.** HBC has resulted in a more positive outlook on the part of organizations involved with HIV/AIDS care. The need for hospital beds has been reduced, and, as a result, hospitals have been able to admit new patients in need of treatment.

4. **Impact on the family and society.** HBC has resulted in patients being more accepted by their families and community members.

**MODELS OF HBC**

There are three models of HBC for HIV/AIDS in use in Thailand. They are differentiated according to the types of initiators and major care providers.

**Hospital-Based Home Care Model or Outreach Model**

This formal system of HBC is initiated by formal caregivers who work in a health-care facility to provide outreach services and a continuum of care and treatment for patients who are discharged from the facility. The patients’ needs are assessed, and care activities are planned before discharge from the hospital. Members of the HBC team consist of staff from the hospital or health center. Administration and management are located at the health-care facility. The main focus of services is to maintain a continuum of clinical care and promote medication adherence.

**Community-Based Home Care Model**

This model is conducted as a nonformal system by groups of people, CBOs, or religious organizations. In northern Thailand, home- and community-based care is initiated and conducted by people living with HIV who volunteer and work as part of a group or network of HIV-positive people. This type of care is more likely than hospital-based home care to emphasize psychosocial support and welfare, as well as spiritual care.

**Integrated Community-Based Home Care Model**

This model is co-initiated and conducted by AIDS-related organizations and health-care institutions. People living with HIV receive care and treatment services from health professionals and receive psychosocial and economic support from non–health professionals. A local health-care facility may provide training, supervision, and supplies for home care kits as well as referrals for patients to return to the hospital when needed. This model of care tends to provide more comprehensive care for people living with and affected by HIV/AIDS. In some instances, this integrated model of HBC has been developed and run by a research project that aims to investigate
a holistic care program using a multidisciplinary and multisectoral team.

**THE ROLE OF PARTNERS**

In HBC programs for HIV/AIDS, partnerships may occur at multiple levels. At the personal level, partnership occurs between care providers and those receiving care, and between and among care providers who together are responsible for achieving care-related goals. At the organizational level, partnerships may occur across structures in one organization, with representatives of various divisions or levels coming together to address more general issues of treatment and care, or across organizations, to fulfill shared responsibilities and goals for overall services.

HBC for people living with HIV cannot be accomplished by only one sector or one type of service. All institutions and organizations, including health care, education, social and welfare development, local government, CBOs, and faith-based organizations (FBOs), can contribute to the process of HBC. Generic roles and responsibilities are influenced by the core services and missions of each organization. Following is a description of the various sectors and individuals that have a role to play in providing quality HBC.

**Health Institutions**

This sector is considered part of a formal system of HBC. Care services are provided by formal caregivers who are health-related professionals (e.g., doctors, nurses, psychologists, physical therapists, and social workers). The main focus of service is to provide continuing care and treatment at home. To implement an HBC program, policies must be developed in terms of management, team and accountability structures, standards for service, codes for disciplinary management, and complaint procedures.

HBC is integrated into the existing services of health-care facilities. HIV-positive patients who need home-based services are assessed and identified. Service providers (e.g., doctors, nurses, psychologists, physical therapists, and social workers) are assigned according to the main types of services needed. Health-care institutions also need to provide supportive systems, such as referral and follow-up procedures, and caregiver support, such as training and capacity building.

**Informal Care System**

Stakeholders of HBC in the informal system include NGOs, CBOs, FBOs, local government, traditional leaders, traditional healers, and community leaders. AIDS-related NGOs work collaboratively with relevant stakeholders in government and among other NGOs and CBOs to provide socioeconomic support to people living with HIV. This assistance can be in the form of job opportunities and capacity building for people living with HIV and their families. Other elements of care provided to people living with HIV and those affected by HIV/AIDS include assessment of needs, including psychosocial and financial needs; provision of direct care, including preventive, curative, therapeutic, rehabilitative, and palliative care; empowerment and capacity building to promote the autonomy and financial independence of people living with HIV and family caregivers; optimization and control of available resources to ensure access to comprehensive support services; and assistance with legal and ethical issues regarding HIV/AIDS.

**Nonprofessional Providers (e.g., Family Members and Community Volunteers)**

The elements of HBC provided by nonprofessional providers include basic physical care, rehabilitation, hygiene, safety, psychosocial support, and household assistance.
People Living with HIV
In the era of ART, people living with HIV have become more involved in providing care and assistance to other people living with HIV. Due to their personal experience, people living with HIV can support and empower others in their community who need assistance. People living with HIV can be trained to counsel others and identify new cases as well as support families of people living with HIV in their own communities. Through the example of positive role models, this approach helps those who are newly diagnosed to accept their situation and take care of their personal health.

In Thailand, several government hospitals have set up collaborative service systems involving people living with HIV to provide care and support to other people living with HIV who are receiving ART. Volunteers from self-help groups work collaboratively with nurses and hospital staff to counsel patients before they receive ART. New cases are followed up during home visits to monitor progress, and suggestions are made on how to adhere to ART protocols and manage side effects. The HBC staff and the HIV-positive volunteers follow the cases of those receiving ART over a long period to monitor their capacity for self-care and ART adherence. Self-help groups also provide training to their members on new HIV-related information, best practices for ART adherence, and how to integrate ART into their daily lives. In this way, self-help groups have become a more formalized part of the continuum of HIV care, often receiving funding from local governments, nonprofit organizations, and others.

An important element of HBC is the promotion of social acceptance through encouraging people living with HIV to lead positive and productive lives. The role of people living with HIV in providing home-based services also helps to enhance their social acceptance and improve perceptions of them among the public. Volunteers who are themselves HIV-positive report that they feel an increase in self-esteem by helping others, which in turn helps them to live positively with HIV.

ESSENTIAL FUNCTIONS OF HBC
Based on case examples, observations of practice, and research in different parts of the world, the essential functions of HBC can be summarized as follows: empowering people living with HIV and their families, maintaining quality of life, enhancing medication adherence, providing care to sick persons (including end-of-life care), and maximizing the use of community resources. These functions are not independent of one another and should be integrated whenever possible in order to provide holistic care.

Empowering People Living with HIV and Their Families
Empowerment within the context of HIV care springs from an equitable balance of knowledge, as well as active participation, of care providers and clients as care partners. Empowerment strategies are incorporated into HBC to promote mutual respect, interconnectedness, and the active participation of the patients as care partners. Health professionals and members of AIDS-related organizations often identify empowerment as one of the desired outcomes of their programs.

Maintaining Quality of Life
Quality of life is a term popularly used to convey an overall sense of well-being and includes one’s happiness and satisfaction with life as a whole. The World Health Organization (WHO) has defined quality of life as “individuals’ perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards, expectations and concerns.” HBC providers need to recognize and deal with the variety of conditions and needs...
of individuals and families to improve the overall quality of their clients’ lives.

The needs of people living with HIV and their families can be categorized into four interrelated domains: medical needs, such as treatment information and treatment itself; psychological needs, such as emotional support; socioeconomic needs, such as welfare provision, household assistance, and orphan support; and human rights and legal needs, including access to care and protection against violence and discrimination. Over the years, relevant responses have been developed in these domains, resulting in comprehensive care and support services.

When people living with HIV experience recurrent illnesses, the types of services they need will change. It is this provision of comprehensive care across a continuum, from home- and community-based care to institutional services, that will ensure that the specific needs of clients and their families are met at every stage of the disease process. Effective referral systems need to be in place to ensure that people living with and affected by HIV and AIDS can benefit from the variety of services available at the community and institutional levels throughout the course of their infection.

HIV/AIDS is often associated with a range of psychological sequelae that must be addressed throughout all stages of HIV infection. Psychological support is critical for all those affected to help them cope with their fears and other emotions. Voluntary counseling and testing provides the bulk of initial psychological support for the newly infected. It also links individuals, couples, and families to follow-up psychological support and other support services, such as legal, financial, and spiritual support within communities; peer support groups; appropriate medical care services for early management of TB and other opportunistic infections; and interventions to reduce mother-to-child transmission of HIV.

Enhancing Medical Adherence: The Collaborative Model

A collaborative model of HBC was developed in northern Thailand in order to enhance medication and treatment adherence among people living with HIV. In this model, the four HBC core partners include HIV-positive volunteers, family of people affected by HIV and AIDS, hospitals and/or health centers, and other supportive organizations such as community organizations, religious organizations, and NGOs. Following is a description of each partner’s roles and responsibilities. Key findings from a recent study conducted by the authors are summarized here from a research report submitted to WHO in 2006.5

1. Volunteers are considered the core components of the model of enhancing medication adherence. There are two groups of people living with HIV involved in the care system, namely, HIV-positive volunteers within the health-care system and HIV-positive volunteers living in the communities. These volunteers also serve as leaders of the self-help groups for people-living-with-HIV located in each district. Most of the volunteers have been trained and have collaboratively worked with the staff of the AIDS divisions in their community hospitals. They perform home visits to monitor adherence to ART among the clients who disclosed their HIV status and refer problems back to the hospital staff. A monthly group meeting is conducted regularly in each district. During the meeting, useful information and new knowledge about ART are distributed to the members.

2. Family members of people living with HIV are an essential factor influencing ART adherence. Well-informed family members can be effective facilitators of ART adherence by, for example, reminding an HIV-positive family member to take his or her medicine. Likewise, family members can also be barriers
to ART adherence. For example, some people living with HIV on ART have reported that a family member told them to quit the medicine after they experienced side effects at the beginning of their treatment.5

3. **Hospitals and/or health centers work closely with groups of people living with HIV in their district.** They have established a system of care aimed at promoting adherence to ART. Some hospitals expand this type of service to health centers. This means that people living with HIV can receive ART and care from the health center nearest their home. HIV-positive volunteers have been trained by the nursing staff on how to conduct home visits and create a written report about the patient’s ART adherence. The authors found that most volunteers were adept at working within the hospital and health center settings.5 This collaboration was an essential factor in the ART adherence outcomes that were observed.

4. **The promotion of quality of life must be emphasized just as much as the patient’s physical health.** Based on direct experiences reported by all participants of the study, the quality of life of people living with HIV is influenced by a complex constellation of illness, poverty, stigma, and discrimination combined with family life, work, and social activities. HIV/AIDS affects not only the infected person but also his or her family, community, and country. Working in collaboration with the community hospital and health centers has been recognized as an essential piece of the puzzle, but the focus cannot be only on medical treatment and care. After those receiving ART experience improvements in their physical and mental health, they then need to attend to other needs, such as the need for financial support, job assistance, and other forms of socioeconomic support.

**Providing Care to Those Who Are Ill**

From the review of research and practice in different countries and settings, it is recognized that home care for people living with HIV should include the following key components and activities14-16:

*Physical Health Care*

During home visits, care providers should be concerned about the basic needs of people living with HIV and their families. The home care activities will focus on ensuring the following:

- Client safety and environmental cleanliness
- Personal hygiene
- Adequate nutrition and fluid intake
- Bowel and bladder integrity
- Skin care and pressure sore prevention
- Adequate rest and sleep

*Symptom Management and Alternative Care*

HBC providers need to have effective symptom management skills in providing care for people living with HIV. Uncontrolled symptoms can lead to poor treatment adherence and reduce the quality of life of people living with HIV. These symptoms may be induced by medications or HIV itself. Therefore, HBC providers need to have the knowledge and skills to assess and manage these symptoms effectively. The most common symptoms experienced by people with HIV are fever, diarrhea, skin problems, pain, fatigue and weakness, nausea and vomiting, and insomnia or difficulty in sleeping.17-19

*Emotional and Social Support*

People living with HIV often live with emotional pain and uncertainty about their health, income, and family life. They need understanding and acceptance from family, community, and friends. HBC providers must understand and respect their feelings and provide information and counseling to help them cope with their illness. In communities where peer support is available, it is important to introduce them
families are able to work in collaboration with other formal and nonformal caregivers. In addition to the family, other partners can include hospital personnel, community-based caregivers, HIV-positive volunteers, members of AIDS-related NGOs, and other social welfare organization workers. These partners can collaborate to provide a continuum of care until the end of life, which will enhance the care experience of people living with HIV as well as support caregivers and increase the understanding of the affected community.

Maximizing Use of Community Resources

To mobilize community resources in the target setting, available resources must be assessed, including human resources, financial support, educational materials and training, health personnel, norms and cultures, organizations working with HIV/AIDS, and welfare. Then strategies should be developed to plan for and mobilize available resources in providing HBC. The strategies may include fund-raising, income generation, and establishing networks and partnerships with different groups in the community.

Human Rights Aspects of Home-Based Care

Human rights advocacy for people living with and affected by HIV and AIDS with respect to HBC may be based on some or all of the following concepts.

Freedom of Association

It is the right of free adults to mutually choose their associates as they see fit. Therefore, permission from the infected and affected people should be ensured before performing home visits or providing HBC. Infected and affected people should be informed about the objective and impacts of the care process. These should be clearly stated in the verbal or written consent form.
Confidentiality
People living with HIV are subject to stigmatization and discrimination in society. Confidentiality of data and information from HIV-positive people and their families is an important part of any activity in HBC. Breach of confidentiality and invasion of privacy may pose the greatest risks of stigmatization for people living with HIV, especially those who have not disclosed their status. Notification regarding sensitive issues or problems found during home visits should be provided only to those individuals specifically involved with the follow-up treatment and care. Respect for confidentiality should be observed at all times.

Equal Access to Education and Training
To enhance the effectiveness of care and treatment, education and training are always provided to people living with HIV and their relatives at the hospital or other health-care institutions. In addition, an education and training program is always conducted by the self-help group of people living with HIV. Some people, particularly those who are undisclosed cases who cannot access education and training provided at health-care facilities, should have the chance to be educated and trained in another way. HIV/AIDS-related education and training can be provided at home for individual patients as well as for the family.

Care and Other Social Services
HBC should be provided based on the premise that everyone, whether or not HIV-positive, should be provided with quality care and support from the available care system.

HIV Testing
HIV testing may be needed in the process of care within a family. In this case, verbal or written consent must be obtained and accompanied by thorough counseling before and after testing. HIV-positive persons should continue receiving posttest counseling and supportive care. Those who are HIV-negative should be counseled on how to protect themselves from infection.

Conclusion
Care for people living HIV can be initiated based on the needs of people living with HIV in the community. Different models of care can be established according to the community context and available resources. HBC aims to provide comprehensive and holistic care to people living with HIV as well as encourage self-care among people living with HIV and their families.

Key considerations in the provision of HBC include the holistic approach enhancing the participation of people living with HIV, their families, community members, and support groups; empowerment of care providers and people living with HIV; multidisciplinary teams; cultural sensitivity; confidentiality; and the upholding of human rights standards.

To ensure the sustainability of care, it is important to maximize the use of community resources through networking and partnerships with different settings or organizations, and learning and sharing best practices among the caregiver community.
REFERENCE LIST


views of patients, carers and providers. AIDS Care. 1993;5:105-116.


LEADERSHIP AND PARTNERSHIPS
Funding for international HIV/AIDS efforts has increased dramatically in recent years, resulting in greatly improved access to critical care, treatment, and prevention services. Along with this increased funding has come an increase in the influence and number of actors driving the international HIV/AIDS policy agenda. This chapter, while not an exhaustive review, highlights some of the key agencies and initiatives involved in shaping the present-day global HIV/AIDS response.

United Nations General Assembly Special Session on HIV/AIDS

The first-ever United Nations General Assembly Special Session on HIV/AIDS (UNGASS) was held in June 2001 to address what was labeled as a “global crisis” requiring “global action.” The meeting brought together heads of state and government representatives who formally pledged to work towards reversing the AIDS pandemic through international and regional partnerships, and with the support of civil society. At the conclusion of the meeting, participants unanimously adopted the Declaration of Commitment on HIV/AIDS. The content of the Declaration was heavily influenced by both civil society groups and governments, including those from developing countries, and stressed the need for an extraordinary, multi-sectoral response supported by a significant increase in resources.

The declaration included a call for strong government leadership and the full and active participation of civil society and the private sector. Partnerships at all levels of society were vigorously encouraged. Governments pledged to develop national plans outlining strategies for the integration of HIV prevention, care, treatment, and support. Special attention was given to the enforcement of legislation, regulations and other measures to stop discrimination against people living with HIV and vulnerable groups, such as women and young people, and to develop strategies to combat stigma and social exclusion. Countries also committed to mitigating the economic and social impact of the epidemic through poverty eradication and economic development.

Other issues addressed within the Declaration included the need to further develop health care and research infrastructure, and to strengthen partnerships in this area; as well as the need to
address the heightened vulnerability to HIV among those living in regions affected by conflict or disaster, including members of the armed forces. Governments pledged to allocate at least 15% of their annual budgets toward improving the health sector response to HIV/AIDS; countries with limited resources would be helped to reach this target. Overall, there was a call for massive increases in resources devoted to HIV/AIDS, and pledges were made to mobilize these resources on behalf of the most severely affected countries.

UNGASS represented a critical turning point in international HIV/AIDS policy, paving the way for subsequent global efforts, such as the World Health Organization (WHO) “3 by 5” Initiative in 2003 and the 2006 Political Declaration on HIV led by the United Nations (UN). While these efforts have received some criticism, they have been widely recognized as important stepping stones on the path to global progress in increasing access to HIV/AIDS services for the most affected populations.

WORLD HEALTH ORGANIZATION

As the directing and coordinating authority on international health within the United Nations system, the World Health Organization (WHO) is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends. The WHO HIV/AIDS Department provides evidence-based technical support to WHO Member States to help them scale up treatment, care, and prevention services as well as drugs and diagnostics supply to ensure a comprehensive and sustainable response to HIV/AIDS.

WHO plays a significant role in the scale-up of prevention, care, and treatment services through the development and dissemination of guidelines and recommendations. This guidance often informs the creation or revision of national guidelines for new or existing HIV/AIDS-related services, allowing for evidence-informed improvements in standards of practice to be more quickly adopted, especially in resource-limited settings. In 2003, WHO set an ambitious global target to provide three million people with life-prolonging antiretroviral treatment by the end of 2005. While this target was not reached, many believe that it contributed to the expansion of treatment programs in less-developed countries, thereby demonstrating their feasibility. These early successes encouraged donors to increase support and resources for antiretroviral treatment programs in resource-limited settings and represented a significant early step toward the goal of achieving universal access to HIV/AIDS prevention and treatment.

JOINT UNITED NATIONS PROGRAM ON HIV/AIDS

The Joint United Nations Program on HIV/AIDS (UNAIDS) provides policy guidance that articulates the broad principles and standards meant to inform national policies on HIV/AIDS throughout the world. Guidance produced by UNAIDS is informed by evidence and best practices gathered from multiple sources and is developed through a systematic process in consultation with relevant constituency groups (both external and internal). UNAIDS policies provide specific guidance and an overarching vision of what is to be done at the global level to policymakers, planners and advocates. Policies include those that reflect commitments made by governments through inter-governmental processes (i.e., the 2001 Declaration of Commitment on HIV/AIDS and the Millennium Development Goals) and technical policies and guidelines, which have been developed by the UNAIDS Secretariat and its ten co-sponsors (Office of the UN High Commissioner on Refugees...
[UNHCR], UN Children’s Fund [UNICEF], World Food Program [WFP], UN Development Program [UNDP], UN Population Fund [UNFPA], UN Office on Drugs and Crime [UNODC], International Labor Organization [ILO], UN Education, Scientific, and Cultural Organization [UNESCO], WHO, and the World Bank).

The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund) is a partnership between governments, civil society, the private sector, and affected communities that was established to finance a dramatic turn-around in the fight against AIDS, tuberculosis (TB), and malaria. It is a unique financing mechanism that attracts, manages, and disburses resources rather than participating directly in program implementation. In this way, it can promote local ownership by individual countries while working closely with other multilateral and bilateral organizations to ensure that programs are coordinated with existing efforts.

As of 2008, the Global Fund had committed US$10.7 billion in 136 countries to support aggressive interventions against all three diseases. While it finances programs in all regions of the world, funds are dispersed in accordance with the regionally disproportionate impact of AIDS, TB and malaria. For instance, 61% of funds go to support AIDS-related programs, with 25% and 14% for malaria and TB, respectively. Over half of all funding (57%) goes to support programs in sub-Saharan Africa. The Global Fund takes a comprehensive approach to AIDS, TB, and malaria, funding both prevention and treatment based on locally determined needs. Three-quarters of countries awarded HIV/AIDS funds will use at least a portion of their grants to provide antiretroviral treatment. All HIV grants include prevention activities, most often focusing on young people.

At the individual country level, national-level partnerships, called country coordinating mechanisms (CCMs), develop and submit grant proposals to the Global Fund based on identified needs. Once a grant is approved, the CCM oversees the implementation process. The CCMs include representatives from both the public and private sectors, including governments, multilateral or bilateral agencies, non-governmental organizations, academic institutions, private businesses, and people living with the diseases.

The President’s Emergency Plan for AIDS Relief (PEPFAR) was developed under the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act passed by the U.S. Congress in May 2003. This act authorized US$15 billion in federal funding over five years to combat the HIV epidemic through comprehensive prevention, care, and treatment services in fifteen highly-affected focus countries, most of them in sub-Saharan Africa. It was widely heralded as a watershed moment, signaling both political will and financial commitment to addressing the global AIDS pandemic. In 2007, over 40% of total government disbursements for HIV/AIDS globally were from U.S. government funding.

To implement this large-scale commitment, the Office of the U.S. Global AIDS Coordinator (OGAC) was created to manage and supervise all U.S. government-led international HIV/AIDS efforts and to oversee and distribute the government’s contributions to the Global Fund. At central headquarters, OGAC also collaborates with the Office of HIV/AIDS in the Global Health Bureau at the United States Agency for International development (USAID), the Global AIDS Program at the Centers for Disease
Additionally, PEPFAR aims to promote HIV/AIDS-related health systems strengthening, monitoring and evaluation efforts, and policy reforms. To facilitate these efforts, PEPFAR funding is administered in a mixture of ways. Centrally managed and centrally funded programs are referred to as “Track 1” awards. These are one-time, five-year awards intended to rapidly initiate and scale-up prevention, care, and treatment services in PEPFAR focus countries. These awards were given to organizations with proven track records, existing operations in focus countries, and the capacity to quickly respond in several countries. Award areas include behavior change, care for orphans and vulnerable children, providing antiretroviral therapy (see sidebar on the Track 1 antiretroviral therapy program), and ensuring safe medical injections.

Funding provided to programs initiated by organizations in individual countries is referred to as “Track 1.5” awards. Lastly, “Track 2.0” funds go to individual countries’ annual operational plans.

PEPFAR has made considerable progress towards meeting its initial targets: As of this writing, approximately 1.73 million people have been provided with antiretroviral treatment; prevention of mother-to-child transmission services have reached women in almost 12.7 million pregnancies, with an estimated 194,000 infant infections averted; and more than 6.6 million people have been supported with care services, including over 2.7 million OVC. Other noteworthy achievements include: provision of antiretroviral prophylaxis to women in over 1 million pregnancies, 33 million voluntary counseling and testing sessions carried out, and 2,217 partnerships with local organizations established.

PEPFAR has demonstrated that rapid, focused and multi-country efforts are possible when organizations already established on the ground in multiple settings are given the resources and support to achieve the urgent scale-up of HIV care and treatment services.
THE PEPFAR TRACK 1.0 ANTIRETROVIRAL TREATMENT PROGRAM

THE PEPFAR ANTIRETROVIRAL treatment (ART) Program is administered by the HIV Care and Treatment Team of the CDC Global AIDS Program, and the HIV/AIDS Bureau at the Health, Resources, and Services Administration. The Track 1.0 ART program was the first major funding program announced in a request for applications in December 2003 following PEPFAR's authorization, and was focused on kick-starting large-scale ART programs. In order to ensure rapid scale-up, organizations would only be considered for funding if they had experience in developing country-level HIV/AIDS care and treatment programs in multiple settings and countries, and had worked in at least three of the PEPFAR focus countries for at least three years prior to their application.

Those selected to receive funding at the end of February 2004 included AIDSRelief (Catholic Relief Services Consortium), the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), the Harvard School of Public Health (Harvard), and the Mailman School of Public Health at Columbia University (Columbia). Countries receiving support via this mechanism, along with their associated partners, are shown in Table 1.

<table>
<thead>
<tr>
<th>Supported Country</th>
<th>AIDS Relief</th>
<th>EGPAF</th>
<th>Harvard</th>
<th>Columbia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>2</td>
</tr>
<tr>
<td>Ethiopia</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Guyana</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haiti</td>
<td>X</td>
<td></td>
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<td></td>
<td>1</td>
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<tr>
<td>Kenya</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>2</td>
</tr>
<tr>
<td>Mozambique</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Nigeria</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Rwanda</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>2</td>
</tr>
<tr>
<td>South Africa</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Tanzania</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>4</td>
</tr>
<tr>
<td>Uganda</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Zambia</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>25</td>
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</table>
In July, 2008, Congress reauthorized PEPFAR for another five years. This reauthorization commits an additional $48 billion in funding during 2009-2013, $39 billion of which is to be devoted to HIV/AIDS over the next five years. The legislation includes new “12/12/3” targets to prevent 12 million new HIV infections, to provide care for 12 million people including 5 million OVC, and to provide antiretroviral treatment for 3 million people. Specific targets concerning PMTCT service coverage, pediatric treatment, and building health care workforce capacity have also been added for the first time: 80% of eligible women should have access to PMTCT services, children should receive antiretroviral treatment in proportion to their percentage within the HIV-positive population in individual countries, and 140,000 new health professionals should be trained. The reauthorization also removed specific requirements for budgetary allocations, with the exception of 10% of funding to support OVC and over 50% of funding to be expended for care and treatment services.
REFERENCE LIST


ZIMBABWE IS ONE OF THE COUNTRIES with the highest numbers of children living with HIV in the world. The Ministry of Health and Child Welfare (MOHCW) has developed initiatives for prevention, care, and treatment of HIV in children. A national situational analysis of the provision of services for children living with HIV in Zimbabwe was performed in 2005-2006 to further inform and catalyze ongoing policy and strategy development. A multisectoral national dissemination workshop provided the platform for raising awareness, developing recommendations, and collaboratively defining the way forward in support of children living with HIV in Zimbabwe. The situational analysis process was an important step in defining key issues to be addressed by diverse stakeholders. National progress in scaling up care and treatment for children living with HIV was made following the situational analysis as a result of several factors, including the assessment. However, resource constraints make continued expansion of services for children living with HIV extremely challenging.

Approximately 165,000 children are living with HIV in Zimbabwe, representing around 3% of all children nationally. In the absence of any intervention, it is estimated that a further 25,000 children would acquire HIV through mother-to-child transmission each year (unpublished data, 2003 estimates, MOHCW, Zimbabwe). While prevention of HIV infection in children remains a priority, the importance of ensuring provision of appropriate services for the thousands of children already infected, and their caregivers, cannot be overstated.

With this in mind, an overall initiative to explore opportunities for enhanced care and treatment of children living with HIV in Zimbabwe was designed and implemented during 2005 and 2006. Key processes included engaging with relevant
ministries, policymakers, donors, researchers, and technical partners to raise awareness and build support around the issues; conducting a national situational analysis of community and health facility services for children living with HIV; and convening an MOHCW workshop to discuss findings of the study and develop recommendations for the way forward. As a result of this collaborative process, a clearer pathway has emerged for scaling up the national response to children living with HIV, aimed at improving the lives of children and families infected and affected by HIV and AIDS.¹

This chapter presents a summary of the situational analysis findings and recommendations developed by stakeholders, with an overview of the actions subsequently taken by agencies within the multisectoral HIV response in Zimbabwe. A survey of this nature can have positive impacts in defining a way forward, and these will be highlighted. Remaining challenges in scaling up pediatric HIV/AIDS programs in resource-limited settings will then be articulated.

**EFFORTS REGARDING CHILDREN LIVING WITH HIV IN ZIMBABWE**

The Zimbabwe national prevention of mother-to-child transmission (PMTCT) of HIV program started as a pilot project at four health clinics in 1999, with subsequent rapid expansion to nearly 96% of health-care facilities by the end of 2005.² By the end of December 2006, 1,422 health facilities nationwide were providing some form of education on PMTCT, basic counseling, and dispensing of antiretroviral (ARV) prophylaxis,² with 547 (38%) of those facilities delivering a more comprehensive package of PMTCT services, including on-site HIV rapid testing for all pregnant women. Despite this progress, access to comprehensive PMTCT services for all pregnant women remains limited, and referral systems that assist eligible pregnant mothers living with HIV to access CD4 testing and HIV care and treatment remain weak.

As the national PMTCT program matured, more attention has been focused on broadening the scope of service delivery. This broadened perspective occurred in tandem with opportunities raised by national HIV treatment roll-out, enabling belated recognition of the need to initiate activities and mobilize resources for improved services targeting children living with HIV. This was an area that was seen as not being given adequate priority within the context of the wider national HIV response. The PMTCT program therefore helped provide some of the initial push to address HIV services for children, given the cross-cutting position of PMTCT within HIV, maternal, and child health. This push came from the acknowledgment that despite the pivotal role of prevention efforts in tackling the HIV epidemic, transmission of HIV from mother to child will continue to occur in the context of high HIV prevalence and insufficient resources to ensure full coverage and utilization of preventive interventions. This reality underscores the importance of ensuring the ongoing provision of appropriate HIV services for children living with HIV, both those already infected and those who will unfortunately become infected in the future.

The effective management of HIV in children requires that a multitude of both medical and non-medical providers work together to address the clinical, psychosocial, nutritional, community, and family dimensions of care, treatment, and support.

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¹ The national PMTCT program in Zimbabwe utilizes single-dose nevirapine in labor for HIV-positive pregnant women and their HIV-exposed infants within 72 hours of delivery at a minimum, recommending triple-drug therapy for immunocompromised women and more complex short-course regimens wherever indicated and available.
A comprehensive package of care for children living with HIV has been defined by community stakeholders (see Table 1). All of these elements require integration within the broader context of a child’s well-being, with this holistic model of care representing a huge public-health challenge in resource-limited settings.

By 2006, the delivery of a comprehensive package of services for children living with HIV in Zimbabwe lagged behind the national responses to adult care and treatment initiatives and lacked clear leadership, coordination, and donor support. Efforts being made to address the plight of orphans, palliative care, and ARV roll-out for children tended to be on a limited scale and had poor formal linkages to each other and to the wider network of service providers. The health system lacked capacity to deliver antiretroviral therapy (ART) to children on an expanded scale; there was minimal awareness about HIV issues in children and limited availability of pediatric syrups or formulas. Moreover, at the end of 2005, detailed policies, guidelines, and strategic plans that specifically addressed pediatric HIV issues in Zimbabwe were still being developed and had not been widely disseminated.

A concerted effort geared toward supporting the scale-up of comprehensive treatment of children living with HIV therefore initially took place in the public health sector through the establishment of 11 “learning” sites estimated to have adequate capacity to deliver HIV care and treatment for children. The concept and support of learning sites was catalyzed by a small donation of pediatric ARV formulations, around which the efforts of the Pediatric Association of Zimbabwe, the MOHCW, and supporting partners were mobilized in the form of a national committee. Working groups supported development and finalization of necessary policies, tools, and training materials to enable the sites to utilize the donated drugs, with a view to further expansion using the tools developed within the wider health system. Many of the same health system challenges were experienced in the learning sites, but nonetheless, by April 2006, over 2,000 children had been diagnosed with HIV and started on HIV treatment nationally, in spite of resource limitations within the country.

### The National Situational Analysis

#### Study Overview

Following discussions with various stakeholders, and in an effort to further catalyze action for children living with HIV in Zimbabwe, a national situational analysis was undertaken.

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**Table 1. Comprehensive Care Package for Children Living with HIV**

<table>
<thead>
<tr>
<th>Medical Care</th>
<th>Social/Community Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Basic medical care</td>
<td>▪ Nutritional counseling and supplementation for appropriate growth and development</td>
</tr>
<tr>
<td>▪ Prophylaxis against opportunistic infections (OIs)</td>
<td>▪ Psychosocial support</td>
</tr>
<tr>
<td>▪ Early diagnosis</td>
<td>▪ Spiritual support</td>
</tr>
<tr>
<td>▪ Appropriate management of HIV and OIs (including antiretroviral therapy and complementary traditional treatment)</td>
<td>▪ Social support (meeting needs of the child—food, clothing, shelter, love)</td>
</tr>
<tr>
<td>▪ Rehabilitation services</td>
<td>▪ Competent caregivers with best interests of child at heart</td>
</tr>
<tr>
<td>▪ Palliative care services when the time comes</td>
<td>▪ Home-based care</td>
</tr>
<tr>
<td>▪ Education and information regarding illness</td>
<td>▪ Caring for caregivers</td>
</tr>
<tr>
<td>▪ Nutrition counseling and supplementation for appropriate growth and development</td>
<td>▪ Maintaining schooling</td>
</tr>
<tr>
<td>▪ Psychosocial support</td>
<td>▪ Stigma reduction</td>
</tr>
<tr>
<td>▪ Spiritual support</td>
<td></td>
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</tbody>
</table>
by the MOHCW, the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), and Catholic Relief Services (CRS). EGPAF and CRS-Strive provided technical assistance to address both the medical/health-sector issues (EGPAF) and community/family issues (CRS). The specific objectives of the study are shown in Box 1.

**Study Methodology**

Interviews were conducted with 51 respondents from different sectors, including organizations involved in providing medical services, nonmedical services, and policy/resources for children living with HIV. Respondents were from the government health sector, the University of Zimbabwe, mission hospitals, local nongovernmental organizations, international organizations, and children's homes based in 18 districts within Zimbabwe.

A questionnaire was administered by the study team consisting of four sections: the first two sections addressed the provision of medical and nonmedical services; the third focused on networking, training, policy, strategy, and resources; and the fourth explored family-centered care. Responses were subjective, based on individual experiences or perceptions, and were not validated using other data or further investigations. In addition, a focus-group discussion was held with a support group for children living with HIV, aged 12 to 16 years, in order to include perspectives of children in the findings and discussion. The individual questionnaire was not administered to this group, and a separate focus-group discussion guide was used to ascertain responses.

Quantitative data were then analyzed, with qualitative data used to supplement the quantitative findings. In many cases results were presented in terms of whether respondents were either medical or nonmedical care providers (the latter category including policymakers and heads of agencies) in order to explore differing perceptions between these groups.

**Study Limitations**

The questionnaire tool underwent limited pretesting, with some questions open to interpretation. Many of the questions were also based on respondents’ perceptions and were not triangulated

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*Medical health providers include doctors and nurses based at a public or mission clinic or hospital. Nonmedical providers include home-based caregivers, children’s residential home coordinators, and representatives from national and international nongovernmental organizations.

*Within this category, interviews were held with representatives from the United States Agency for International Development, Centers for Disease Control and Prevention, United Nations Children’s Fund, and World Health Organization.*
with other sources of data to verify their validity. Therefore, although the findings represented a general picture of the situation for children living with HIV in Zimbabwe, the conclusions of the study had to be interpreted with care. A summary of key findings is included in this chapter and can be found in more detail in the final report that was approved for dissemination by the MOHCW.1

**Significant Findings**

*Diagnosis and Disclosure of HIV Infection in Children*

There are many barriers and challenges to the diagnosis of HIV infection in children beyond access to testing facilities. Children remain undiagnosed because of lack of counseling services, inadequate numbers of trained health workers, lack of treatment services, and negative attitudes concerning the diagnosis of HIV and AIDS in children.

Most health workers confirm a clinical HIV diagnosis by rapid HIV testing, with some health workers initiating cotrimoxazole prophylaxis for HIV-exposed and HIV-positive children. Nonmedical respondents frequently suspect HIV infection in children using a “community diagnosis” based on specific symptoms, a history of chronic or recurrent illness, and/or parents who were suspected to have been living with HIV. Among nonmedical respondents interviewed, 90% estimated that they referred suspected HIV-positive children to government health services; 77% discussed the possible diagnosis with the guardian; 54% referred children for voluntary counseling and testing; and 11% did nothing.

Respondents reported that most children learn their diagnosis after counseling and testing by health workers, although some respondents reported that a small proportion of children learned of their positive status through conversations with guardians, volunteers, or other children. In other cases, children became aware of their HIV-positive status on their own by inferring their diagnosis following curriculum-based HIV/AIDS education in school.

*Comprehensive Care of Children Living with HIV*

The most frequent problems related to the medical care of children were in the area of treatment, especially the availability, cost, and side effects of drugs, including ARVs.

Twenty-seven medical respondents interviewed saw irregular attendance, inadequate compliance, and limited knowledge of caregivers about care and treatment issues as barriers to the delivery of effective care. Most medical and nonmedical service providers stated that they provide nutritional and family support services but highlighted that there was limited access to food supplements. Psychosocial support services were generally provided by home-based care programs or those for orphans and other vulnerable children. Psychosocial support for children was provided by only a minority of respondents.

Availability of medical services, including basic pediatric care, PMTCT, and management of complications arising from opportunistic infections were most frequently rated as satisfactory by both medical and nonmedical providers. Diagnosis of HIV infection and HIV testing in children was rated as poor, and availability of ARV treatment was considered as generally lacking.

Although some medical services were thought to be adequate, all nonmedical services for children living with HIV in Zimbabwe were deemed unsatisfactory. For example, the availability of services provided to guardians (such as the provision of information, counseling, and support groups) was rated as below average. Services provided directly to children, including food supplementation, prevention of stigma, support groups, palliative care, counseling, the provision of information, and spiritual support were most frequently rated as poor or unavailable.
Children with Special Needs

Particular problems, especially those related to continuity of care, were noted for additionally vulnerable children living with HIV. These children include orphans, street children, disabled children, sexually abused children, and children living in residential care. Problems experienced by such children living with HIV included stigma, abuse, lack of material and financial support, poor nutrition, additional psychosocial needs, poor follow-up and adherence, and lack of parental care.

Training in the Care of Children Living with HIV

During 2005 and 2006, training in areas related to care and treatment for children living with HIV was noted to be limited and urgently required for all sectors, especially for nonmedical service providers. Among all respondents, 86% thought that health workers were inadequately trained to care for HIV-positive children. Training in psychosocial support, ARV treatment, nutrition, treatment of opportunistic infections, and community home-based care were identified as the main topics that should be included in a national curriculum.

Advocacy and Networking of Organizations

Few organizations were identified as strong advocates concerning the neglect of the needs of children living with HIV in Zimbabwe; UNICEF (United Nations Children’s Fund) was cited as the most involved in advocacy initiatives for children. Even fewer organizations were identified that provided a forum for networking between medical and nonmedical service providers, and the National AIDS Council was mentioned most frequently with regard to providing a platform for regular networking.

Referral Systems

Medical service providers frequently referred children living with HIV to other tiers of the healthcare system. Referrals by medical service providers to nonmedical service providers were infrequent, with the least referrals occurring from the health sector to community home-based care services. One-half of respondents rated referrals from the nonmedical to the medical sector and within the medical sector as unsatisfactory, the latter due to lack of feedback from hospitals, lack of availability of skilled workers and drugs at clinics, and inadequate availability of transport. Less than one-third of respondents thought referrals from the medical to the nonmedical sector were satisfactory. Health workers were often unaware of the availability of nonmedical services, and there was a lack of formal networking between the two sectors.

Family-Centered Care

Stakeholders expressed a common understanding of the principles behind family-centered care (FCC), with the majority of respondents understanding the care and services described as being both directed at and provided to the whole family, rather than the individual. Diversity was demonstrated in proposed definitions of “family” in Zimbabwe, with a majority of definitions including household members or birth family with or without extended family members. Stakeholders viewed delivery of FCC as both a solution to stigma-related issues and a cause of stigma-related problems. The main barriers to delivery of FCC were perceived as limited health infrastructure and capacity, stigma issues, and lack of resources within the family.

Views of Children Living with HIV concerning Service Delivery

In the small focus-group discussions with children living with HIV, children stated that they valued the ease with which they could access medical services but complained about inconsistency in their care by different medical practitioners (“Some doctors refuse to treat you if you are not their patient.”) (unpublished data, focus-group discussion with a group
of HIV-positive children aged 12-16 years, EGPAF Zimbabwe). They were concerned about stigmatization because of their appearances (e.g., short stature, skin rashes) and avoided disclosing their diagnosis to friends. They placed considerable value on the support group of which they were members and considered this a place of safety. They also found religion as a source of comfort. Mild depression was common among this group, with many children harboring residual sadness and guilt concerning their parents’ illnesses, deaths, and funerals.

Policy, Strategy, and Resources
No respondents were able to identify policies and strategies that ensured the provision of comprehensive services for children living with HIV. At the time of the study, there were no specific national initiatives identified by the respondents to develop HIV/AIDS services for children, either in terms of national policies on the provision of children’s services or strategic plans to ensure that comprehensive services for children were developed. Out of all respondents, 42% thought that insufficient consideration was given to the incorporation of services for children living with HIV in the design of ART programs in Zimbabwe. Services for children living with HIV were perceived as being frequently delivered as a vertical program, and decentralization of services was thought to have been largely overlooked by the health sector.

NATIONAL WORKSHOP TO DISSEMINATE FINDINGS
Following the study, the MOHCW convened a multistakeholder meeting to present findings from the study. Participants discussed the current status of the national response to children living with HIV and the implications of the study findings, and generated detailed and wide-ranging recommendations for further action. Following the workshop, members of the study team streamlined the deliberations and presented them as final recommendations in the study report. There are over 50 specific recommendations in 12 key areas covering both the optimal holistic continuum of care and policy development needed to ensure that children living with HIV are included in a national response. These recommendations are described in detail in the final report, a summary of which is given in Box 2. It was anticipated that the MOHCW would lead policymakers, donors, and other stakeholders to use these recommendations to inform a concrete implementation plan.

WHAT HAS CHANGED?
The process of carrying out this assessment provided a legitimate platform to build momentum among policymakers and service providers and to continue to consider and address the challenges of providing comprehensive HIV services for children. The objectives of the study were to lead to a better understanding of the situation of children living with HIV in Zimbabwe, to ensure that children are central to the national HIV/AIDS response, and to facilitate improvements in service provision.

Since the study was completed in 2006, a number of recommendations have been taken up and addressed, although much work remains to be done. A subcommittee for care and treatment of children living with HIV within the AIDS and TB unit was formed at the national level during the process of carrying out the assessment. Chaired by the MOHCW, it has representation from different health departments, pediatricians, and international and local nongovernmental agencies and donors. The committee meets on a monthly basis to discuss ways to drive efforts forward and keep momentum going. The committee has worked on a number of the recommendations resulting from the study; however, its effectiveness has been limited due to the other commitments of its
Box 2. Recommendations from the National Situational Analysis Report

1. Strengthen prevention of HIV in children by maximizing efforts to enhance quality, integration, and access to comprehensive PMTCT services in Zimbabwe.
2. Strengthen national leadership within the Ministry of Health to ensure that issues related to children living with HIV are given greater priority, including securing of additional resources and developing national guidelines, policies, and strategic plans that strengthen a multisectoral response to care and support for children living with HIV.
3. Promote greater child participation and develop child-focused HIV programs and services, including support and advocacy groups to protect and promote the rights of children.
4. Create an effective forum for action, coordination, and networking by establishing a coordinating body to focus specifically on issues for children living with HIV, including for the development of guidelines and policies, and definition of mechanisms to improve linkages between the community and the health sector to ensure efficient use of resources while addressing the needs on the ground.
5. Strengthen linkages between relevant stakeholders by improving communication channels and strengthening referral mechanisms.
6. Provide psychosocial support for children living with HIV through the development and roll-out of national psychosocial guidelines, and mobilize resources to support innovative strategies addressing the holistic psychosocial needs of children.
7. Promote wider HIV testing and counseling for children by increasing access to testing services, developing specific guidelines that address concerns over age-appropriate consent and disclosure issues, and supporting this by producing relevant information and training materials to build capacity in this area of pediatric HIV management.
8. Develop national HIV/AIDS information materials for and by children to be spearheaded by a national task force, making use of existing materials and initiatives both nationally and within the region. In addition, information, education, and communication (IEC) materials to support caregivers in providing appropriate care to children living with HIV should also be created and supported by a dissemination plan and communication strategy.
9. Roll out and scale up the national pediatric HIV training programs for both communities and health workers by finalizing training materials and mobilizing both financial and technical resources for these activities.
10. Strengthen the nutritional component of the national HIV response through the participation of multiple stakeholders and agencies to support both supplementary and therapeutic feeding programs for children living with HIV on a wider scale.
11. Ensure equitable access to free care and treatment for all children living with HIV by building capacity to maintain, expand, and decentralize pediatric HIV services; advocate for and mobilize additional resources through the national AIDS and TB unit.
12. Develop a national strategic plan for children living with HIV that establishes links with other sectors to ensure a holistic approach to prevention, care, and treatment.

The national strategic plan for PMTCT and children living with HIV has been completed, with a focus both on the prevention of HIV in children and on the provision of care and treatment services for mothers and children. The plan is now being used by the MOHCW to guide implementation, monitor progress, and mobilize additional resources.

National training materials addressing HIV in children (including modules on psychosocial support, palliative care, and nutrition) have been completed to support health workers in the delivery of ART to children. By March 2007, over 160 health workers had been trained in comprehensive HIV care and support for children in line with the report recommendations. This training was completed through a consultative, participatory process, resulting in national training materials that are “owned” members and limited human, material, and financial resources to meet the scale of the challenge.
by those spearheading the training program. The number of health facilities providing ART services for children has nearly tripled, from 11 to 32 as of July 2007, with an estimated 7,000 children living with HIV being managed on ART in the public and private sectors by July 2007.

Furthermore, pediatric formulations are now being provided with donor support beyond the initial “learning sites,” with expansion to 23 ART sites around the country, and many both adult and pediatric clinics are also supported with diagnostic reagents for CD4 analysis and polymerase chain reaction (PCR) testing. Infant diagnosis algorithms are being finalized to support earlier identification of infants under 18 months acquiring HIV through vertical transmission, and PCR testing will soon be made more widely available with support from international donors.

In addition, affirmative steps have been taken by at least two international nongovernmental organizations to develop treatment literacy materials for children living with HIV. More psychosocial support groups for children are beginning to emerge, and support for such groups is included as part of the national strategic plan.

A focus has therefore been placed upon ensuring that some of the building blocks have been put in place for a systems-based scale-up of HIV services for children. It is possible to criticize the pace at which these changes have taken place relative to adult services and to the numbers of children affected, but in Zimbabwe HIV services for children are being given greater priority, as is evident from the increasing number of HIV-positive children receiving care, treatment, and support despite an increasingly difficult operating environment. Continuous effort is still needed to ensure that the developments taking place at the national level translate into improved services, wider coverage, and access at the grassroots level. Advocacy at both a national and international level will be of fundamental importance if the issues for children living with HIV are to be kept on the agenda and sufficient resources mobilized.

Integration of services and the establishment of a continuum of care continue to signify gaps within the overall national HIV response in Zimbabwe. As in many other countries, the HIV program in Zimbabwe largely provides a vertical package of HIV-specific care with poor linkages and evolving referral systems. This has particular implications for comprehensive care of children living with HIV, as their dependency on caregivers, potential lack of supportive caregivers, and diverse psychosocial and health needs frequently combine into complex care scenarios. Development of an effective, integrated continuum-of-care system for children must therefore be given urgent and at least equal priority to that of adults.

The human resource crisis being experienced in Zimbabwe and many other countries in Africa represents perhaps the most serious challenge to the health-care system. Zimbabwe is facing a “brain drain” of trained personnel to other countries within the region and beyond, as well as coping with the death of staff members themselves from HIV. The current efforts of health workers to provide care and treatment for children in Zimbabwe are nothing short of heroic, given the human resource constraints within the country. Nonetheless, the human resource crisis poses immense challenges in further scaling up care and treatment for children living with HIV and ensuring quality, given the resource- and time-intensive nature of providing comprehensive HIV care for children.

Without strategies to address the ongoing challenges of human resources, such as task shifting or perhaps staff retention packages and an integrated continuum of care, issues for children living with HIV are likely to remain a low priority on the ground.
CONCLUSION

The undertaking of a national assessment has been an important process for galvanizing stakeholders and has proven useful in guiding the overall direction of the national HIV program, particularly as it relates to children. This outcome, in turn, has ensured the continued progress of scaling up services for all families infected and affected by HIV, including children. The national strategic plan for PMTCT and children living with HIV provides some evidence that the assessment recommendations have, at the very least, been considered in planning. While the country still faces limited capacity to address all of the issues, Zimbabwe has attempted to prioritize those that can be tackled with available resources.

Although the recent achievements of the national program cannot be solely attributed to the assessment findings, the findings have certainly provided an important platform from which to lobby, mobilize resources, and hold the national program accountable for its performance and progress. The report has therefore become a useful tool that can be shared with a multitude of government departments, donors, and stakeholders, both nationally and internationally, in order to build awareness and support for the issues relating to children living with HIV in Zimbabwe. Despite this exposure, the report could and should be more widely disseminated, particularly at a grassroots level and to children themselves. A workshop bringing together community-based groups in which the results of the reports were shared was organized for such a purpose, and more opportunities for grassroots-level exchanges are hoped for. By continuing to present their findings to relevant stakeholders, the MOHCW, EGPAF, and CRS hope to help sustain the national and international momentum around the need to care for children living with HIV.

One of the successful outcomes of the assessment was the productive nature of the participatory processes used. As a result of these processes, a multitude of relevant government departments and national and international representatives of key stakeholders and donor agencies were able to work collectively in a meaningful way. The recommendations that were made were based on the experiences of a wide range of practitioners and experts familiar with the local context. Many of the recommendations could have been very generic in nature, but an effort was made to make them as practical and targeted as possible. Moreover, with so many different players involved from the outset, government departments, stakeholders, and donors can now be reminded of their commitment to address the issues that were raised during the assessment. The challenge is then to ensure that ongoing pressure is maintained; with many departments and agencies limited to narrow, traditional mandates, this can present a significant challenge.

One of the challenges has also been to find sufficient human, technical, and financial resources to take many of the recommendations forward. Further attention could have been given to the “next steps” needed to take the issues forward and translate them into a time-bound framework. This could include calls for formalized commitments to achieving further progress (something only partially achieved by the national strategic plan). Donor support for pediatric initiatives still remains relatively muted compared with adult initiatives, in part because of the prevailing economic climate within the country and increasingly difficult operating environment.

It is, however, clear from the Zimbabwe experience that using this type of assessment should be considered by other countries as a relatively “nonthreatening” advocacy tool that can promote greater dialogue, raise awareness, and be applied as a useful planning tool. Issues for children living with HIV are all too often neglected, and such
an assessment can also be performed by countries as an initial step in articulating the problem, and then facing and addressing the challenges. The process requires diplomacy, patience, and strong leadership in order to be successful. Moreover, it should not be carried out as a finite effort; concerted efforts are required to keep the issues alive once the findings have been produced.

ACKNOWLEDGMENTS

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REFERENCE LIST


Part of the Solution: Faith-Based Responses to HIV and AIDS in Africa

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Peter Piot, Head of the Joint United Nations Program on HIV/AIDS (UNAIDS), recently stated that the new face of AIDS is an African woman, given that three-quarters of all young Africans living with HIV are female.1 But bearing in mind the significance of faith-based HIV/AIDS responses, it might be more appropriate to assert that the new face of AIDS is an African woman of faith. Women and men of faith and the faith-based organizations (FBOs) to which they belong are increasingly establishing support and prevention initiatives to assist people affected by HIV/AIDS, especially in the most rural and impoverished regions of Africa.

Driven by compassion and a devotion to their faith, churches, mosques, and other faith-based groups and individuals in sub-Saharan Africa have responded to HIV/AIDS with spontaneous, home-grown solutions to the pressing problems lying at their doorsteps. The solutions vary wildly in scope and scale. Some are professionally run projects coordinated by large religious organizations. Many are community-level projects implemented by congregations serving a small number of beneficiaries. Individuals are also responding as a result of their faith—a person sharing food with a neighbor who is dying in a nearby hut or a traditional healer advising a client on how to avoid HIV infection.

For the most part, the work of FBOs and individuals continues unnoticed by governments, nongovernmental organizations (NGOs), and international organizations.

This chapter outlines the dimensions of and describes the characteristics of FBO HIV/AIDS initiatives, utilizing where possible evidence from published studies. It explains why FBO initiatives remain poorly understood and receive insufficient support from government sectors and development organizations. The chapter concludes with lessons learned in mainstreaming FBO HIV/AIDS initiatives, suggesting ways in which external agencies can strengthen faith-based HIV/AIDS initiatives and help them align with accepted best practices and public-health strategies.

Religion is an overwhelmingly significant part of life throughout Africa and in many other parts of the developing world. President Mwai Kibaki of Kenya once commented that 80% of Kenyans pass through the doors of a church or mosque between Friday and Sunday.2 From the educated elite to the urban slum dweller and the village peasant farmer, 99% of Africa’s 750 million people have a
religious connection. Some two million churches, mosques, and traditional gatherings blanket the African continent. Religion forms the basis for living; helps determine attitudes, perspectives, and decision-making frameworks; and is at the root of the African search for well-being. Faith has always shaped the ways people respond to one another. Traditional belief systems are the backbone of Africa’s extended families and communities and have shaped the structure of African societies since time immemorial. More recently, Christianity and Islam have built on that foundation, bringing with them new ways of looking at the individual, the family, and society as a whole. The establishment of modern health, education, and social welfare services in sub-Saharan Africa was largely the result of Christian missionary endeavors. A substantial proportion of existing service provision and infrastructure is still provided by religious organizations. Many religious groups also have a strong commitment to social justice and a track record of standing up for the poor and underprivileged against the rich and powerful.

Early on in the course of the pandemic, many felt that religious organizations were part of the problem rather than part of the solution. FBOs were criticized for having delayed responses, failing to acknowledge the implications of rising HIV infection rates, and taking moralistic and judgmental stances toward people living with HIV that contributed to the creation of stigma and the perpetuation of silence and secrecy. Negative attitudes of faith communities toward people affected by HIV/AIDS are changing. FBOs are increasingly establishing activities and programs in response to the widely felt impacts of the AIDS pandemic. But the negative attitudes of some FBO detractors persist. The mention of religious involvement in HIV/AIDS activities still sometimes leads to antagonism or even downright hostility. A regional director of the World Health Organization has been quoted as saying, “The churches are impossible to work with because they have so many agendas that are actively hostile to HIV prevention.” Unfortunately, that statement reflects the views of many working in the field of HIV/AIDS. To strengthen effective HIV/AIDS responses, it will be important to bridge the divide between the sacred and the secular. Agencies and government departments need to better understand the unique contributions religion can make to shape HIV/AIDS responses so that they can assist FBOs to align with national HIV/AIDS strategies.

DESCRIPTION OF FAITH-BASED HIV/AIDS RESPONSES

Definition of a Faith-Based Organization
The United States Agency for International Development (USAID) defines a faith-based organization as “a group of individuals who have come together voluntarily around a stated spiritual or belief system that informs and guides their work together.” Over the past decade, the decision to set aside a portion of U.S. government funding for faith-based HIV/AIDS programs has led to heated discussions about labeling groups “faith-based” in order to access earmarked resources and has raised suspicions of right-wing political agendas and conspiracy. These controversies have catapulted the initials “FBO” into the HIV/AIDS arena. Some activists erroneously discuss FBOs as if they consisted solely or predominantly of American church organizations.

The term faith-based organization encompasses a broad range of organizations. It is helpful to distinguish different categories of FBOs to appreciate their diversity. Worldwide, congregations—churches, mosques, and the like—constitute the majority of FBOs; most congregations are small, with less than 100 members, and are led by a single religious leader. Congregations are
frequently supported and supervised by religious coordinating bodies (RCBs), such as Christian denominations and Muslim muftiats. Many local, national, or international nongovernmental organizations are established and staffed on faith principles. Examples of those include mission clinics and hospitals, schools, orphanages, service delivery organizations, and training facilities. Less visible yet more numerous than faith-based NGOs are self-governing voluntary associations (e.g., support groups and home-based care initiatives) and more established community-based organizations run by volunteers. While many community-based organizations and community initiatives have organizational values and practices that are faith-based, most are not governed by any single religious organization.

It is wise to view the rigid classification that specifies whether or not an organization is an FBO with caution. The concept that religion is somehow removed from other areas of life, such as health and education, is a Western, post-Enlightenment construct that is unrelated to much African thought and practice. Although religion and health are two distinct entities in most Western thought, that notion is foreign to the language and beliefs of many cultures in Africa and elsewhere. For example, the Sesotho people of Lesotho consider that faith and health are inextricably entwined in the single term bophelo (holistic well-being). Many community-based organizations in Africa, while not considered to be faith-based, hold similar values and implement identical practices to neighboring FBOs. Organizations may not feel it necessary to follow dictums requiring them to formally state the spiritual or belief systems that inform and guide their work if, like most people in Africa, they consider religious principles to be implicit in every aspect of one’s life.

Scale of Faith-Based, Health-Related Activities

It is important to remember that until relatively recently, churches, mosques, and monasteries were the primary healing centers in the West—ministering to both body and soul. Many of the best hospitals and health programs in the developed world were started by the faith community. Religious organizations continue to play a major role in the establishment of health initiatives in developing countries. Yet despite the long history of faith-based health-care provision in Africa, no comprehensive assessment of the scale of FBO contribution to national health-service provision has occurred since 1963. It is estimated that one-third to one-half of national health-service provision in many African countries is provided by religious organizations. In Lesotho, 40% of health-service delivery is provided by nine Christian hospitals and 75 health centers. In Zambia, 30% of services are provided by 30 church hospitals and 66 rural health centers. The Christian Health Association of Kenya and Kenya Episcopal Conference support 780 church health facilities responsible for 40% of health care in Kenya. Although mission hospitals and clinics are more visible and their contribution to the health sector is apparent, they nevertheless represent only a minority of FBOs involved in health-related activities. Every administrative district in sub-Saharan Africa is home to hundreds of health-focused initiatives implemented by congregations, faith-based support groups, and community-based organizations.

Faith-based HIV/AIDS responses are widespread throughout sub-Saharan Africa and have expanded rapidly in the last decade, especially in the “AIDS belt” of East and southern Africa. An FBO survey conducted in six African countries found that 220 out
of 464 (47%) initiatives supporting children affected by HIV/AIDS had been established in the preceding four years. A study of 28 churches in Lesotho found that two-thirds of their HIV/AIDS responses had been established in the preceding five years.

The growth of support groups for people living with and affected by HIV has been especially dramatic. Most focus on home-based care, supporting people living with HIV, and assisting orphans and vulnerable children. Community members established most support groups themselves without external assistance. The activities carried out by such groups throughout sub-Saharan Africa are remarkably similar, suggesting that their responses are catering to existing needs. In Lesotho the international agency CARE estimated in a 2004 report that there were approximately 5,000 support groups, most of which were faith-based although independent of any specific church. Support groups are established as a result of the economic inability of community members to access formal health and social services and the stressed economic situation of local churches that prevents effective church-based responses to HIV/AIDS. Many were established by deeply religious people who are motivated by a concern for the health of the community. Women constitute a majority of members of support groups. Most groups rely on the resources of community members to feed, clothe, hospitalize, and medicate patients since they are unsupported by either public health systems or churches. Support groups have been rated by community members as being highly effective in addressing their health and well-being in practical ways.

In Namibia, a national survey of 109 FBOs found that only 13%—mostly small independent churches—had no HIV/AIDS response whatsoever (Figure 1). Around one-quarter had “minimal” HIV/AIDS responses—typically a few volunteers providing counseling and spiritual support and promoting awareness and prevention through teaching abstinence and Christian marriage. FBOs with “developing” responses were from larger, mainline churches, such as Anglican and Methodist as well as some larger Evangelical and Pentecostal denominations. Congregations usually had between 2 and 15 volunteers involved in one or two interventions, such as home-based

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Figure 1. Level of development of HIV/AIDS responses among 109 FBOs in Namibia
involved in different activities. All established congregation initiatives were part of larger national programs involving dedicated staff, substantial funding, training, facilities, and a range of HIV/AIDS interventions. Most of the FBOs implemented several different prevention, care and support, or outreach activities (Figure 2).15

Figure 2. HIV/AIDS activities of 109 FBOs in Namibia15

care, youth HIV prevention, or temporary shelters for orphans, with technical support provided by an HIV/AIDS coordinator employed at the denominational level. Around one-quarter of FBO respondents had “established” HIV/AIDS responses. At the congregational level, this usually meant having 10 or more trained volunteers involved in different activities. All established congregation initiatives were part of larger national programs involving dedicated staff, substantial funding, training, facilities, and a range of HIV/AIDS interventions. Most of the FBOs implemented several different prevention, care and support, or outreach activities (Figure 2).15
Another study carried out in four regions in Zambia attests to the scale of faith-based responses. The study mapped 265 “entities” delivering health, education, and other development services; 73% of these provided HIV/AIDS-related services while 62% were faith based. Of 60 congregations surveyed, 56 (93%) offered one or more HIV/AIDS services. Of 36 religious support groups surveyed, 32 (89%) offered an HIV/AIDS service (Figure 3). Of nine traditional healers surveyed, four (44%) offered either HIV/AIDS support or prevention activities. Around three-quarters of the religious entities were involved in prevention activities, slightly more than those implementing care-and-support activities. Other FBOs conducting HIV/AIDS activities were

Catholic AIDS Action, which represents the largest faith-based response to HIV/AIDS in Namibia, was established in 1998 and has more than 44 full-time staff working in nine regions. As of 2003, Catholic AIDS Action had 110 volunteer groups with 1,686 active volunteers offering home-based care and counseling to approximately 3,000 households. The Evangelical Lutheran Church in Namibia established an HIV/AIDS program that supported 48 home-based care groups operating with more than 400 volunteers. Another evangelical Lutheran denomination had two coordinators supporting HIV/AIDS committees in 55 congregations with home-based care and orphan support programs involving some 1,800 volunteers in 35 congregations.15
leadership and partnerships

characteristics of faith-based HIV/AIDS responses

Intangible Contributions to Health
FBOs possess a number of significant advantages in delivering HIV/AIDS interventions. When asked, “What does religion contribute to health?” respondents in Zambia and Lesotho considered that “intangible” factors were the most important, ranking higher than more visible, “tangible” factors such as comprehensive care, material support, and curative interventions (Figure 4). The principal intangible factor was *spiritual encouragement*, a collective description for contributions such as “hope,” “faith,” “trust,” “prayer,” and “spiritual counseling.” Spiritual encouragement encompassed the way in which religion gave people the inner strength to proceed with resilience, courage, and determination in the midst of mostly clinics, schools, development organizations, or denominations.

Few faith-based HIV/AIDS responses are as comprehensive as the Integrated AIDS Program, an NGO established in 1993 and administered by the Catholic Diocese of Ndola in Zambia. The program operates in 32 shanty compounds of five towns in northern Zambia with a total population of 400,000. Eleven different agencies, most of which are church related, coordinate the provision of home care to patients with chronic illnesses. More than 15,000 orphans were identified through the program, with 750 community volunteers providing home care to around 9,000 people in 2005; coverage was estimated to be 77% of chronically ill patients. Roughly 80% of identified households were eligible for food and other welfare support through the program.

Figure 4. Responses of 358 participants at 16 workshops to the question, “What does religion contribute to health?”

CHARACTERISTICS OF FAITH-BASED HIV/AIDS RESPONSES

- Spiritual encouragement
- Compassionate care
- Knowledge giving
- Moral formation
- Respectful relationships
- Curative interventions
- Material support

Lesotho (n=163)
Zambia (n=195)

Number of Respondents
ill health, poverty, and misfortune. Another intangible factor was *knowledge giving*—the contribution of religion in the areas of education, training, and prevention. *Moral formation* summed up contributions such as “morality,” “behavior change,” “self-control,” “positive living,” “patience,” and “temperance” and described the way in which religion was perceived to shape the behavior and lifestyles of people. It was the combination of both tangible and intangible contributions to health and well-being that gave faith-based activities, in the eyes of those receiving services, an advantage over non-faith-based programs. Recipients of FBO health services place great value on the intangible factors. Faith-based health services were said to provide better quality of care than government-run services. The quality of the services was said to result from the compassion and love that stemmed from the religious motivation of healthcare providers, especially volunteers, and from the delivery of medical, physical, and material support supplemented with spiritual and psychosocial care by faith-based providers. In a Kenyan study, 53% of respondents from the general public had confidence in church-related services, while government health services only received a 3% confidence rating. A World Bank study of 155 randomly selected healthcare facilities in Uganda found that FBOs, generally altruistically motivated, often provided services of better quality than government facilities.

**Volunteers**

Volunteers play a central role in HIV/AIDS responses. One of the most important strengths of religious groups is their ability to mobilize large numbers of volunteers to implement HIV/AIDS activities. For Christians and Muslims, volunteerism stems from religious teachings that encourage followers to care for the sick, visit widows and orphans, and feed the hungry. In a six-country study of 690 FBOs in Africa, more than 9,000 volunteers were reported to be involved in the care and support of some 156,000 orphans and vulnerable children. In another study, the vast majority of home-based caregivers were noted to be women of faith between the ages of 25 and 50. When volunteers were asked why they had chosen to become involved in home care work, they ranked the different motivating factors as follows:

1. I see that my neighbors are sick and many children have become orphaned, and I want to help them.
2. It is my Christian duty to follow the teachings of the church, including the example of Jesus.
3. I am willing to help out because I see that my community and my nation need me.
4. As a volunteer, I want to become educated and learn new skills that can help others.
5. I realize that today it is you and tomorrow it may be me; becoming a volunteer will prepare me in case my own family needs help, too.

Experience within faith-based programming has shown that retention rates of volunteers are extremely high. This is especially true when sufficient training, regular supervision, and necessary supplies are provided, even where financial incentives are lacking. An indication of the level of volunteer commitment is that only 1 volunteer out of 800 dropped out over several years of program history in 25 community-based orphan programs associated with two FBOs in Zimbabwe. The fiscal contribution of this army of faith-based volunteers throughout Africa is enormous—their labor was conservatively estimated to be worth US$5 billion per annum in 2006, an amount similar in magnitude to the total funding provided for HIV/AIDS by all bilateral and multilateral agencies.

**Sustainability**

For centuries, religious groups have proven their resilience and sustainability. They have continued their work despite conflicts, natural disasters, political oppression, and disease. People of faith
have demonstrated their commitment to respond to human need based on the teachings of their religion, and they do so voluntarily and over long periods. FBOs addressing the universal need for community and spiritual life endure for the long term when others tire, drop out, or shift energies to other crises. Within the context of HIV/AIDS, FBOs typically work with smaller budgets and over longer time frames than secular agencies, based on a realistic assessment of what is sustainable in the long term.

The substantial amounts of resources that FBOs contribute to support their activities is evidence of the sustainability of their HIV/AIDS initiatives and stands in marked contrast to programs implemented by governments and NGOs that are funded mostly by taxpayer dollars. A study of the South African National AIDS Database looked at 162 FBOs in the database. The sample was not representative of FBOs nationally, since less than a quarter worked in rural areas; most were projects, social service agencies, or NGOs; and only 18 were congregations. The study nevertheless found that donations were by far the major source of funding for the FBOs. Congregations stood out from other FBOs because they stated that they needed additional resources mainly to meet basic needs, an indication of the sustainability and service mentality of grassroots FBOs.22

A Namibian study of 109 congregations, NGOs, and RCBs found that contributions from church members, private individuals, and local fund-raising constituted the majority of their resources for HIV/AIDS activities (Figure 5). Seventy-nine percent of FBOs reported that they received no external HIV/AIDS funding whatsoever. Only seven respondents stated that they required funds for core support; the vast majority would like to see additional funds used to support orphans and vulnerable children, home-based care, and prevention

Figure 5. Main sources of support for HIV/AIDS activities of 109 FBOs in Namibia15

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<th>Source</th>
<th>Percent of FBOs</th>
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<tr>
<td>Government assistance</td>
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<td>Network contributions</td>
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<td>Overseas churches</td>
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<td>Private individuals</td>
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activities. FBOs raise most of their own funding locally to support their activities, which suggests that those activities will be sustained regardless of external funding. At the same time, FBOs were unable to respond to increasing needs because of lack of resources and an almost complete reliance on contributions from people living in severely affected communities. There is urgent need for external agencies to develop mechanisms that “drip feed” FBO initiatives with appropriate levels of resources to enable them to increase their effectiveness and expand the scale of their responses.

**Individual Responses to HIV and AIDS**

In addition to encouraging believers to get involved in organization-led HIV/AIDS activities, congregations also influence members to engage in acts of compassion in an individual capacity. HIV/AIDS activities are frequently provided by women and men of faith acting independently. For example, church women might visit a sick member or non-member living in the church neighborhood and pray for healing without any formal call from their religious leader. Such actions are spontaneous and not specifically sanctioned by religious leaders since they are neither centralized nor organized. The influence of religion on HIV/AIDS responses extends beyond FBO-implemented project activities. It is difficult, and for the purposes of grassroots religious groups, completely unnecessary, for FBOs—even those with the most elaborate monitoring systems—to capture data on individual responses to people affected by HIV/AIDS.

Traditional healers are one group of individuals that are often overlooked in discussions of faith-based responses. Studies suggest that less than 10% of Africans are “one hundred percent” followers of traditional belief systems. That low figure belies the influence of traditional belief in African cultures. In much of sub-Saharan African, syncretism is common and there is a complex blending of multiple religious practices. In a study from Zambia and Lesotho, traditional healers were noted to be isolated from public-health and religious networks. Most HIV/AIDS responses led by traditional healers are individual rather than being a part of an FBO-managed activity. Traditional healers ranked lowest—even lower than markets—as contributors of every tangible and intangible factor contributing to people’s health and well-being in this study. Most study participants held Christian beliefs, and it was noted that they were antagonistic toward traditional healers, especially those that practiced divination.

**Prevention**

Religion is an important determinant of personal risk behaviors. FBOs have focused on promoting abstinence and marital faithfulness as effective methods of HIV prevention and for general well-being. FBO efforts are believed to have contributed to reductions in numbers of sexual partners, delayed sexual debut, and stabilization of HIV prevalence in countries as diverse as Uganda, Senegal, Zimbabwe, and Jamaica. Lessons learned in these countries suggest that successful national HIV/AIDS prevention responses involve generating high levels of social capital by engaging a wide range of actors from the state, the religious sector, and other parts of civil society.

Senegal’s success in maintaining national adult HIV prevalence below 2% over several years may have resulted in part from the prevalence of male circumcision and low levels of alcohol consumption. Vigorous and early government response is also thought to have played a central role. The key, however, may well have been the mobilization of

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*The Concise Oxford English Dictionary, 11th edition, defines syncretism as “the amalgamation (union) of different religions, cultures or schools of thought.”*
LEADERSHIP AND PARTNERSHIPS

WORLD HEALTH ORGANIZATION STUDIES SHOW FAITH-BASED ORGANIZATIONS’ ENGAGEMENT IN HIV/AIDS CARE IS EXTENSIVE AND CRUCIAL

Ted Karpf

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Increased demand on health systems and the challenge to reach the target of universal access to HIV/AIDS treatment, care, and prevention services by 2010 are creating pressure to include nongovernmental actors in health care. To more effectively document what is needed, the World Health Organization (WHO) contracted with the South Africa–based African Religious Health Assets Programme (ARHAP) to conduct an in-depth survey assessing the role and breadth of health services offered by faith-based organizations (FBOs) not often included in public funding schemes by governments in sub-Saharan Africa. ARHAP surveyed health-service districts in Lesotho and Zambia and published its findings in the report Appreciating Assets: The Contribution of Religion to Universal Access in Africa.


All these studies consistently found that FBOs play a much greater role in disease prevention, treatment, and care than previously recognized; often about 40% of health services are either owned or operated by FBOs. Such services tend to operate outside governmental planning and therefore tend to go unrecognized or unsupported as critical actors in the health system. Religious health assets (RHAs), a term coined in the ARHAP study, include hospitals, clinics and dispensaries, community congregations, support groups, intermediary bodies, pressure groups, media, and traditional healers. In other words, RHAs are more complex health systems.

According to the Appreciating Assets report, many of these expanded resources are invisible or taken for granted as part of the normal service structure of faith community services. Because faith communities and family life are mutually supportive of each other, the crucial role FBOs play in providing health-care services is implicitly understood and recognized at the community level. Therefore, while the research results are not surprising to families and health-policy officials, they are critical to those who would support family and children’s health services. With the goal of universal access to HIV prevention, care, and treatment services by 2010, urgent efforts are needed to encourage greater collaboration among public-health agencies and faith-based groups.
ARHAP STUDY APPROACH

The WHO/ARHAP study was undertaken by researchers from the Interfaith Health Project at Rollins School of Public Health at Emory University in the United States and partners in ARHAP at the universities of Cape Town, KwaZulu-Natal, and Witwatersrand in South Africa. Both qualitative and quantitative information was collected at participatory workshops together with data from WHO’s Public Health Mapping and Global Information System (GIS) Program and its HealthMapper and Service Availability Mapping programs. The ARHAP study was the first to use participatory workshops coupled with GIS technology to map RHAs in Africa.

Study workshop participants gave high ratings to the tangible and intangible health services provided by many FBOs, leading researchers to conclude that these “exemplars” could help government and other agencies overcome common barriers to scaling up HIV services, such as overly centralized services and lack of coordination between different health programs. Often methodological challenges make it difficult to determine the exact proportion of faith-based health-care provision. Given the complex interweaving of ownership and resourcing, many FBO coordinating bodies lack clarity on assets at their disposal.

For example, a recent WHO-commissioned mapping study on the outreach of the worldwide Anglican Communion revealed a lack of coordinating capacity and information systems in central coordinating bodies. Only through field visits can the quantity and nature of Anglican health assets be ascertained. Further, many FBOs are not centrally organized; they are local faith communities responding to local needs.

FBOs can therefore be considered significant health-service providers in developing countries. If health systems are to be strengthened, especially with a view to offering universal access to health care, many faith-based projects and assets could be used to meet that and other strategic aims of national health plans.

THE VALUE ADDED IS VALUES

The researchers worked from the premise that religion, health, and well-being are deeply influenced by local context and cannot be understood as a single, simple cultural variable. They also employed a holistic African perspective, which considers health and religion as part of an indivisible “healthworld.” By contrast, Western-educated health leaders and policymakers tend to think of religion and health as being separate. The term healthworld is derived from the Sesotho word bophelo (Sesotho is the main indigenous language of Lesotho), which has a range of meanings from biological life (of humans, animals, and plants) to the social life of individuals, families, villages, and countries. Religion and health are an intertwined part of the social aspect of bophelo. Zambian concepts of health and religion are very similar to those found in Lesotho.

The ARHAP study was based on the assumption that these holistic perspectives define the health-seeking strategies of many Africans, and it argues that the failure of health policymakers to understand the influence of religion in African healthworlds could seriously undermine efforts to scale up health services.
For example, compassion is the primary value underlying major religious systems. This is often summarized in the ethic of reciprocity (i.e., the “Golden Rule”): Do unto others as you would wish them to do unto you. For persons of faith to reflect on how they would feel if they were in the position of another is to elicit the compassion that drives them to act on the other’s behalf. There appears to be a connection between beliefs in the divine origin of compassion that may cause believers to offer compassion to others.

In caring for others, religious communities act not only out of compassion but also out of an ethic of decency. That ethic of decency prescribes values and principles about how to treat others in accordance with their humanity and establishes an imperative to abolish conditions that would damage or degrade people’s inherent dignity. The ethic demands that care be provided in a way that meets people’s individual needs and respects their dignity and self-worth. Out of respect for the individual’s dignity and agency, it is imperative that health-care systems and FBOs in particular provide individuals with decent care (comprehensive or holistic care) services that address the person’s medical, physical, mental, social, and spiritual well-being and place him or her at the center of the services.

Although such an understanding and practice of decent care is not new—it has been a critical component of nursing and provision of care to people in some community, hospital, hospice, and assisted-living settings—it is critical in relation to HIV/AIDS. Decent care includes treatment literacy, patient advocacy, and person-centered care, according to a WHO consultation report from 2006.\textsuperscript{27} Decent care not only focuses on the quality of care, which is crucial, but also carefully considers the input of those receiving care. In this process, care recipients help define and manage the care they need and receive in collaboration with health-care providers and those providing supportive services. To successfully provide decent care, however, health-care providers and recipients must overcome the damaging stigma and discrimination often associated with particular behaviors and diagnoses.

Religious values have relatively deep and indivisible purposes given that they seek to promote a humane and spiritual environment under the terms of their ethical construct with a service philosophy that encompasses a holistic set of practices. In addition, religious values suggest a greater range of human assets than might be expressed in a secular economic development model. In an attempt to fulfill the physical needs of the global population, religious tradition critiques the materialist basis upon which development models are often built. FBOs not only relieve poverty and bring health gains to vulnerable communities, they also offer less-tangible means for self-fulfillment and communal well-being and offer hope for life.
people at all levels, including teachers, soldiers, religious leaders, and NGOs. Religious groups, such as Jamra, an Islamic NGO, and Sida Service, a Christian NGO, promoted abstinence and fidelity as methods of HIV prevention.25

In Uganda, national HIV prevalence fell from around 20% in 1990 to 1993 to 6% to 7% in 1999 to 2000. Several studies indicate that Uganda’s dramatic reduction in national HIV prevalence was more strongly associated with behavioral change involving fewer partners and delay of sexual debut than increased condom use. Evidence suggests that the efforts of religious organizations and other opinion leaders in Uganda—such as political leaders, school authorities, and traditional healers—who advocated abstinence and fidelity contributed to the observed decline in HIV prevalence. Leaders of the main religious groups began working closely with the Ministry of Health on HIV prevention activities in the late 1980s. Religious groups stated that they wished to promote “fidelity” and “abstinence” while steering clear of condom promotion or distribution. At that time, many people working in AIDS prevention believed that it was unlikely that the promotion of abstinence and faithfulness would lead to any reduction in the spread of HIV. Nevertheless, grants were issued on the condition that FBOs should agree not to criticize condom promotion being implemented by other groups. Two of the FBO projects later became involved in some condom promotion activities. The Islamic Medical Association of Uganda implemented a project covering 11 of Uganda’s 45 districts. In each district, workshops were organized for imams from 850 mosques as well as 6,800 female and male community volunteers. The workshops covered sexually transmitted infections, behavior change, safer sex, and the responsible use of condoms. Another project, implemented in five of the 27 dioceses of the Anglican Church of Uganda, trained 863 leaders and 5,702 community health educators and distributed 1.2 million condoms in the first 18 months of activities. A USAID-funded evaluation of sexual behavior change among those reached by the project found that the proportion of adults reporting two or more sexual partners declined from 86% to 29% among men, and from 75% percent to 7% among women; use of condoms rose from 9% to 12%.28

LIMITATIONS OF FAITH-BASED RESPONSES TO HIV AND AIDS

Lack of Skills
Although FBOs possess a number of distinct advantages in delivering HIV/AIDS interventions, they also suffer from certain limitations that hamper their effectiveness. One important constraint is that they lack personnel with the necessary skills to implement effective HIV/AIDS activities. When asked what challenges they faced in carrying out HIV/AIDS initiatives, 99% of FBOs in Namibia identified their need for training in HIV/AIDS-related technical skills; lack of skills prevented FBOs from establishing or expanding their activities. The second most important identified need, lack of funding, was mentioned by 69% of the sample.15 Having embarked on HIV/AIDS activities, many FBOs now have an overwhelming desire to be more effective in their responses, and developing their skills is one way in which their effectiveness may be increased.9

Limited Networking
Many FBOs function independently and do not network with other FBO-led HIV/AIDS initiatives, even those within their own faith grouping. In a study of 109 FBOs in Namibia, 61% of respondents with HIV/AIDS programs did not belong to a network or affiliation that supported their response. An additional 19% belonged to a network but had not received any support. Almost all respondents
stated that they would like to be affiliated with a network supporting HIV/AIDS work.\textsuperscript{15}

A number of different types of organizations provide networking services to FBOs responding to HIV/AIDS. RCBs have established coordinators at the national or subnational level to support members’ existing HIV/AIDS responses or to establish their own projects implemented through member congregations. Faith-based NGOs have taken on networking roles with FBOs, such as the Zambia Interfaith Networking Group on HIV/AIDS, Zimbabwe Orphans through Extended Hands, and the Church Alliance for Orphans in Namibia. Some secular, interfaith, and inter-religious umbrella bodies, councils, and fellowships (such as national HIV/AIDS networks, church hospital associations, and religious council bodies) provide members with networking services. But with some quarter of a million congregations alone in the AIDS belt of East and southern Africa, FBO networking needs are enormous. Hundreds of thousands of congregations and faith-based support groups implement small HIV/AIDS responses, and most remain unconnected to external sources of support.

**Lack of Linkages with Government Sectors**

The AIDS pandemic has exposed how threadbare collaborative responses to health really are. A study in Lesotho of 75 religious groups with HIV/AIDS activities found minimal integration with public health facilities. James Wolfensohn, former president of the World Bank, summed up the situation succinctly: “Half the work in education and health in sub-Saharan Africa is done by the church . . . but they don’t talk to each other, and they don’t talk to us.”\textsuperscript{14} It is not just FBOs that lack connectedness. Civil society organizations (CSOs) involved in health issues generally have limited interactions with government departments. A study of one district in Senegal identified 550 committees, associations, or community-based organizations that performed a variety of functions that contributed to health. Yet there was little connection between those groups and the formal health sector. The notion of “multisectoral responses” is a mantra that is more an article of faith and a statement of intent than a principle of implementation. The study recommended that the formal health sector reorient its work so that it could encourage and support the health development groups.\textsuperscript{14} FBOs are even less likely than other categories of CSOs to link with government departments and are more likely to lack integration into larger service delivery frameworks.

Funding is one way through which linkages between government and FBOs can be strengthened. Yet none of the 18 congregations surveyed on the South African national HIV/AIDS database received financial support from government sources.\textsuperscript{18} Only 2\% of 109 FBOs in Namibia received any financial support for their HIV/AIDS activities from government.\textsuperscript{15}

**WHY FAITH-BASED HIV/AIDS RESPONSES HAVE BEEN OVERLOOKED**

Development practitioners and researchers have over the years systematically avoided the subject of religion and development.\textsuperscript{29} A 15-year review of three leading development journals found scant references to the topics of spirituality and religion.\textsuperscript{30} Understanding some of the reasons why FBO responses have been overlooked might assist external agencies to take actions to strengthen FBO HIV/AIDS and development responses.

**Religious Terminology Is Confusing**

 Outsiders have difficulty comprehending how religious organizations function, given an assortment of governance structures ranging from congregational to hierarchical, as well as mystifying terminologies. These include the names of religious
leaders, the titles by which they are to be addressed, and a bewildering array of religious organization names such as synods, brigades, dioceses, muftiats, parishes, circuits, unions, fields, conferences, supreme councils, national spiritual assemblies, and associations.

**Faith-Based Discourse Is “Value Laden”**
Religious groups stress personal morality and individual responsibility. Their HIV/AIDS discourse is ingrained with notions of right and wrong, good and bad, sin and virtue, guilt and innocence. Many development and public-health practitioners engaged in promoting safer sexual behaviors struggle with this value-laden approach. It is as if religious and public-health groups are talking two different languages, a “language of faith” and a “language of development.” Agencies wishing to work with FBOs might usefully invest in developing the religious literacy of their personnel utilizing a “lexicon of religious terms” drawn from the FBO sector.

**External Assistance Might Promote Religion**
The vast majority of FBOs are nonpartisan service providers. That is consistent with religious theologies that build missionary endeavors around humanitarian relief and development. For most religious organizations, the twin aims of humanitarian response and promotion of religion are difficult to untangle. Many examples exist of religious organizations using development activities to influence the religious beliefs of beneficiaries. External agencies give support to FBOs to strengthen the health or education components of their service delivery and are frequently wary that their resources might assist in the promotion of religion. That leaves agencies in a difficult predicament: how much should they tolerate religious promotion conducted through the FBO development activities that they support? Should they try to regulate or proscribe proselytizing? Some agencies decide not to support religious groups because it might lead to them being accused of supporting religious activities.

Some agencies are uncomfortable supporting religious groups because of a social science tenet stating that one should not impose one’s own values or religious beliefs on others; psychologists, sociologists, and health professionals seek, in most circumstances, to remain neutral and nonjudgmental in their practice, accepting the views and values of their clients even if they conflict with their own. That perspective leads many development theorists that hold a materialistic worldview and to avoid the topic of religion “out of respect for local culture.” But the consequence of that position is to promote a nonreligious worldview among local cultures that hold religious viewpoints. The notion that secular organizations have “neutral” religious perspectives while FBOs are “biased” is untenable and condescending. If secular agencies provide resources to religious groups with the precondition that the funds should not go to support religious activities, the materialistic precondition weakens the religious motivations that drive FBO humanitarian activities, thus breaching their non-prescriptive social science tenet.

**Agencies Have Concerns about FBO Accountability**
External agencies and FBOs sometimes have difficulties forging partnerships because of their diverse working practices. Most development agencies cannot implement partnerships that trust partners to determine how they will use donations based on the partner’s ongoing perception of local needs. In an era of target-driven funding initiatives, agencies expect partners to implement projects with clearly defined objectives, specified activities, and measurable results. To satisfy those expectations, they constrain their partners with agreements, plans,
conducted at the community level by unpaid volunteers, yet insignificant proportions of the massive amounts of HIV/AIDS funding now available trickle down to benefit the poorest—a situation that can be characterized by the saying “Water, water everywhere, yet not a drop to drink.”

In the face of a pandemic with long-term repercussions, thousands of community groups with low administrative capacity are struggling to sustain social structures. Although external funding can indeed create dependency, reduce local contributions, and affect FBO self-reliance and sustainability, it is wrong to use such concerns to justify why external agencies hold on to the bulk of financial resources. The provision of external funds has the potential to build the capacity and increase the sustainability of FBOs. It is not so much funding as the operating practices of grantmakers that consume local capacity and undermine sustainability.

**FBO Sustainability May Be Undermined**

The awareness that external financing could damage grassroots responses may lead to agencies being reluctant to partner with and fund FBOs. A common criticism of development aid is that most taxpayer development dollars from rich countries get spent within those rich countries themselves. External agencies, rather than local organizations, determine how most development dollars are spent. Because of institutional constraints or the need to maintain national interests, many donors make large grants to a small number of contractors. Many grants involve complicated and time-consuming application procedures, stringent reporting requirements, and short time frames. Local organizations are peripheral to the design of most large projects and the proposal submission process, and few agreements contain preconditions to ensure local participation and local accountability for project grants. It is an anachronism that the majority of HIV/AIDS responses are being conducted at the community level by unpaid volunteers, yet insignificant proportions of the massive amounts of HIV/AIDS funding now available trickle down to benefit the poorest—a situation that can be characterized by the saying “Water, water everywhere, yet not a drop to drink.”

In the face of a pandemic with long-term repercussions, thousands of community groups with low administrative capacity are struggling to sustain social structures. Although external funding can indeed create dependency, reduce local contributions, and affect FBO self-reliance and sustainability, it is wrong to use such concerns to justify why external agencies hold on to the bulk of financial resources. The provision of external funds has the potential to build the capacity and increase the sustainability of FBOs. It is not so much funding as the operating practices of grantmakers that consume local capacity and undermine sustainability.

**CONCLUSION: STRENGTHENING FAITH-BASED HIV/AIDS RESPONSES**

A great deal of public-health activity is being undertaken by religious groups that are perceived to have several strengths, including the scale of their infrastructure, the philanthropic values that underpin their personnel and activities, and their deep roots within communities that inspire trust among their constituents. At the same time, there is general acknowledgment that FBO responses need to be improved and coordinated, not just expanded. Despite the scale of faith-based responses, the evidence base on FBO functioning is surprisingly thin. More studies are needed to evaluate FBO effectiveness and assess ways of scaling up FBO HIV/AIDS initiatives.

Funders must go beyond providing funds and reexamine and modify their operating practices if they are to engage effectively with FBOs. They need to ensure the development of simplified funding mechanisms that recognize local decision making and channel small amounts of resources over...
longer periods (i.e., “drip feeds”). In addition to funding, agencies need to engage strategically with FBO HIV/AIDS initiatives and help them align with accepted best practices and public-health strategies. Some local FBO practices are suboptimal given that religious groups have had little contact with development organizations or public-health systems. For example, the recent proliferation by FBOs of institutions for children affected by HIV/AIDS is a largely inappropriate response that has often resulted from contacts with overseas religious groups.

Supporting the development of local networking initiatives is an important strategy for strengthening FBO HIV/AIDS initiatives. The formal health sector is well placed to draw together the many efforts at the community level to respond to HIV/AIDS, including those of congregations and support groups. Current large-scale approaches to HIV/AIDS, characterized by external decision making and short-term projects, are unlikely to provide FBOs with the type of support they really need.

Agencies wishing to work with FBOs might do well to learn from faith-based donors, NGOs, and RCBs that have experience in building the capacity of and working collaboratively with FBOs.

The devastating impact of HIV/AIDS presents us with one of the great moral challenges of our time. FBOs are responding to the challenge with compassion, hope, and courage, and external agencies have an extraordinary opportunity to assist them in their response.

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REFERENCE LIST


MORE THAN A QUARTER OF A century into the AIDS pandemic and at the end of the initial five-year phase of the President’s Emergency Plan for AIDS Relief (PEPFAR), there is increasing international consensus about the imperative to target women and girls when designing HIV/AIDS programs. With women now constituting 60% of those living with HIV in sub-Saharan Africa, and young women accounting for three-quarters of 15- to 24-year-olds living with the virus in that region, comprehensive care for women should be at the top of the international HIV/AIDS agenda. One of the ways that PEPFAR and other international HIV/AIDS initiatives should build upon this consensus is to make the integration of reproductive health and family planning with HIV/AIDS services a major new priority. Reproductive health–HIV integration presents important opportunities for PEPFAR and national programs to expand their impact and improve the prospects of achieving prevention, care, and treatment goals. It is also a new way of thinking in larger terms about how to enhance the sustainability of PEPFAR and other bilateral and multilateral programs and to overcome the barriers to broader access to HIV/AIDS services.

Integration is a feasible means to achieve multiple key goals: prevention of new HIV infections among women and girls, prevention of mother-to-child transmission (PMTCT) of HIV, reducing the number of AIDS orphans, and supporting the reproductive rights and fertility choices of HIV-positive women. Reproductive health and HIV services have generally been funded separately and operated

More, the core obstacles to addressing reproductive health are the same as those fueling the AIDS pandemic, including the vicious cycles of poverty, gender-based violence, discrimination in access to education and services, and women’s lack of control over their sexual and reproductive lives. Adolescent girls in particular bear the brunt of the intertwined issues of unintended teenage pregnancy, sexually transmitted infections (STIs), and HIV, exacerbated by intergenerational sex and sexual violence.

Integration in the health sector means that a facility is offering two or more services during the same operating hours, with providers of both services encouraging clients to consider using the other service. When integrated services are not colocated, they include a strong referral system. Services can also be integrated outside clinic settings, through community outreach, youth programs, and education activities. See Family Health International (FHI). Network: Integrating Services. Arlington, VA: FHI; 2004:23(3).
vertically, which means that clients see a different provider or must come on a different day for each health service. Yet with over 80% of HIV infections being sexually transmitted, addressing reproductive health and HIV together would serve the needs of clients and health-care providers in a more comprehensive, cost-effective, and efficient manner.

Inevitably, some U.S. policymakers will be uncomfortable with the premise of integrating reproductive health and family planning into HIV/AIDS programs, given their strong opposition to abortion. Yet reproductive health covers a broader range of women’s health issues, including detecting and treating STIs and supporting HIV-positive women’s desires for safe labor and delivery. PEPFAR officials can use new evidence from the field to make the persuasive case that integration represents a bridge to achieve PEPFAR’s objectives.

With women and girls in PEPFAR focus countries so acutely vulnerable to HIV infection, the United States has ample motivation to ensure that its AIDS programs recognize and address emerging gaps in treatment, care, and prevention services. On ethical and operational grounds, those women and girls accessing HIV testing and treatment through PEPFAR programs have a compelling need for reproductive health and family planning services, especially relating to their fertility choices, just as women and girls accessing reproductive health and family planning services have a critical need for HIV information and services.

Integration of services is fraught with many challenges, notably the shortage of trained health professionals; reductions in donor funding for reproductive health and family planning, as well as separate funding streams for reproductive health and HIV; issues of provider bias, especially against HIV-positive women who are sexually active; U.S. congressional and policy restrictions pertaining to both reproductive health and HIV funding and activities; and the lack of political conviction to date on the part of donors and national governments alike to make reproductive health–HIV integration a policy priority. In addition, reproductive health/family planning programs have been weakened in those instances in which the response to the HIV pandemic has drawn health professionals and resources away from reproductive health programs. Promoting linkages between HIV programs and women’s reproductive health services is an important way forward, and one that can help capitalize on the increased resources available for HIV/AIDS and supplement the limited funding for reproductive health.

While reproductive health–HIV integration is a logical step for PEPFAR to take in pursuit of its goals for treatment, prevention, and care, it has only recently begun to emerge as an important issue. Yet this chapter shows that integration is gaining prominence in AIDS programs and that there are relevant examples of integrated reproductive health–HIV programs funded by PEPFAR.

One critical next step is for the Office of the U.S. Global AIDS Coordinator (OGAC) to proactively support funding for integrated reproductive health–HIV programs and to promote efforts to operationalize strategies toward that end.

The Case for PEPFAR Support for Integrated Reproductive Health–HIV Programs

Integrating reproductive health and HIV programs can expand entry points for accessing HIV/AIDS services, increase the efficiency and cost-effectiveness of

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*The goals of PEPFAR’s first five-year phase were to support treatment for 2 million people infected with HIV/AIDS, to prevent 7 million new infections, and to support care for 10 million people infected and affected by HIV/AIDS.*
programs, and help address the shortage of health-care workers. While vertical, program-specific approaches may be useful in some cases as a way to maintain a clear focus, there is increasing concern that the creation of parallel programs within the broader health-care system can lead to duplications, distortions, and disruptions in services.\(^4\) Reasons for supporting integration include the following:

- **Reproductive health/family planning and HIV programs share a common target audience (i.e., women and girls of reproductive age), especially in countries with generalized epidemics.** By increasing entry points along the life cycle of women and girls, PEPFAR can increase access to HIV prevention, care, and treatment services for vulnerable women and girls while helping to maintain their dignity and ensure their safety.

- **Integrated programs can reduce the stigma and discrimination associated with attending stand-alone HIV facilities.** Integration can also help address the shortages of health-care workers, since most acutely affected countries cannot afford to develop parallel programs that duplicate human resource requirements. Integration may be a more efficient way to reach both HIV and reproductive health goals since reproductive health/family planning providers and nongovernmental organizations (NGOs) are already equipped to offer services to women, including young women involved in unprotected sex who require information and access to services.\(^5\)

- **Preventing unplanned pregnancies can reduce costs related to PMTCT services, ultimately reducing the number of children orphaned by HIV and in need of care and support.\(^6,7\)**

- **Meeting the huge unmet need for contraception also has important HIV-related outcomes.** Providing contraception can prevent unintended pregnancies and mother-to-child transmission of HIV.\(^8\)

- **Data increasingly demonstrate that some HIV-positive women, especially those on antiretrovirals (ARVs) who are feeling better and functioning more normally, would like to become pregnant; many women also report strong family pressure to have children.** With the increasing availability of PMTCT programs, more HIV-positive women may want to become pregnant.\(^8\) PEPFAR programs should help providers counsel HIV-positive women on the risks and benefits of childbearing and respect women’s reproductive choices.

- **Reaching adolescent girls, including married adolescents, with reproductive health and HIV information and services represents a critical challenge.** This is an area that demands greater innovation and attention, through both facility-based approaches and other activities to reach young people.

### Promising Programs: Examples from the Field

An increasing number of programs are integrating reproductive health/family planning and HIV services for women and girls in affected countries. Some of these programs focus on integrating reproductive health/family planning into HIV prevention, treatment, and care services; others focus on integrating HIV services into preexisting reproductive health/family planning programs; and still others focus specifically on reaching young people, including adolescent girls, with reproductive health and HIV information and services. The following section provides brief descriptions of some of the innovative initiatives in each of these categories. While there is still a significant need to document what works and to measure impact, these programs show the importance of investing in operations research and monitoring mechanisms to expand the evidence base.
Integrating Reproductive Health Services into HIV/AIDS Programs

There is a logical link in addressing reproductive health concerns and health risks within the voluntary counseling and testing (VCT) setting. VCT sites are increasingly becoming places to determine one’s HIV status and learn about HIV; in some cases, they are also becoming places to access reproductive health/family planning information and services. In addition, some VCT clients, such as married adolescents, men, and couples, may not necessarily be visiting family planning clinics, and VCT can help fill that gap.

Integrating Reproductive Health Services with VCT: Webuye Hospital, Western Province, Kenya

The Kenyan Ministry of Health (MOH), with support from Family Health International (FHI) and other partners, is testing a national strategy for integrating family planning and VCT services. This strategy followed a 2002 assessment that found that few VCT providers were referring clients for family planning services, despite the fact that some VCT clients wanted to prevent pregnancies and that most VCT providers and clients in the study supported integrating family planning services within VCT clinics.

In late 2004, the MOH, with support from FHI, the AMKENI project, and Jhpiego, and with funding from PEPFAR, began integrating family planning into VCT and antiretroviral therapy (ART) services in over 60 centers throughout Kenya, including Webuye Hospital in the Bungoma district of Western Province. VCT sessions now include family planning information, with oral contraceptive pills and condoms provided free of charge. Other family planning methods are available through referral to the Maternal and Child Health (MCH) department in another part of the hospital building. The program staff have reported an increased uptake in reproductive health services since they’ve been integrated, although they acknowledge that it is difficult to attribute the uptake solely to the integrated services (Webuye Hospital staff, oral communication, February 2006).

Integrating HIV Care with Antenatal Care Services: The Reproductive Health Research Unit at Johannesburg General Hospital, South Africa

The Reproductive Health Research Unit (RHRU) of the University of the Witwatersrand established an ART clinic in the department of obstetrics and gynecology at Johannesburg Hospital, funded by PEPFAR and the South African government. By setting up a pilot ART clinic within the obstetrics department of an antenatal clinic, the project is able to provide reproductive health and HIV services to its antenatal clients, and to rapidly initiate pregnant women on ARVs with close monitoring and support.

Integrating HIV/AIDS Services into Reproductive Health Programs

Integrating HIV/AIDS services into reproductive health programs offers many benefits to clients, not least of which are the opportunities for women to learn their HIV status and access services before they fall ill or pass the infection on to their unborn children. Too often, people are referred to VCT only after they become sick, contributing to high AIDS-related morbidity and mortality. Integrating services may also increase family planning uptake, which would help reduce vertical transmission. Finally, linking family planning and HIV services helps to address the sexual and reproductive health needs of people living with HIV.

Using reproductive health, including antenatal clinics, as an entry point for HIV services increases access for women and girls by expanding the number of HIV service delivery outlets. In Kenya, for example, 90% of women receive antenatal care from a trained medical provider, providing a good opportunity to reach large numbers of
women with HIV information. In addition, 40% of women in Kenya deliver in a health facility, which provides an additional opportunity for HIV integration. Though only small numbers of Kenyan women receive postnatal care, some 75% of children under five years of age are immunized, which provides another opportunity to reach the mothers and their potentially HIV-exposed babies in a safe, nonstigmatizing environment.\footnote{IPPF, the largest organization focused on sexual and reproductive health issues, has 150 member associations working in 167 countries; IPPF is also active in a further 15 countries where there is not currently a member association. See http://www.ippf.org. Because IPPF advocates for liberalized abortion policies, the work of many of its member associations on unsafe abortion has suffered or been neglected as a result of the U.S. Mexico City Policy, which denies reproductive health funding to foreign NGOs that support, provide, or refer for abortions.}

**Integrating VCT into Family Planning: Population Council in Northwest Province, South Africa**

This PEPFAR-supported project seeks to increase access to quality HIV and family planning services by integrating VCT into family planning in South Africa’s Northwest Province. Given the relatively low uptake at stand-alone VCT sites, and that some 40% of reproductive health clients present with STIs, the aim was to improve VCT access, increase the use of dual protection, and continue to offer quality family planning services. The pilot project has set up two models, which differ in the degree of integration: high-integration clinics provide pre-and posttest counseling and rapid tests by family planning providers in the family planning counseling room, while low-integration clinics refer family planning clients for VCT services, on-site but in a different room (Saiqa Mullick, Population Council, oral communication, May 2006).

**Integrating HIV/AIDS Services, Including VCT, with Reproductive Health: Family Guidance Association of Ethiopia**

The Family Guidance Association of Ethiopia (FGAE), an NGO in Ethiopia, is an IPPF member association. In 2002, based on an assessment of client needs and preferences, FGAE expanded its reproductive health services to include HIV/AIDS services. While reproductive health services are usually used by women and girls, the HIV component has attracted men not usually targeted by reproductive health programs. FGAE...
reports having had over 40,000 VCT clients in 2005, making it the country’s largest VCT provider after the Ethiopian government. FGAE has implemented different integration models: facility-level integration, where HIV and family planning services are colocated in the same facility and clients are referred to a different part of the facility for different services; room-level integration, where HIV and family planning rooms are rotated weekly to avoid the problem of clients being identified as seeking VCT services; and counselor-level integration, where health providers offer both HIV and family planning services in the same session.

Examples of Programs Reaching Adolescent Girls

Family Health Options Kenya

FHOK is working to make its VCT sites youth friendly and to attach youth resource centers to its clinics, thereby linking reproductive health and HIV information and services. Its outreach activities include having teams of young people go into communities and visit schools and churches to provide information about HIV/AIDS. FHOK also provides outreach VCT services, and individuals who test positive are referred to the clinic. Outreach VCT services are offered in Nakuru, Eldoret, Kisumu, Mombasa, Nairobi, and Thika. FHOK is finding that its integrated youth centers are experiencing good uptake of reproductive health and HIV services. Between 2004 and 2006, some 9,000 girls were counseled and tested for HIV at the organization’s six sites (Edward Marienga, FHOK, oral communication, February 2006).

Family Guidance Association of Ethiopia

FGAE youth centers in Bahir Dar and Nazareth offer diagnosis, treatment, information, counseling, and services relating to family planning, STIs, HIV/AIDS, emergency contraception, pregnancy tests, postabortion care, treatment of opportunistic infections, and other medical services. The centers also offer VCT, and they have found that more girls than boys are accessing these services. The centers offer recreational and entertainment facilities as well as library services. To address the problems of out-of-school youth facing poverty and unemployment, FGAE youth centers provide some skills-training, assertiveness-training, and leadership-training programs. The centers also sponsor posttest clubs for HIV-positive young people, as well as girls clubs, which are a way to overcome girls’ reluctance to come to centers dominated by boys. The girls clubs also reach out to vulnerable girls, including sex workers, housemaids, and street children, with information about HIV/AIDS and family planning.15

loveLife, South Africa

loveLife is South Africa’s national HIV-prevention program for youth, promoting healthy living to reduce HIV infection and unwanted pregnancy among young people aged 12 to 17. loveLife combines national-scale clinical and community-based

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1Between January and December 2005, FGAE tested 40,692 clients—20,812 female and 19,880 male. Of those, 4,573 (2,863 female and 1,710 male) were HIV positive (FGAE, Addis Ababa, Ethiopia, unpublished data).

2According to data from FGAE, between June 2002 and June 2004, a total of 15,028 young people were tested, of whom 8,628 were female.

3loveLife was launched in late 1999 by a consortium of leading South African NGOs in partnership with the South African government and major South African corporations, including the South African Broadcasting Corporation, and with the support of private U.S. funders. loveLife has been funded by the South African government; the Kaiser Family Foundation; the Bill and Melinda Gates Foundation; the Nelson Mandela Foundation; the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund); and more than 20 private South African corporations. The Global Fund, whose grant accounted for one-third of loveLife’s funding, withdrew its funding in late 2005.
services and outreach programs with a sustained multimedia education and awareness campaign. loveLife’s “franchises,” which implement loveLife programs locally, include youth-friendly public clinics, multipurpose youth centers (at least one in each of South Africa’s nine provinces), schools, and community-based organizations. Key elements of loveLife include a community-level HIV-prevention education and youth mobilization program led by national corps of 18- to 25-year-old “groundbreakers” and volunteer peer motivators (mpintshis); the National Adolescent-Friendly Youth Clinic Initiative (NAFCI), which has established youth-friendly HIV-prevention services in many government health clinics; a national network of youth facilities (“Y Centers”); loveLife games, a school sports competition; and a sustained multimedia HIV and AIDS education and awareness campaign. At the end of 2005, loveLife was reaching over half a million young people a month, including 300,000 young people seeking information and counseling via loveLife’s toll-free helpline (David Harrison, CEO, loveLife, oral communication, February 2006). In the public clinics that are part of loveLife’s youth-friendly program (NAFCI), more girls than boys access services. Most girls access family planning services but are also referred to VCT by the family planning counselors.

PMTCT AS AN ENTRY POINT FOR REPRODUCTIVE HEALTH SERVICES

PMTCT programs provide an essential entry point to address women’s family planning needs and fertility intentions during antenatal and postnatal care. Too often, however, PMTCT programs miss this opportunity. Despite the fact that most PMTCT programs are offered within existing maternal and child health facilities, little family planning counseling appears to be provided, and the extent of integration with other services varies widely. The World Health Organization (WHO) framework for PMTCT highlights the importance of family planning in HIV prevention. The framework focuses on preventing HIV in young women, avoiding unintended pregnancies in HIV-positive women, providing ARVs to prevent vertical transmission (as well as safe delivery and support for safer infant-feeding practices), and providing care and support to mothers and their families. However, PMTCT programs have traditionally focused on providing ARVs, while family planning has been an underutilized intervention.

Yet little family planning is being offered as part of PMTCT programs because PMTCT services are largely limited to HIV testing in antenatal care and the provision of ARVs to those who test positive. Family planning discussions are limited in antenatal care due to the fact that family planning messages in this context often do not result in contraceptive uptake, since women are focused on pregnancy and childbirth, not on preventing pregnancies. The ideal would be to provide family planning services in the early postpartum period, but family planning programs have struggled for years to reach women with postpartum family planning services, especially in areas where few women deliver in health facilities. It is therefore essential to develop strategies to provide a continuum of care and access to services in order to reach more women during the early postpartum period, since this period is critical for PMTCT and reproductive health/family planning interventions.

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1The four prongs of PMTCT include primary prevention of HIV; prevention of unintended pregnancy in HIV-positive women; preventing HIV transmission from HIV-positive women to their children; providing care for HIV-positive mothers and their infants.
RECOMMENDATIONS FOR STRATEGIC INTEGRATION

The United States, bilateral and multilateral donors, and national governments have an important opportunity to enhance the sustainability and effectiveness of their programs by promoting greater integration of reproductive health and HIV services. This approach helps to meet program goals and improve the quality of programs, while also addressing the compelling needs of women and girls in regions severely affected by the HIV pandemic. This is a crucial time to reflect on the evolution of the pandemic and to apply the lessons learned in order to strengthen strategies to integrate reproductive health and HIV/AIDS services. In addition to PEPFAR, national and international AIDS programs should implement proactive strategies to move forward with reproductive health–HIV integration; they can begin in five key priority areas.

1. Communicate with country programs and partners.
   - Formulate written instructions and guidance to country teams and partners outlining the importance of programs that integrate reproductive health and HIV, and provide information about how to meet the reporting requirements of different funding streams in integrated programs.
   - Encourage the Global Fund to make reproductive health–HIV integration an essential component in its HIV/AIDS proposals. This means providing technical guidance on integration and designing indicators for the monitoring and evaluation toolkit.
   - Solicit successful examples of reproductive health–HIV integration and wraparound services from country programs and partners.

2. Incorporate reproductive health/family planning components into existing HIV programs, and incorporate HIV services into existing reproductive health/family planning programs.
   - Expand work with HIV-positive women to support their fertility decisions and respect their reproductive rights. Determine clients’ reproductive intentions in order to provide appropriate information and services within the context of VCT, PMTCT, and ART services; identify operational barriers and gaps in providing family planning services within HIV services; and provide informed-choice counseling.
   - Include family planning and reproductive health as part of an essential package of HIV services, and colocate services wherever possible.
   - Encourage ART programs that incorporate family planning components during scale-up, and proactively provide information and family planning methods, backed by guidelines and protocols. Working with country programs and partners, ensure that ART protocols include family planning, and ensure that adequate counseling and access to family planning and reproductive health services are available at ART sites.
   - Support additional training in family planning and reproductive health for VCT and ARV providers. At the same time, family planning providers should receive basic training in HIV and VCT.

**“Wraparound” funding and services refer to ways that PEPFAR funds can be leveraged with other programs that are supportive of HIV/AIDS programs, such as nutrition, family planning services for women with HIV, education, and microeconomic activities.**
3. Reach and solicit input from those most affected by HIV and AIDS.
   - Include women’s health advocates and networks of women living with HIV in HIV/AIDS programming and resource allocation decisions.
   - Expand youth-friendly health services for young people, including adolescent girls. Criteria for youth-friendly services should include involvement of young people, affordability and availability at convenient times, inclusion of skills training and assertiveness building for prevention, and extensive work with service providers to sensitize them to the special needs of young people (as nurses’ attitudes are widely seen as one of the greatest deterrents to young people accessing services).
   - Ensure that health worker and client needs are being solicited and evaluated in order to continually improve services and efficiency.

4. Expand PMTCT coverage and strengthen linkages with reproductive health and family planning.
   - Call for country-specific strategies to increase PMTCT coverage and to strengthen linkages with maternal and child health and reproductive health programs. Such strategies should also address barriers that women face in accessing PMTCT programs and postnatal care services, including lack of education, stigma and discrimination, fear of violence, distance to health facilities, and cost of services.
   - Ensure that women accessing PMTCT services receive a minimum package of reproductive health services, including information about preventing unplanned pregnancies, contraceptive commodities, and Pap smears and cervical cancer screening. Increase the capacity of service providers to address the reproductive wishes of HIV-positive women.
   - Support training for PMTCT service providers that includes additional training on family planning and reproductive health issues.

5. Make the case for integration to national and international policymakers.
   - A growing body of evidence points to the important benefits of integrating HIV services with family planning and reproductive health services. These benefits include the expansion of entry points to reach those most at risk, a reduction in mother-to-child transmission of HIV, more efficient use of existing infrastructure and health personnel, and a contribution to long-term, sustainable national HIV responses and other health services.
   - PEPFAR officials should bring the attention of Congress, the administration, and the U.S. public to this growing body of evidence supporting integrated strategies, and build support for a streamlined approach that successfully addresses both reproductive health and HIV imperatives.
   - The Global Fund should be pressed to provide resources and support for reproductive health–HIV integration programs and to prioritize proposals that focus on integrated services. As part of this, the Technical Review Panel (TRP) and the Country Coordinating Mechanisms (CCMs) should include members with expertise in reproductive health–HIV integration.
   - Bilateral donors, United Nations agencies, and independent foundations should improve coordination to support leadership for and financing of reproductive health–HIV programs.
CONCLUSION
The innovation and richness of the field experiences profiled in this chapter show that moving forward with reproductive health–HIV integration offers great promise. The valuable evidence that is emerging from these programs demonstrates that a new threshold has been crossed, exposing a critical new dimension of the global response to the HIV/AIDS crisis.

At a time when many policymakers, experts, and advocates are debating whether funding for HIV/AIDS is undermining other critical health priorities—including child survival, maternal health, and family planning—promising approaches to integration illustrate both the important overlaps between these sectors and ways in which the greater integration of services can help strengthen the health sector overall. Reproductive health–HIV integration represents the kind of efficiency and long-term cost-effectiveness that should make it a priority area both for PEPFAR and for other international AIDS-funding institutions.

ACKNOWLEDGMENTS

With women increasingly bearing the brunt of the AIDS pandemic, especially in sub-Saharan Africa, this is a critical time to focus on new opportunities to ensure the success of prevention, care, and treatment programs. The field experiences under way in numerous countries provide innovative examples of approaches that have been implemented and that point the way forward for global AIDS policy.
REFERENCE LIST


The linkage or integration of sexual and reproductive health services to HIV prevention and care, particularly in sub-Saharan Africa, is increasingly being highlighted as a critical strategy to increase the overall effectiveness of the HIV and AIDS response and to ensure the success of programs to improve sexual and reproductive health. In many settings with a high prevalence of HIV, sexually active people have regular contact with the health-care delivery system for reproductive-health-related services. Providers working in sexual and reproductive health already have regular contact with millions of women who are at the center of the global HIV pandemic; increasingly, this contact is expanding to adolescents and to men. Therefore, sexual and reproductive health services provide an opportunity and a platform upon which interventions for HIV prevention, care, and treatment can be built. These interventions include voluntary counseling and testing (VCT) for HIV, condom promotion, management of sexually transmitted infections (STIs), contraceptive services and dual protection from unintended pregnancy and STIs (including HIV), and prevention of mother-to-child transmission (PMTCT) of HIV services.

Conversely, HIV and AIDS services offer an opportunity for increasing access to sexual and reproductive health services. People at risk of infection or already living with HIV can be given access to vital sexual and reproductive health information and services. For instance, models suggest that contraceptive uptake to prevent unintended pregnancy among HIV-positive women is potentially an effective and less costly intervention to prevent mother-to-child transmission of HIV than antiretroviral (ARV) prophylaxis.1

In general, integrating HIV prevention and care with sexual and reproductive health and family planning services, where appropriate, can help decrease stigma associated with HIV and AIDS, while simultaneously addressing the existing need for both types of services. Making such services available in nonstigmatizing environments serves to further promote access to these critical interventions while increasing their overall effectiveness.
**OPERATIONAL DEFINITIONS**

The following terms are used throughout this chapter:

**Integration.** The impetus for integration of services related to reproductive health emerged from the 1994 International Conference on Population and Development and is based on the need to offer comprehensive reproductive health services simultaneously. It implies that individuals with several reproductive health needs can be served within the same facility.

**Linkages.** Linkages are alternative ways of combining services, including creating opportunities for systematic referrals between programs. When interventions are linked, it implies that they can be combined, connected, or systematically tied so that users can be served within the same facility or referred for complementary services. Linkages can extend to program operations and policy frameworks to reflect coordination between programs. Thus, linkages between sexual and reproductive health and HIV can be based on programmatic, behavioral, or service interventions in addition to their biological linkage. This chapter addresses linkages mainly in the context of service provision or program operations.

**Synergies.** Synergies are the combined outcomes of integrated or linked services that are greater than the outcomes of individual services.

**INTERNATIONAL COMMITMENTS TO INTEGRATION AND LINKAGES**

Over the past decade, the international community has renewed its calls for the integration and strengthening of linkages between sexual and reproductive health services and strategies, and services for HIV prevention and treatment. In June 2006, at the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS, member states acknowledged “the need to strengthen policy and program linkages and coordination between HIV and sexual and reproductive health.” However, the benefits of these linkages have not been fully realized, due in part to the lack of policies and programs and normative guidance on what constitutes effective linkages.

**OPPORTUNITIES FOR OPERATIONALIZING LINKAGES, EXPERIENCES, AND INDICATORS**

Linking health-care services or offering integrated approaches provides opportunities for health-care providers to address the broader health and social

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**Box 1. Rationale for Linkages or Integration of HIV Prevention and Care with Sexual and Reproductive Health Services**

- Serves the same target population: sexually active men, women, and young people
- Promotes safe and responsible sexual behavior (behaviors that prevent HIV also prevent STIs)
- Potentially increases dual protection and condom use
- Reduces mother-to-child transmission and stigma of HIV/AIDS
- Minimizes missed opportunities for increasing service uptake, access, and coverage for underserved, vulnerable, and high-risk groups
- Builds on existing programs, structures, and institutions and promotes universal access to each
- Provides tailored sexual and reproductive health services for people living with HIV
- Potentially saves costs, eliminates duplication, and promotes coordination and efficiency
- Targets unprotected sex—the common denominator of HIV, STIs, and unplanned pregnancy
- Potentially increases impact on HIV prevention, quality of care, and user convenience
Box 2. International Commitments to Reproductive Health–HIV/AIDS Integration and Linkages

**United Nations General Assembly World Summit (2003)**
At this high-level plenary meeting of the United Nations General Assembly, heads of states and governments committed themselves to “achieving universal access to reproductive health by 2015.” They advised that universal access to reproductive health information and services would have far-reaching effects for both the maternal health and child health Millennium Development Goals (MDGs) and for virtually all other goals, including those for HIV/AIDS, gender, education, environment, hunger, and income poverty.

**The Glion Call to Action on Family Planning and HIV/AIDS in Women and Children (2004)**
The Glion Call to Action emphasized the global emergency created by HIV/AIDS and sexual and reproductive ill health; the urgent need for much stronger links between sexual and reproductive health and HIV/AIDS policies, programs, and services; and the centrality of these intersecting efforts toward the achievement of the MDGs. The Call to Action recommends actions to strengthen the potential synergies between family planning and programming for PMTCT. When implemented alone, PMTCT programs are estimated to reduce transmission by 2%–12%. Preventing primary infection in women and unintended pregnancy among women living with HIV, however, has intrinsic benefits to women and could decrease the proportion of infants infected by HIV by 35%–45% in some countries.

A global consultation drafted the Call to Commitment, urging stronger efforts to ensure universal access to sexual and reproductive health services and an effective global response to HIV by making these initiatives mutually reinforcing. The conveners recognized that without these efforts, the MDGs adopted by the United Nations in 2000 would not be achieved.

**World Health Organization World Health Assembly (2004)**
The 57th World Health Assembly, comprising health ministers of 192 member states, adopted the World Health Organization’s first Global Reproductive Health Strategy. Five target activities are included in the strategy, each of which can contribute to strengthening research as well as policy and programmatic aspects of linkages between sexual and reproductive health and HIV.

needs of their clients. In so doing, providers can anticipate the need for, and ultimately provide, services beyond those which the client originally sought.

**Reproductive Health Services**
Reproductive health services are often provided within the primary health-care system. The key components of reproductive health services, as defined in the World Health Organization (WHO) Global Reproductive Health Strategy, include improving antenatal, delivery, postpartum, and newborn care; providing high-quality services for family planning, including infertility services; eliminating unsafe abortion; combating STIs (including HIV), reproductive tract infections, cervical cancer, and other gynecological morbidities; and promoting sexual health.

National reproductive health program strategies should include policies on HIV prevention and care, with integration or linkages supported at various levels (e.g., policy, program, and service delivery levels). Such linkages can be assessed and monitored by including indicators that capture the key elements of integration, as proposed in Table 1. Such indicators can also be used to spur or trigger action and thus serve as input indicators, or they can be used during implementation as process and outcome indicators.

**Primary Health-Care Services**
Entry points for HIV prevention and care exist within reproductive health services offered as part of primary health care, or within individual components of reproductive health services. Proposed
A proposed framework for service linkages to increase access to HIV prevention and care within primary health care and thus to improve the quality of sexual and reproductive health is shown in Figure 1.7.

Indicators to monitor linkage of primary health-care services include the following:
- Proportion of primary health-care services offering family planning, including condoms and HIV counseling, testing, or referral

### Table 1. Indicators of Linkages between Sexual and Reproductive Health and HIV/AIDS Programs (WHO)^

<table>
<thead>
<tr>
<th>Type of Indicator</th>
<th>Suggested Indicators of Linkages</th>
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<tr>
<td><strong>Policy</strong></td>
<td>- Existence of a national reproductive health strategy that includes HIV prevention, care, and support</td>
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<td>- Existence of a national behavior change strategy for HIV prevention and care within sexual and reproductive health policies and programs</td>
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<td><strong>Social determinants</strong></td>
<td>- Proportion of HIV-discordant couples using condoms and treatment for prevention of partner infection</td>
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<td></td>
<td>- Proportion of primary health-care service delivery points that (a) are adolescent friendly and (b) promote male involvement in sexual and reproductive health</td>
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<tr>
<td><strong>Access: service availability</strong></td>
<td>- Number of sites per 500,000 population offering sexual and reproductive health services—including HIV prevention, care, and support—as part of essential basic health care</td>
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<td>- Proportion of primary health-care service delivery points that offer (a) three or more or (b) six or more of the following sexual and reproductive health and HIV/AIDS services: family planning, antenatal care, postnatal care, STI services, VCT, provider-initiated testing and counseling (PITC), PMTCT, ARVs, cervical cancer screening, and prostate cancer screening</td>
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<td><strong>Access: information</strong></td>
<td>- Incorporation of sexual and reproductive health and HIV prevention within late-primary and secondary education curricula</td>
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<td>- Proportion of primary health-care service delivery points that offer (a) VCT, including follow-up of partners for treatment and counseling, and (b) behavior change communication (BCC)</td>
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<td><strong>Use of services</strong></td>
<td>- Proportion of HIV-positive antenatal women receiving (a) appropriate ARV, and (b) PMTCT services at delivery</td>
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<td></td>
<td>- Proportion of partners of HIV-positive or syphilis-positive antenatal women receiving appropriate treatment and counseling</td>
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<tr>
<td><strong>Outcome/impact</strong></td>
<td>- Prevalence of HIV among antenatal clinic attendees</td>
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<tr>
<td></td>
<td>- Incidence of HIV transmission from women with HIV to their infants</td>
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not intending to get pregnant is a major pillar in PMTCT. Features of an integrated family planning service are shown in Figure 2.7

Indicators to monitor family planning linkages include the following:
- Proportion of family planning service sites offering counseling and HIV testing or referral
- Proportion of family planning service site users counseled on HIV and referred or tested
- Proportion of people using any family planning method who plan to use condoms (for family planning, STI, or HIV prevention)
- Proportion of family planning service site users receiving BCC
- Proportion of family planning service site users counseled, referred, or treated for STI

**Family Planning Services**
Many countries have integrated family planning services within primary health care, in addition to providing vertical family planning services. Integration of HIV prevention and care, in particular VCT, within stand-alone or integrated services, reduces stigma associated with stand-alone HIV facilities and serves a common client: individuals of reproductive age at risk of unintended pregnancy or infection. According to the 2004 Joint United Nations Program on HIV/AIDS (UNAIDS) annual report, nearly half of all HIV-positive persons are child-bearing-aged females and are both sexually active and in need of contraceptive services. Access to and utilization of family planning by HIV-positive women who are

**Maternal Health-Care Services**
Entry points for HIV prevention and care within maternal health-care services include providing services to women during antenatal clinic (ANC) intrapartum and postpartum care, such as VCT and PMTCT (Figure 3). Such services should include
Figure 2. Proposed linkages of HIV prevention and care to family planning services

Figure 3. Proposed linkages of HIV prevention and care to maternal health-care services (ANC and intrapartum care)
or link to family planning, STI services, and male involvement. PMTCT services should include the four-pronged approach comprised of (1) primary prevention of HIV infection among women; (2) prevention of unintended pregnancies among women living with HIV; (3) prevention of HIV transmission from women living with HIV to their infants; and (4) provision of treatment, care, and support to mothers living with HIV, their infants, and their families.

Indicators to monitor progress include the following:

- Proportion of ANC and delivery service promoting the four-pronged approach to PMTCT
- Proportion of ANC and delivery service users counseled and treated for STIs, including following up with the male partner for treatment

Another maternal and child health service component is postpartum care services. A framework for sexual and reproductive health and HIV prevention and care components integrated or linked to postpartum care is shown in Figure 4.

Indicators to monitor progress include the following:

- Proportion of postpartum care service sites counseling and offering family planning methods, including condoms

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**Box 3. Lessons from the Field: Primary Health-Care Linkages**

The following perspectives come from a number of different programs linking reproductive health with HIV/AIDS services in resource-limited settings.

“In a context of limited resources, integration of reproductive health and HIV care services is a cost-effective and sustainable approach and provides synergy of actions. In Kenya, the Division of Reproductive Health and the National AIDS and STI Control Program in the Ministry of Health jointly run the respective services. The rationale and motivation include high burden of disease, limited resources, same population being targeted, and activities implemented by the same staff. Initially, integration had mainly focused on PMTCT, family planning and VCT, and integration of RTIs [reproductive tract infections] into reproductive health settings. Newer areas include adolescents and youth programs and integration of gender issues into reproductive health / HIV activities. Enabling factors include a conducive structure, such as both programs report to the Department of Preventive and Promotive Health Services; HIV/AIDS is a component within the country’s reproductive health strategy; majority of those targeted by HIV/AIDS programs are people with reproductive health needs; resources for HIV/AIDS have been on the increase.”

“In Nigeria, condoms are distributed within all PHC [primary health-care] services in the country, but services are not yet fully integrated. Since 2006, partners are supporting the process of integrating HIV prevention and care within PHC services.” (Dr. O. Odujinrin, questionnaire response, 2007)

“In Zambia, PHC services include HIV prevention and care. Some facilities have integrated VCT services, while in some, there is only counseling, and clients are referred to testing sites or to NGOs [nongovernmental organizations] within the community.” (Mrs. P. Kamanga, questionnaire response, 2007)

“In Sudan, VCT/ART [antiretroviral therapy] sites are located within hospitals in the states. Only a few are also located at a PHC-level facility. There are no data being collected to measure the effectiveness of the linkage of services but rather general program performance.” (Dr. A. Alagabany, questionnaire response, 2007)

“In Uganda, HIV services are linked to and not integrated within PHC services. It overloads the system because it requires relatively well-trained service providers to be able to do VCT, together with the other PHC services at service delivery points. The resources are not enough to cater for the massive numbers that require the service.” (Dr. O. Sentumbwe-Mugisa, questionnaire response, 2007)

“In Tanzania, HIV services such as information on prevention and VCT are provided in all PHC services.” (Dr. T. John, questionnaire response, 2007)
the high number of unsafe abortions taking place in settings with a high prevalence of HIV.\textsuperscript{10}

Indicators to monitor progress include the following:
- Proportion of postabortion care users counseled on HIV and offered or referred for testing and treatment
- Proportion of postabortion care users counseled and referred for STI/HIV testing and treatment

Postabortion Care Services
Postabortion care services, which include treatment for complications arising from unsafe abortions, benefit from including family planning counseling and services, referral to or integration with VCT, and information on STIs and reproductive tract infections (RTIs) (Figure 5). Where family planning has been integrated into postabortion care services, reduction in the incidence of recurrent abortion has been reported.\textsuperscript{9} However, much less is reported on linking postabortion care services to HIV prevention, particularly in high-burden countries. This could be a missed opportunity, given the current estimates on the high number of unsafe abortions taking place in settings with a high prevalence of HIV.\textsuperscript{10}

Indicators to monitor progress include the following:
- Proportion of women receiving postabortion care who are counseled and offered a family planning method and condoms
- Proportion of women receiving postabortion care who are counseled and referred for STI/HIV testing and treatment

STI Prevention and Control Services
Sexually active men, women, and young people who present for STI diagnosis or treatment are also at risk of HIV infection and transmission. Client needs for integration within STI services include condom promotion and distribution and BCC, with linkage to or integration of VCT. Few STI services include systematic linkage to family planning services.
**Box 4. Lessons from the Field: Family Planning Linkages**

The following perspectives come from a number of different programs linking family planning with HIV/AIDS services in resource-limited settings.

<table>
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<tr>
<th>Perspective</th>
<th>Source</th>
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<tr>
<td>“Good-quality family planning services have great potential for reducing MTCT [mother-to-child transmission] of HIV. In Kenya, 62 sites in eight provinces provide integrated family planning/VCT services.”</td>
<td>(Mrs. P. Kamanga, questionnaire response, 2007)</td>
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<td>“In Zambia, family planning guidelines emphasize the need to include HIV in all family planning service provision. Where it has been feasible, providers have integrated HIV into their services, and where they cannot provide testing, they refer clients to other facilities. Within bigger hospitals, the referral is between departments.”</td>
<td>(Mrs. P. Kamanga, questionnaire response, 2007)</td>
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<tr>
<td>“In Sudan, there is both linkage to and integration of family planning services. The Sudan Family Planning Association and several NGO [nongovernmental organization] family planning facilities also provide VCT. However, there is need for systematic data collection to assess the outcome or impact of the linkages.”</td>
<td>(Dr. A. Alagabany, questionnaire response, 2007)</td>
</tr>
<tr>
<td>“In Nigeria, family planning services provide information, education, and communication on HIV. Counseling is carried out and clients are referred for further treatment. Clients are also offered male or female condoms for HIV prevention.”</td>
<td>(Dr. O. Odujinrin, questionnaire response, 2007)</td>
</tr>
<tr>
<td>“In Uganda, family planning and HIV services are linked, but not integrated. According to program managers, it overloads the system, because it requires relatively well-trained service-providers to be able to do VCT together with family planning services at service delivery points. The resources are also not enough to cater for the massive numbers which require the service of VCT. Integration of HIV information in family planning requires training and therefore resources to do this, and yet it is an area with severe constraints in terms of funding and training.”</td>
<td>(Dr. O. Sentumbwe-Mugisa, questionnaire response, 2007)</td>
</tr>
<tr>
<td>“HIV counseling and sometimes testing are offered together with family planning services in Tanzania. The training package for family planning also includes a chapter on HIV information and counseling.”</td>
<td>(Dr. T. John, questionnaire response, 2007)</td>
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</table>

A randomized trial evaluated the feasibility, acceptability, and effectiveness of HIV prevention information and routine offer of provider-initiated counseling and testing for HIV into family planning services in 18 health facilities in South Africa. It concluded that integration of HIV prevention and routine offer of testing in family planning services was feasible, acceptable, and effective, without compromising quality of family planning services.

In a Tanzania study, a total of 1,928 women attending family planning received VCT. Of these, 155 tested positive and were referred for care and treatment. Overall, use of modern contraceptive methods significantly increased, and in one district, family planning clients increased from 699 to 2,317 in six months following integration, which was attributed to “improved quality of services, improved counseling skills after training, stigma reduction training and, through VCT approach, attraction of clients for multiple services.” In this study, integration attracted more women than stand-alone services did. Implementation involved participatory planning of health facility staff, community health committees, council health management teams, and others. Integration also helped to strengthen other sexual and reproductive health services and health systems.
Indicators for monitoring availability of services include the following:

- Proportion of STI service sites providing counseling and testing for HIV
- Proportion of STI service sites promoting BCC
- Proportion of STI control service users counseled on family planning and offered condoms

Linking HIV services with components of sexual and reproductive health in the context of achieving universal access to sexual and reproductive health, including HIV prevention and care, is crucial. Where HIV services are offered, such as VCT, PMTCT, antiretroviral therapy (ART), or BCC programs, elements of sexual and reproductive health services to be offered or for which there could be systematic referral include family planning services, condom promotion, STI prevention and control, and BCC (Figure 6).  

Indicators to monitor progress include the following:

- Proportion of HIV service delivery points offering condoms
- Proportion of HIV service sites incorporating BCC materials

STI = sexually transmitted infection; VCT = voluntary counseling and testing; BCC = behavior change communication

Figure 5. Proposed linkages of HIV prevention and care to postabortion care services

Box 5. Lessons from the Field: ANC and Postpartum Care Linkages

In many countries with a high prevalence of HIV, PMTCT is now routinely offered as part of ANC. For example, according to questionnaires collected in 2007, women in Nigeria, Zambia, Sudan, and Uganda are offered VCT during antenatal care, and HIV-positive women are offered or referred for antiretroviral therapy (ART). Family planning is an important component of PMTCT that has been shown to be effective; yet family planning counseling is seldom provided, and its integration varies widely. In Tanzania, for example, HIV counseling, information, and testing are offered in ANC and postnatal care. However, PMTCT services are only available in roughly 10% of facilities in the country (Dr. T. John, questionnaire response, 2007). In most countries, postpartum care is the weakest component of the PMTCT program and should be strengthened.
Challenges to ensuring effective linkages or integration to improve sexual and reproductive health, particularly HIV prevention and care, include the following:

- Proportion of HIV-positive people offered treatment and counseled on sexual and reproductive health
- Proportion of HIV service sites offering or referring for STI treatment

**CHALLENGES, NEEDS, AND LESSONS LEARNED**

Challenges to ensuring effective linkages or integration to improve sexual and reproductive health, particularly HIV prevention and care, include the following:

- Training needs (training is a requirement for capacity building and enhancing and expanding skills for service providers)
- Poor motivation and attitudes of some service providers
- Instances of provider and service overload
- Traditional orientation of services with limited privacy and space
- Vertical donor programs
- Priority accorded only to HIV by some donors
- Lack of political will and poor conceptual understanding

Figure 6. Proposed linkages between HIV/AIDS prevention, care, and treatment services and sexual and reproductive health services

**Table 6. Lessons from the Field: Postabortion Care Linkages**

<table>
<thead>
<tr>
<th>VCT, PMTCT, ART, BCC</th>
<th>Improved access to and coverage of sexual and reproductive health services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family planning</td>
<td></td>
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<tr>
<td>STI services</td>
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<tr>
<td>Condom promotion</td>
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<td>BCC</td>
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</table>

VCT = voluntary counseling and testing; PMTCT = prevention of mother-to-child transmission; ART = antiretroviral therapy; BCC = behavior change communication; STI = sexually transmitted infection
• Sexual and reproductive health and HIV programs managed by different program managers with autonomy, resulting in the need for closer collaboration and joint planning and implementation
• Paucity of data for advocacy on effectiveness and acceptability of linkages

Suggestions to overcome these challenges include the following:
• Continued generation of multicountry evidence to further demonstrate effectiveness, cost-efficiency, service uptake, access being achieved, intervention coverage, effect on quality of care, stigma reduction, and acceptability and feasibility of integrating or linking programs and/or services
• Establishment, through operations research, of requirements for scaling up integrated programs
• Training and reorientation of service providers on various components proposed within integrated programs and on requirements for efficient linkages
• Increasing the capacity of sexual and reproductive health services and health workers to contribute to HIV prevention and care
• Ensuring advocacy for integration or linkages at all levels of service provisions
• Development or strengthening of services to enhance technical capacity to meet a range of user needs
• Development of a package of essential HIV prevention and care services within sexual and reproductive health services and vice versa
• Top-level planning of HIV / sexual and reproductive health resource-sharing and programming via seeking joint funding (e.g., for condom purchase and distribution with the view to promote dual protection)
• Establishment of task forces or management communities comprising representatives of sexual and reproductive health and HIV programs
• Involvement and sensitization of policymakers or decision makers

Reported benefits from the field of efforts to integrate services include the following:

“Patients would be seen at a one-stop center, therefore reducing the time spent trying to access different services. It increases client confidence in the service and satisfaction for the service offered.” (Dr. O. Sentumbwe-Mugisa, questionnaire response, 2007)

“Limited availability of human resources in health makes it necessary to offer integrated services. Long distances to facilities make it necessary for all needs to be made available at the same place or visit. Every visit to a health centre is an opportunity to prevent disease or offer services.” (Mrs. P. Kamanga, questionnaire response, 2007)

“By integrating HIV and sexual and reproductive health services, it will save time and resources for the client . . . it will minimize missed opportunities . . . and is cost-effective for the programs, planners, and government.” (Dr. T. John, questionnaire response, 2007)

CONCLUSION

It is widely believed that stronger linkages between sexual and reproductive health programs and those for HIV prevention and care contribute to a number of public-health benefits. There is need for resources that take into account the potential benefits of these linkages. Data must be collected on the outcomes of linked programs or services as part of ongoing monitoring and evaluation of activities. Additional evidence needs to be generated to support advocacy efforts, in particular on the best approaches to strengthening linkages. In the words of one program officer from Tanzania (Dr. T. John, questionnaire response, 2007), “It will be a good idea if opportunities are taken to strengthen integration or linkages as it will accelerate the availability of both services . . . and leverage the available resources towards achieving universal access to sexual and reproductive health and HIV prevention and care.”
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Expanding Access to HIV Care and Prevention through Successful Public-Private Partnerships: Lessons Learned from Botswana

Joan Sullivan, Lesego Busang, L.R.G. Manthe, and Themba L. Moeti

African Comprehensive HIV/AIDS Partnerships (ACHAP), Botswana

The African Comprehensive HIV/AIDS Partnerships (ACHAP) is a country-led public-private partnership (PPP) between the government of Botswana (GOB), the Bill & Melinda Gates Foundation, and Merck & Co. Inc. / The Merck Company Foundation. Created in 2000 at the height of Botswana’s HIV epidemic, ACHAP was designed to provide significant financial and technical resources to the GOB (an ACHAP partner and its main grantee) to accelerate the national comprehensive response to the epidemic. One of ACHAP’s major success areas has been its support of government efforts to establish and rapidly scale up provision of free antiretroviral therapy (ART) to all individuals requiring treatment, through the provision of significant technical, human, and infrastructural resources. ACHAP is widely credited with having catalyzed the establishment of Africa’s first public sector ART program.

This chapter describes some of the lessons learned from the ACHAP experience during the first six years (2001–2006) of the partnership. It also highlights the challenges encountered in a severely human resource–constrained environment in the context of rapid scale-up. At the time ACHAP was being conceptualized, there were few models to inform the design of a PPP for a generalized epidemic in sub-Saharan Africa. While some errors were made during the initial phase of the PPP with regard to strategy and approach, the lessons learned from the Botswana experience are relevant to other countries on the road to universal access in the context of severe generalized epidemics.

HISTORICAL CONTEXT

Since independence from Britain in 1966 and the discovery of diamonds in 1967, Botswana has transitioned from an agrarian economy to the highest per capita income economy in sub-Saharan Africa, excluding the island nations of Seychelles and Mauritius. As one of Africa’s longest-running stable democracies, and with an average gross domestic product (GDP) growth of 10% over the last four decades, Botswana has reaped substantial development gains only to watch them melt away under the relentless spread of HIV. For example, the United Nations system reports that life expectancy at birth fell from 65 years in 1990–1995 to 51.9 years in 1995–2000 to 46.6 years in 2000–2005. It is, however, projected to increase to 50.7 years during the period 2005–2010, due to recent declines in HIV
Based on the Botswana population censuses of 1981, 1991, and 2001, the Central Statistics Office in Botswana estimated life expectancy at birth to be 56.2, 65.3, and 55.6 years, respectively, indicating the negative impact of HIV/AIDS.4

Since 1992, Botswana has conducted annual HIV sentinel surveys among a representative sample of pregnant women attending select antenatal clinics. These surveys indicate that HIV prevalence peaked at 38.5% in 2000 and declined significantly (P≤.0001) to 32.4% between 2001 and 2006.5 On a population level, the most recent government and Joint United Nations Program on HIV/AIDS (UNAIDS) estimates (25.3% and 24.1%, respectively) for adult HIV prevalence point to the same conclusion: that one-quarter of sexually active adults aged 15–49 in Botswana are infected with HIV.5,7

Against this background, the GoB has consistently demonstrated strong visionary leadership to respond aggressively to the epidemic. Among its many achievements are three “firsts” for sub-Saharan Africa: first country to roll out prevention of mother-to-child transmission (PMTCT) services to all public health facilities (2001), first country to introduce free ART for all its citizens through public health facilities (2002), and first country to institutionalize the routine offering of HIV testing in public health facilities (2004).

In the six years since Botswana’s national program began, provision of ART has scaled up rapidly; a total of 90,543 patients were receiving ART as of September 2007, of which 73,759 were in the public sector and 16,784 in the private sector. Over 7,000 private sector patients are funded by public sector resources in a contracting arrangement. According to World Health Organization (WHO) estimates, Botswana’s adult ART coverage rate was 79% in 2006, the highest in Africa.6 This correlates with current government estimates of 82% coverage based on the country’s original estimate of 110,000 people infected with HIV.9

Part of Botswana’s success may be attributed to its ability to have attracted, in the words of President Mogae, “unprecedented partnerships” in its war against AIDS.10 This is particularly relevant in the context of Botswana’s reclassification as an upper-middle-income economy in the mid-1990s, which resulted in the departure of most bilateral and multilateral donors from Botswana just as the HIV epidemic was escalating.11

It is within this context that the GOB responded positively and swiftly to a proposed partnership with Merck & Co. Inc. and the Bill & Melinda Gates Foundation.12 A statement of intent was signed in July 2000, and in January 2001 ACHAP began operations in the capital, Gaborone. Exactly one year later, following a period of intense consultation and an influx of human and infrastructural resources facilitated largely by ACHAP, Botswana’s first public sector antiretroviral (ARV) patient began treatment, on January 21, 2002.

On the ground, ACHAP is credited by both government officials and development partners as having made an invaluable contribution to the initiation and roll-out of Botswana’s national ART program.12 Although other HIV/AIDS partnerships in Botswana preceded ACHAP, ACHAP was the first public-private partnership in Botswana created specifically to strengthen government efforts to develop and implement a comprehensive national response to the epidemic. Other PPPs followed suit, mostly from the pharmaceutical sector. To date, at least 12 PPPs of varying duration and objective have been created to support the GOB’s national response.

**DESCRIPTION OF ACHAP**

The steps leading up to the creation of ACHAP and its governance structure are described elsewhere.9,12-15 Briefly, ACHAP is governed by a five-member
board of directors represented by the two foundations (Gates and Merck) and a senior professional from the Harvard AIDS Institute. The central point of contact between the board and the government is through ACHAP’s Gaborone-based managing director. The initial partnership involved a pledge of US$50 million from each of the two foundations, for a total of US$100 million over a period of five years (2001–2005). In addition, Merck & Co. Inc. donated two ARV medicines, Stocrin (effavirenz) and Crixivan (indinavir), to the GOB for five years. This initial partnership was extended for an additional four years (2006–2009) with the signing of a second memorandum of agreement on December 19, 2005. For this second phase of the partnership, the two foundations each pledged an additional US$6.5 million as well as the continued Merck drug donation to the end of 2009.

The partnership handles significant resources; therefore, various structures are in place to ensure accountability. ACHAP management is accountable to the board of directors, which, in turn, is supported in its governance role by the Madikwe Forum, a governance structure that includes the board of directors, the managing director, and the heads of key government ministries and the National AIDS Coordinating Agency (NACA). In line with good corporate practice, standard operating procedures are in place to guide management processes, with a performance appraisal system in place to monitor staff performance. Furthermore, the organization’s accounts undergo an external audit annually, with the submission of reports to the supporting foundations to track both expenditure and program implementation.

ACHAP’s guiding principle was to act as quickly and as decisively as possible to help the GOB jump-start a rapid scale-up of ART. Within its first three months, ACHAP negotiated the pro bono services of the international management consulting firm McKinsey & Company to conduct a national feasibility assessment for ART. Five months after the results of this exercise were presented to the Ministry of Health (MOH) and the Cabinet in August 2001, Botswana’s first public sector ARV patient was started on treatment. While only part of an ongoing process of dialogue and consultation, this assessment is widely recognized within Botswana as having had a profound impact on the initial design and launch of Botswana’s national ART program by providing the government with its first tangible estimates of latent demand for ART as well as the original blueprint including human resource and infrastructural needs for the continent’s first public sector treatment program.

The doctor-centered treatment model approved by the government required an influx of ART-competent clinicians. In the absence of a medical school, Botswana urgently needed a training program to quickly update and standardize the skills of its existing and newly recruited health workers to provide ART to the estimated 110,000 patients in need of treatment in 2001.9 ACHAP committed nearly 100% of the funding for the start-up and implementation of a national standardized AIDS training program known by the acronym KITSO (Knowledge, Innovation, and Training Shall Overcome AIDS), which also means “knowledge” in the local language, Setswana. The KITSO AIDS training program represents an important collaboration between the MOH and the Botswana–Harvard AIDS Initiative Partnership for HIV Research and Education, made possible through ACHAP support.16

As of August 2007, a cumulative total of 5,395 health professionals had been trained in KITSO’s flagship course, AIDS Clinical Care Fundamentals, representing approximately 75% coverage of Botswana’s health professionals in the categories trained, according to government estimates. This course enabled the creation of a truly national
In addition to building human capacity for national ARV roll-out, ACHAP has committed 9% of its budget (US$8.9 million) to date for the construction of critical space and the procurement of laboratory monitoring equipment at both central and peripheral health facilities. In collaboration with the MOH, ACHAP has constructed 31 infectious disease care clinics (IDCCs) since 2002. It has also procured patient monitoring equipment (CD4, viral load, and sequencer) to equip the state-of-the-art Botswana-Harvard HIV Reference Laboratory in Gaborone. To support GOB efforts to decentralize ART patient enrollment and monitoring, ACHAP procured an additional 10 CD4 and six viral load machines for select district sites. Between May 2006 and April 2007, treatment sites with CD4 machines procured by ACHAP have performed more than two-thirds (68%) of all CD4 tests carried out in public sector laboratories, a significant contribution to diagnostic and monitoring capacity. In addition, ACHAP support for district laboratory capacity has relieved pressure on the nation’s main referral laboratory, reducing turnaround time for district patients from several weeks to less than one week, according to referral and district laboratory reports.

LESSONS LEARNED FROM THE ACHAP PPP MODEL

We have identified the following five lessons from the ACHAP PPP model that are relevant to partnerships in the context of the global universal access initiative.

1. It is possible to implement effective ART in a resource-limited setting in Africa. An essential precondition for success is bold political leadership. In the case of Botswana, President Mogae’s strong personal and political commitment to launching the continent’s first public sector ART program has attracted important partnerships, such as ACHAP, which provided...
significant additional resources (financial, technical, infrastructural) that leveraged government efforts to respond to the epidemic. ACHAP’s long-term commitment to supporting Botswana’s national response has allowed government resources to go further, given that many public resources were diverted from other development areas to address HIV/AIDS. Under President Mogae’s leadership, Botswana has funded the lion’s share of its own national response, providing a strong incentive that attracts new partnerships and makes existing partnerships more effective. In 2005, government estimates show that international development partners collectively committed about 20% of national spending on HIV/AIDS, with the remaining 80% coming from public sector funds.18

2. The primary purpose of any PPP for HIV/AIDS should be to support and scale up only those efforts aligned with one national guiding framework. When ACHAP started in 2001, Botswana did not have such a blueprint; thus, one of ACHAP’s first activities was to support the development of Botswana’s first National Strategic Framework (NSF) for HIV/AIDS (2003–2009). In addition, ACHAP has committed 5% (US$4.8 million) of its portfolio to date to building capacity within NACA to strengthen coordination of the national response, including the establishment and implementation of a monitoring and evaluation (M&E) framework. Following a midterm strategic review in 2004, ACHAP shifted from its initial proposal-driven strategy to one that was firmly anchored within the NSF. This decision reflected the growing maturity of the ACHAP PPP model, which recognized (a) the importance of respecting structures in place and (b) the primacy of ensuring that the government had a meaningful say in the nature of programs and interventions to be supported. To further strengthen the collaboration, ACHAP facilitated the creation of a local governance structure known as the Madikwe Forum in 2004, which facilitated quarterly consultation with top policymakers in seven key ministries and agencies as well as with mid-level technical and managerial staff to improve implementation and remove roadblocks. As ACHAP has become more adept at working within government systems, it has resolved at least some of the differences in approach and work culture—issues that affected the early years of the partnership.12

3. The ability of a partnership to be responsive to and evolve within a changing landscape of priorities and challenges is essential to maintaining relevance to any national response. While initial focus is key, partnerships must not remain static. In 2001, ACHAP was the largest HIV/AIDS donor agency in Botswana, and its primary objective at that time was to inject significant financial and technical resources to help the government kick-start a national public sector ART program. Over time, as the national treatment program matured and other development partners arrived (e.g., the President’s Emergency Plan for AIDS Relief [PEPFAR]; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and the Clinton Foundation), ACHAP was able to focus more attention on HIV prevention in the context of increased treatment access. To this end, ACHAP is supporting the development and implementation of a national business plan to scale up prevention interventions. This plan informs increased investment by the government, development partners, and other stakeholders in prevention initiatives at all levels, including within districts and communities. ACHAP’s evolution also included broadening its support to seven health districts beginning in 2005 to strengthen the coverage and impact of the national response.

Within its ongoing support of Botswana’s national ART program, ACHAP has also recognized the need to evolve in line with international
recommendations for integrated treatment models in resource-limited settings. Concern about the long-term costs and sustainability of Botswana’s original treatment model has resulted in recent policy decisions to move away from a doctor-centered treatment model toward a more sustainable, integrated public-health model in which nurses and other allied health professionals will assume greater responsibilities. The expansion of the role of nurses in ARV service delivery and the increased use of appropriately trained lay and peer counselors, among others, are initiatives currently receiving ACHAP support.

4. The success of any partnership should ultimately be determined not by the total numbers of people being treated or by the percentage of a study population reporting behavior change, but rather by tangible improvements in systems capacity to ensure more cost-effective and sustainable national responses. As in many sub-Saharan countries, the greatest challenge facing Botswana and its development partners in the fight against AIDS is the critical shortage of skilled human resources with which to address all aspects of the national response: conceptualization, coordination, planning, implementation, M&E, and documentation. A recent government decision to build a medical school over the next five years will eventually reduce Botswana’s reliance on expatriate clinicians but will have little immediate impact on the chronic shortage of qualified program planners, administrators, financial officers, managers, coordinators, M&E officers, and information technologists that currently plagues all sectors, not just the health sector.

ACHAP’s primary response to this challenge is to help the GOB identify, acquire, and employ the necessary resources and technical assistance to strengthen the institutional and human capacity to carry out the national response. In close collaboration with the GOB, ACHAP has recruited or seconded more than 160 technical staff to various ministries and civil society organizations since 2001. A further commitment of 120 staff in 2007 is intended to address emerging needs, including the next phase of roll-out of ARV services to clinics. However, the lack of a clear capacity-building strategy with measurable outcomes has resulted in a somewhat ad hoc technical assistance recruitment mechanism, with suboptimal use of the resources provided. ACHAP has joined other development partners to support the MOH in developing a Human Resources for Health Plan, which should enable more strategic capacity development in the future.

5. Botswana and other sub-Saharan African countries need to nurture a culture of information use to strengthen the monitoring of current programs, as well as to inform the design of new “evidence-based” initiatives. The underdevelopment of M&E expertise in Botswana deserves special mention. The local and regional marketplace is conspicuously lacking in strong M&E skills; it took ACHAP almost one year to identify seven M&E officers for secondment to the Ministry of Local Government to strengthen the monitoring of district responses. The strengthening of M&E capacity is essential not only for United Nations General Assembly Special Session on HIV/AIDS (UNGASS) reporting requirements, but, more importantly, to accurately assess the long-term impact of program interventions, such as the quality of life of ARV patients and measurable changes in social norms and individual behavior as a result of ART access.

OUTCOMES
The ultimate measure of ACHAP’s success will be the extent to which the GOB has achieved its national goals and objectives in addressing Botswana’s AIDS crisis; it will be several more years before this effort can be fully evaluated.
Prior to the implementation of the ACHAP PPP, Botswana’s response to the epidemic was similar to that of most other sub-Saharan countries in the late 1990s—in other words, the glaring gap was the treatment component. Within one year of ACHAP’s arrival in Botswana, the continent’s first public sector ART program was launched, in spite of international skepticism. While ACHAP could be criticized for allocating so many resources to ART at the expense of HIV prevention during the first phase of the partnership, the level and intensity of such focused grant making helped Botswana move one step closer to universal access by facilitating the transition from an incomplete to a complete response. The scaling up of Botswana’s response was a watershed moment; once one country in the subregion had successfully rolled out public sector ART, other countries felt compelled to follow suit. Most African countries have since gone on to build more cost-effective national ART programs, jump-starting continental action toward universal access. Botswana is benefiting from their collective experience and currently transitioning toward a more sustainable, integrated public-health treatment model.

Based in part on the timely and focused infusion of PPP resources, Botswana is now well on the road toward universal access. Botswana now has a well-established treatment program at the secondary care (hospital) level. However, to improve access at the primary care level, ACHAP has, at the request of the government, committed additional funds to support the next phase of national roll-out to an additional 50 clinics, which will require the rapid scale-up of human and infrastructural resources to meet increasing demand for HIV prevention, testing, and treatment services across the country.

Recognizing that HIV prevention efforts in Botswana are not keeping pace with increased treatment access, ACHAP is committed to helping the GOB achieve the same gains in prevention that it has made in treatment. In collaboration with NACA, ACHAP is facilitating the development and implementation of a national business plan to guide efforts to strengthen the coordination and scale-up of government and development-partner prevention efforts. Over seven years (2001–2007), the ACHAP PPP has evolved from its initial treatment niche to become one of Botswana’s main partners advocating for and supporting a comprehensive approach to the epidemic.


Secure the future (STF) was launched in 1999 as a US$100 million commitment from Bristol-Myers Squibb (BMS) to fund HIV/AIDS community outreach, education, medical research, and care projects in the five southern African countries: Namibia, Botswana, Lesotho, Swaziland, and South Africa. As of 2008, STF had grown to a grants budget of US$150 million (all administrative costs of the program were paid directly by the Bristol-Myers Squibb company) and was active in 12 African countries.

From the outset of activities, close consultation and collaboration with the government of each country led to the formation of partnerships to ensure that the projects were compatible with and complementary to the countries’ health-care policies and priorities. These partnerships were further solidified by the inclusion of Ministry of Health (MOH) representatives in independent Technical Advisory Committees, which were established to evaluate proposals submitted from community organizations, academic institutions, and healthcare facilities and to advise STF on which proposals to consider for funding. For example, all ministries stipulated that the proposals selected for funding should be sensitive to the local context, ethically sound, innovative, sustainable, and replicable and have the potential to promote equity, but they also needed to be in line with each country’s national HIV/AIDS plan. Because the objectives of STF were often in alignment with those of the government, the partnership represented an opportunity for both parties to pursue their strategic objectives.

The public-private partnership model was not only applied at the government level, but also continued at the project level among grantees and their organizations. The strength of these organizations, namely, their knowledge of the situation on the ground, was enhanced by the skills and core competencies that a private organization such as BMS could bring to the table, such as good governance, financial and project management, and expertise in research and information technology.

STF initially funded individual organizations to conduct small- to medium-sized projects, usually with simple and discrete objectives. However, the real strength of these partnerships and the greatest promotion of equity are most visible in the work of the Community-Based Treatment Support (CBTS) program. This program was initiated by STF in 2003 in close collaboration with ministries of
Figure 1. The Community-Based Treatment Support Program model of care

ART = antiretroviral therapy; CBO = community-based organization; FBO = faith-based organization; IGA = income generating activities; NGO = nongovernmental organization; PLHIV = people living with HIV; PMTCT-plus = prevention of mother-to-child transmission plus family-based care and treatment; WHO = World Health Organization
health, in order to target poor and disadvantaged populations living in settings with very limited resources.

THE STF COMMUNITY-BASED TREATMENT SUPPORT PROGRAM FOR PEOPLE LIVING WITH HIV

The CBTS model emphasizes that people living with HIV in resource-limited settings need both clinical services and community services to effectively enhance their quality of life and clinical outcomes. It employs supportive services such as food security and home-based care to help people manage their chronic HIV disease outside the clinic, in their homes and communities. The program leverages the strengths of government, the private sector, and community-based organizations to offer a true continuum of care, or as STF refers to it, “23½ hours” (the time outside the clinic) of disease management and psychosocial support that takes place in the patient’s home and community following a “half hour” of medical care in the clinic.

The model is represented diagrammatically in Figure 1. The top diagram illustrates the three-way partnership between the public sector (government, local health authorities, and facilities), the private sector (STF, private physicians, traditional healers, and other private companies) and the community (nongovernmental organizations, community-based organizations, faith-based organizations), which STF established at each of its CBTS sites. The bottom diagram contrasts the service provided at the clinic with those delivered by community organizations.

The key to success in implementing this type of program is partnership, the dynamics of which will be examined in detail in this chapter.

Based on a three-year, five-site experience in southern Africa, STF has characterized and documented the implementation of the model according to seven steps, as follows:

- Step 1: Engage Government and Community
- Step 2: Establish Leadership and Management Structure
- Step 3: Adapt and Define CBTS Model
- Step 4: Build Partner Capacity and Infrastructure
- Step 5: Deliver Services
- Step 6: Monitor and Evaluate Implementation
- Step 7: Improve and Revise Services

These seven steps are cyclical in nature, following a sequence of planning, action, and reflection as illustrated in Figure 2.

The rest of this chapter describes how this model was put into practice through a public-private partnership to deliver much-needed treatment and care to a remote and poverty-stricken town in Botswana.

The Setting

Only a few years ago, Bobonong, in the sub-district of Bobirwa, (Figure 3) was a dying community, both figuratively and literally. The small town in eastern Botswana was ravaged by HIV/AIDS, poverty, unemployment, illiteracy, and hopelessness. The town is home to about 20,000 people and is the center of activity within the Bobirwa sub-district, which has a total of 66,000 inhabitants.

Unemployment in the sub-district increased from nearly 25% in 2001 to 33% in 2003. The prevalence of HIV among pregnant women was close to 37.4% in 2003,¹ making it one of the places in the world hardest hit by HIV.

The government of Botswana recognized the profound impact that HIV/AIDS was having on communities throughout the country, and began providing antiretroviral therapy (ART) to its citizens in January 2002 under the MASA program (a Setswana word meaning “new dawn”). Initially, the principal beneficiaries of MASA were the larger cities, such as Gaborone, Francistown, and Serowe. Isolated communities with scattered populations...
such as Bobonong were not earmarked to receive a clinic in the program at this early stage. Therefore, residents of the village had to travel approximately three hours each way to either Francistown or Serowe to access antiretroviral drugs (ARVs). As Gabaitse Marope, treasurer of the Ward AIDS Committee in Bobonong, described it, “Those who made the trip had to factor in the time and expense. This was not easy for people here; it was demoralizing.”

**Engaging and Partnering with Government and Community**

When STF started consulting with the government in 2003 regarding the relevance and acceptability of implementing a CBTS model in Botswana, the MOH representative on the STF Technical Advisory Committee championed the selection of Bobonong because of the presence of the Bobonong Home-Based Care Society (BHBCS), a dedicated community-based organization that had pioneered home-based care in the country. Negotiation with the MOH proceeded rapidly, in part because of the excellent relationship STF had been developing with the government of Botswana since 1999. This relationship started with the building of the country’s first HIV reference laboratory, which facilitated the roll-out of MASA, as well as the establishment of a state-of-the-art facility for treating children with HIV, the Botswana-Baylor Children’s Centre of Excellence. The national AIDS and STD Unit took the lead in engaging with intergovernmental, district, and local stakeholders to develop a proposal for Bobonong based on the STF model and adapted to the local context.
STF consultation with the government led to an appropriate sharing of roles and responsibilities between the public and private partners as follows:

- The Ministry of Health and the Ministry of Local Government provided ARVs and related drugs, supervised institutional coordination, and ensured that the monitoring and evaluation system met the national ARV guidelines. Focal persons were appointed by the two respective ministries to work closely with fund manager KPMG and the project team.

- Bobonong Primary Hospital (BPH), representing the MOH, provided ARVs, laboratory and radiology services, social work services, and dietetic services, and conducted operational research associated with the project. BPH, the only hospital in Bobonong and one of only two in the subdistrict, also housed the Project Secretariat and served as chair for the Project Management Committee.

- Borotsi Clinic, representing the Ministry of Local Government, also located in Bobonong, conducted community outreach activities, screened and referred patients to the hospital, provided psychosocial support and patient follow-up, and participated in the operational research of patients who did not require treatment after an HIV-positive diagnosis (based on a CD4 lymphocyte count above 200 cells/mm³ without any AIDS-defining illnesses).

- The District Health Team, under the guidance of the Ministry of Local Government, oversaw community outreach and education on all public-health programs and also served on the Project Management Committee.

- Bobonong Community Home-Based Care Society (BHBCS), representing community-based organizations, community mobilization and counseling, peer education and patient follow-up, income-generating activities, home-based care, psychosocial support, and food security services. The 70-member organization, formed in 1996, began with only 12 volunteers and is viewed as one of the best community-based organizations in southern Africa.

- KPMG Management Services, a private organization, is a fund management company that oversaw project activities using rigorous financial controls. KPMG was required to sign off on any expenses over 3,000 pula (approximately US$430 in 2006). According to John Botsewelelo, project manager, “We wanted to be certain that the funds were being used for their intended purpose.”

- STF helped build the institutional capacity of the project by funding new facilities, equipment, and staff; conducting recruitment and training, and providing technical assistance. The core competencies of BMS were leveraged in order to build capacity in governance, project management, financial management, Good Clinical Practice (code of conduct underlying research involving human subjects), and monitoring and evaluation.
The existing national HIV/AIDS response structure was built into the CBTS program in the subdistrict, including voluntary counseling and testing (VCT), prevention of mother-to-child transmission, and orphan care services. The program was further aligned with the country’s National Strategic Framework for HIV/AIDS (2003-2009) that sought to increase access to care and support services by 50%, and usage of HIV/AIDS treatment and support services by 25%, by 2009.

In December 2003, the MOH signed a memorandum of understanding with BMS concerning the sustainability of the Bobirwa subdistrict ARV project. In essence, the ministry agreed to assume responsibility for the continuation of the program beyond the three years of funding provided by STF. As of January 2007, the government of Botswana has respected this clause of the agreement. This is a testimony to the strength of the partnership, a strength imparted by mutual respect and trust between the government and STF.

Engaging with local community-based organizations was relatively simple in Bobonong compared to some of the other STF CBTS sites, because of the strength of the partnering nongovernmental organization, the BHBCS. This group had established a solid home-based care practice in the subdistrict and was already providing services to a large number of clients. This was good for STF, but it was also good for the BHBCS, since it meant an infusion of funds, resources, and training. The partnership also resulted in the construction of new facilities to house BHBCS offices, providing space for activities such as staff training, patient support groups, and income-generating activities.

Strengthening Partnerships through Leadership and Management

The management structure that was developed (Figure 4) gave considerable responsibility to the project manager, who had direct authority over the implementing team and administrative authority (i.e., the District Health Team and the medical team at BPH). STF encouraged this structure and understood the advantage of identifying a strong project manager from the early stages of planning. After six months of searching, an exceptional project manager was recruited who galvanized the team and brought the project to a level of performance ultimately recognized by an award from STF.

The structure reflects some key principles underlying the CBTS model: partnership, linkage, and interdependency between the various stakeholders.

Partner Adaptation of the Model

The partnership model is by nature generic and its adaptation to the local context is required. This process was simplified in Bobonong by the fact that the community component was entrusted to one organization, the BHBCS. Nonetheless, in addition to the HIV clinic established at BPH, the Borotsi Clinic and other satellite clinics in Mathathane, Semolale, and Tsetsebjwe would also provide services. As STF discovered for all the CBTS programs, the elaboration of a detailed patient flow is the starting point from which the program design should be developed. In keeping with the philosophy of partnership, this patient flow (Figure 5) was determined at a workshop attended by stakeholders from clinical, community, and government sectors.

The strong partnership with government, at both the MOH and district health levels, allowed for an approach that enabled satellite clinics to provide VCT, ongoing care of patients not yet requiring ARVs, and referral of more advanced cases to higher-level facilities. The relative advantages and disadvantages of decentralized service provision at different levels of health facilities are outlined in Table 1. It is important to note that regardless of whether a decentralized or centralized approach is chosen, the system and the patient flow only
Figure 4. The Bobirwa ARV project management structure
of the HIV clinic at BPH, “People in our community have a strong belief in traditional healers. You cannot overlook them. We therefore needed to train them on HIV/AIDS issues.” While recognizing that he and other traditional healers take a very different approach to HIV/AIDS than the health professionals at BPH and BHBCS, Ngwako Nkawana, a member of the traditional healer group Botswana Dingaka Association, said he was viewed as a member of the team from the outset: “Here people are appreciative of traditional healers and I have worked well with others in the program.”

In this way, partnerships between public, private, and community sectors were clarified during the adaptation process. Once this step was completed, capacity building was needed before service delivery could begin.

**Training and Capacity Building**

Bringing diverse organizations together as implementing partners requires capacity building for clinical staff, private physicians and/or traditional healers, and community organizations, both prior to the launch and throughout the program’s function well if the community members and community organizations are involved.

The community partner, BHBCS, decided that community education, mobilization, care, and support activities (including home-based care, psychosocial support, food security, and income-generating activities) should be developed. The patient flow diagram (Figure 5) indicates how referrals can occur from the clinic to the community and vice versa. Thus a patient could, for example, be referred from the clinic to BHBCS to receive home-based care and food security services. The same patient might be referred back to the clinic by a community health worker who finds that the patient has developed side effects to ART. In the event that the patient does not turn up for a scheduled clinic visit, the community health worker is alerted to go and trace the patient rapidly to avoid treatment interruption. This technique was instrumental in maintaining a very low treatment default rate of 5.2% in STF-sponsored CBTS programs.

The project leaders also recognized early on the importance of partnering with traditional healers in the surrounding area. According to Dr. Kabengele of the HIV clinic at BPH, “People in our community have a strong belief in traditional healers. You cannot overlook them. We therefore needed to train them on HIV/AIDS issues.” While recognizing that he and other traditional healers take a very different approach to HIV/AIDS than the health professionals at BPH and BHBCS, Ngwako Nkawana, a member of the traditional healer group Botswana Dingaka Association, said he was viewed as a member of the team from the outset: “Here people are appreciative of traditional healers and I have worked well with others in the program.”

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**Table 1: Advantages and Disadvantages of Various Facility Types**

<table>
<thead>
<tr>
<th>Type of facility</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>District hospital</td>
<td>Can be dedicated solely to HIV/AIDS or jointly provide HIV/AIDS and other needed services (e.g., TB treatment, sexually transmitted infection treatment, family planning) Often located close to other critical hospital services, including inpatient care, surgical care, pharmacy, and laboratory services</td>
<td>Can put patient at a greater risk of stigma, as he or she may be identified as being HIV-positive by observers Depending on geography, patients may have to travel long distances to site</td>
</tr>
<tr>
<td>General outpatient department</td>
<td>Normalizes HIV and thus can reduce associated stigma</td>
<td>Services not focused on HIV, personnel not specialized to treat people living with HIV</td>
</tr>
<tr>
<td>Primary health clinic linked to district hospital</td>
<td>Generally closer to patients’ homes, which minimizes transport challenges</td>
<td>Less comprehensive and specialized care</td>
</tr>
</tbody>
</table>

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Figure 5. Patient flow in the Bobirwa ARV Project

HBC = home-based care; PLHIV = people living with HIV; TCM = total community mobilizers

Notes
1. Tebelopele (voluntary testing centers) are using the rapid test method. Government policy currently uses the ELISA method as a confirmatory test. The current directive of ELISA test (as confirmatory) is being reviewed by the government.
2. (a) Most people in the home-based-care program know their status.
   (b) TCM—total community mobilizers tend to refer patients to the hospital with unknown status.
   (c) PLHIV—most of these patients are self-referred and know their status.
   (d) Referrals from community clinics tend to be patients who know or don’t know their status.
   (e) Orphans tend to have unknown status.
operation. In communities where ARVs have not previously been available, as was the case in Bobonong, training on many aspects of therapy and follow-up care is essential.

Training was coordinated by STF and provided to all partners according to their needs. It included HIV/AIDS education for all groups; training in governance, project management, and financial management for the program leaders; Good Clinical Practice for research-associated staff; and monitoring and evaluation for most staff. In keeping with the MOH mentorship program, the Children’s Centre of Excellence in Gaborone (also funded by STF) provided ongoing clinical training on general HIV care and treatment with teams from the center visiting Bobonong on a monthly basis over a period of six months.

Capacity can also be enhanced by upgrading physical facilities. The partnership resulted in the creation of a new HIV clinic at the hospital, a dedicated HIV care facility at the Borotsi Clinic, and a new facility for the BHBCS. In addition, the full cadre of implementers was educated about the CBTS model so that they became acquainted with the principles of the program. This helped keep them motivated, as they were able to understand how their individual contributions fit within the broader continuum of patient care.

Service Delivery

The objectives of service delivery were defined as follows:

- To build and strengthen the institutional capacity of program partners for effective implementation of ART
- To mobilize, educate, and sensitize the community in general, and people living with HIV in particular, on ARVs and HIV/AIDS
- To provide ART at the project site, and improve accessibility, availability, and effective utilization of ARV services
- To improve food security at both the household and community levels
- To monitor and evaluate the implementation and impact of the project

The best way to demonstrate the effectiveness of service delivery is to show results. Monitoring and evaluating the program’s progress is important to ensure that patients are receiving the services they need and program outcome goals are being achieved. With assistance from Family Health International (FHI), which was contracted by STF, the stakeholders established a monitoring and evaluation framework, data collection tools, and indicators, and trained personnel on data collection methods. This framework focused on the community component of the program, especially the link between community indicators and clinical outcomes. Clinical data were collected at BPH and the satellite clinics according to national requirements and according to an operational research protocol designed by STF.

Program Outcomes

In September 2006, the experience and data from Bobonong that had been collected since the beginning of 2004 were combined with those of the three other CBTS sites in southern Africa (Namibia, Lesotho, and South Africa). Overall, the results demonstrated the effectiveness of the CBTS model. Highlights of these results are as follows:

- Overall, the uptake of VCT increased approximately tenfold within two to three months from the start of community mobilization. By November 2006, more than 16,000 patients had been enrolled in CBTS sites in southern Africa. In Bobonong, over 3,500 had been enrolled by this date and of these, more than 1,500 were on ARVs—three times the number that had been forecast.
- An intent-to-treat analysis from the first 941 patients on ART for 12 months at the four sites...
Another dramatic effect of the program relates to the job description of home-based care workers themselves. “When we began, home-based care was associated with people who were about to die,” said Nkhori, secretary of BHBCS. “That has changed dramatically. Many of our clients are not even bedridden now. Our volunteers do not visit the clients as often as they did before. In fact, some clients no longer need home-based care. They have gone back to work now and care for their own children.”

Noted Dr. Wanless, former medical director of STF, “I recall when I first visited Bobonong, I met this team of very dedicated ladies who walked from homestead to homestead, caring for the dying. And frankly and understandably, they were depressed. Two years later, they were transformed and reinvigorated, now looking after people getting well and helping them to live full lives again.”

There is further dramatic evidence of the program’s impact in the decline in the HIV/AIDS bed occupancy rate at BPH—from 93% in 2003 to 52% in 2005; during the same period, the HIV/AIDS mortality rate at the hospital dropped from 23% to 13%. This impressive outcome could be demonstrated because of the fact that all patients within the BPH catchment population (which comprised approximately 20,000 people) could only be referred to this hospital since no other facilities were in existence.

Challenges and Lessons Learned

With regard to partnership, the CBTS program experience, and that of Bobonong in particular, demonstrates the following:

• Governments can be engaged if the program model aligns with national policies and addresses critical challenges.

• A strong project manager trained in project management should be identified early in the planning stage and that person should be given adequate authority to coordinate the activities.
Key reasons for the success of the Bobonong CBTS program include the following:

- Strong and methodically nurtured partnerships with government, public, private, and community sectors.
- A strong project manager who placed equal emphasis on the roles of all partners and worked tirelessly to develop a high-performance team, whose motto could be described as “seamless partnership.”
- The implementation of community support services to extend the support provided to patients into their communities. This was complemented by strong and clear linkages and referral systems between the clinic and community partners.

of all partners. Then a management structure needs to be established with clear roles, responsibilities, and reporting relationships developed through collaborative and transparent workshops. The structure should place equal importance on the roles of all partners.

- The configuration of clinical services must match the partners involved and the geography of the targeted patient population. A clear patient flow and referral points need to be defined. Once the patient flow is defined, everything else will fall into place and the roles of the various partners will be further clarified.
- Training partners will make them better able to execute the plan and fulfill their part of the partnership.
DIVING IN: THE EARLIEST DAYS OF THE BRISTOL-MYERS SQUIBB SECURE THE FUTURE PROGRAM

Responding to HIV/AIDS on a scale commensurate with the epidemic is a global imperative. The task has barely begun, but at least we are at the end of the beginning, with the needs recognized together with the proven elements of an effective response.

—Peter Piot et al

WITH THE REAUTHORIZATION of the President’s Emergency Plan for AIDS Relief (PEPFAR) by the United States Congress in April of 2008 at US$50 billion over five years and the Global Fund to Fight AIDS, Tuberculosis and Malaria having attracted $4.7 billion in financing through 2008, it is difficult to remember a time not that long ago when both the public and private sectors of the global community were not receiving significant financial resources to address the HIV/AIDS crisis in Africa. Yet large initiatives such as PEPFAR and the Global Fund did not in fact lead the way. Rather, it was nimble private philanthropic efforts, such as those led by Bristol-Myers Squibb (BMS) and others, that were the first to devote significant financial resources to international HIV/AIDS efforts.

By 1999, the AIDS pandemic had reached alarming proportions, and its impact was being experienced most severely by people living in sub-Saharan Africa. At that time, 16 million people had died of AIDS, 25.3 million were living with HIV, and 10 million children had become AIDS orphans in the region since the beginning of the pandemic. Yet in 1999 the global community was just beginning to wake up to the speed and scope of HIV transmission worldwide, the disparity between the treated and untreated, and the urgent need to begin taking action. The challenge was to adequately resource and coordinate these efforts while simultaneously addressing the social issues that fuel the spread of the disease.

As a global company and leading developer and manufacturer of antiretroviral treatments, BMS was acutely aware of the impact of the AIDS pandemic around the world. The company had been involved in the field of HIV medicine since 1985 when the virus was first discovered and efforts to develop treatments began. From that point on, HIV became a constant focus of the company. Ongoing interaction with researchers, clinicians, advocates, policymakers, people living with HIV, and the company’s own African business strengthened the understanding among senior management that the creation of a dedicated philanthropic program was the necessary, responsible, and right thing to do.

The company also recognized that philanthropy could provide an opportunity for leadership. BMS could combine its knowledge of HIV/AIDS with its independent and flexible philanthropic resources and be one of the first to step forward and seriously address a complex social issue. In so doing, corporate philanthropy would help take the risks that individual governments and multilateral organizations could not, would not, or were slow in undertaking. Encouragement to act
boldly came from the secretary general of the United Nations, Kofi Annan, who personally approached the company’s CEO and asked BMS to take a leadership role in helping to fight the pandemic in Africa and to do so in an unprecedented way.

In May of 1999, BMS and the BMS Foundation (BMSF) announced a groundbreaking five-year US$100 million initiative called Secure the Future: Care and Support for Women and Children Affected by HIV/AIDS (STF). STF was the first major corporate philanthropic program to target the AIDS pandemic in Africa. The goal of the initiative was to identify and support innovative, cost-effective, sustainable, and replicable models to manage the impact of HIV/AIDS in resource-limited settings. Initially, the program focused on the five countries in southern Africa that had been hardest hit by the pandemic—Botswana, Lesotho, Namibia, South Africa, and Swaziland. In 2001, an additional commitment of US$15 million allowed the program to expand to four low-prevalence countries in West Africa—Mali, Côte d’Ivoire, Senegal, and Burkina Faso—and further commitments have enabled expansions to Uganda, Malawi, and Tanzania. To date, BMS has committed US$150 million under STF, which has been operating for nearly 10 years.

It is important to view the initial as well as subsequent financial commitments from BMS in the context of the limited public and private sector funds being targeted for HIV efforts in Africa in the late 1990s and the early 2000s. In 1998, international assistance funds made available for HIV/AIDS totaled $300 million. In July of 1999—two months after the announcement of STF—United States Agency for International Development (USAID) announced the Leadership Investment in Fighting an Epidemic (LIFE) initiative, which committed US$100 million to support projects in 13 focus countries. In September of 2000, the World Bank launched the Multicountry HIV/AIDS Program for Africa with commitments of US$500 million for a two-year phase of immediate funding and US$500 million for the second phase commencing in 2002. As late as 2001, BMS was contributing more than some of the 22 wealthy donor countries of Europe’s Development Assistance Committee. As for private foundations, according to Funders Concerned About AIDS, in 1998, only US$7.3 million in grants—largely from the Bill & Melinda Gates Foundation—had been made by U.S.-based foundations to support AIDS programs outside the United States. Though the US$150 million contributed by BMS pale in comparison to the US$10 billion that economists have estimated is needed annually to reverse infection trends and treat the millions living with HIV, it was an unprecedented sum for a company like BMS and perhaps made even more significant by the fact that it came from a pharmaceutical company that was also in the throes of developing the proper business response to the pandemic.

The creation of STF helped to propel the medicines business to make certain that its contributions to defeat the AIDS pandemic were reflected in its business practices as well. For example, in May 2000, on the first anniversary of the establishment of STF, the company became a founding member of a new initiative by the United Nations and the research-based pharmaceutical industry to speed access to treatment. The Accelerating Access Initiative
LEADERSHIP AND PARTNERSHIPS

(AAI) is a collaborative program with nine research-based pharmaceutical companies, as well as UNAIDS, and four other United Nations agencies and governments, to facilitate the availability of antiretroviral medicines in countries that have clearly developed national AIDS strategies. The initiative helped lead to the availability of BMS HIV medications at significantly reduced pricing. In addition, by March of 2001, the company announced that it would make its two HIV medicines, Videx and Zerit, available in sub-Saharan Africa at even lower prices. At the same time, BMS announced that it would ensure that its patents did not prevent access to inexpensive HIV/AIDS therapies in sub-Saharan Africa. Through the years, other significant business actions would follow, including an agreement to help ensure sustainable access to treatment for millions of HIV-positive individuals in sub-Saharan Africa and India through a technology transfer of BMS’s newest antiretroviral, atazanavir, to two generic-drug companies, Aspen and Emcure.
REFERENCE LIST


REV. GIDEON BYAMUGISHA IN FRONT OF HIS CHURCH IN UGANDA
When Rev. Canon Gideon Byamugisha, the prominent HIV-positive Anglican priest from Uganda, was two years old, he became very ill with smallpox. His family lived in a village in southwest Uganda, and the nearest doctor was 30 miles away on an island in Lake Bunyonyi. His mother carried him all the way to the lakeshore and found a girl with a canoe to take them to the doctor.

On the way, the boy wiggled free from his mother’s arms and fell into the water. Unable to swim, the mother feared she had lost him. But the boy emerged, and she fished him out. Unfortunately, his struggle to regain his health was less successful. The doctor gave him numerous injections for smallpox but none appeared to work, and his mother returned to her village, virtually hopeless.

written by John Donnelly
photographs by Dominic Chavez
For days, the boy’s family prayed for his life. Then his grandmother told everyone an angel had appeared during her prayers, informing her that the boy would live and grow up to be a church leader like his father.

“That’s how I survived,” Byamugisha said in his home in the hills outside Kampala.

That’s also how he received his last name, which means “blessing.” His life, in turn, has been a blessing to those fighting against HIV and AIDS. The first of 14 children, Byamugisha has emerged as one of the forceful and innovative actors in Africa’s response, especially among church leaders and those living with the virus.

In 1992, he became the first religious leader in Africa to declare publicly he was HIV-positive. He first told his fellow priests and students, then his family, and finally the world in a speech at an AIDS conference in Kampala. In 1998, the virus had turned into full-blown AIDS, and a few years later a doctor gave him six months to live. But a woman from California who had gotten to know him paid for his antiretroviral treatment, which then cost thousands of dollars per year, and he lived. “That saved me,” Byamugisha said.

He went on to start the African Network of Religious Leaders Living with or Personally Affected by HIV & AIDS, as well as the Friends of the Canon Gideon Foundation, which supports orphans and other vulnerable children with vocational and professional training.

But none of this has been easy. Byamugisha, 48, has faced one trial after the other, starting when his sister-in-law, Eunice Mari, told him that his wife, Kellen, had been HIV-positive when she died in 1991; they had two children together, but only one survived. He has since remarried, and he and his second wife, Pamela, who is also HIV-positive and widowed, have two children. They also take care of many orphans.

“Don’t feel helpless about HIV. AIDS is vulnerable to supportive community and people are willing to talk about it. “
Q: What was your reaction to the news your first wife was HIV-positive?
“It was like a bombshell. I entered a kind of panic. I said, ‘You mean since my wife died of AIDS, I could also be positive? Me? A pastor, a born-again Christian?’ They had told us this was a disease of prostitutes.”

Q: How did you deal with your shock?
“My sister-in-law said something that changed my life. ‘Go for a test,’ she said. ‘And let me assure you of the love for you in our family.’ It was a statement that dried my tears. The eldest daughter of my wife’s family was not judging me, and instead assuring me of unconditional love. Sometimes, I look back and think without Eunice, I would be dead.”

Q: Once you learned you had HIV, how did you decide to make it public?
“I struggled. Should I talk or should I keep quiet? But on my mind was that if I kept quiet, I would be living a double life. It started with going to Eunice. She embraced me. She cried with me. She prayed for me. I went to the principal of the [Episcopal Theological] college. He was shocked. He told me he would do everything possible to help me, but I should not tell anyone about it. I told him blankly that I would not follow that advice. I went before my fellow brothers at the college, in a staff room, while we were having tea. I said to them, ‘Brothers, I want to tell you I’ve been to have an HIV test and I am positive.’ A hush fell on the staff room. Some patted me on the shoulder. No one said a bad word.”

Q: What are some of the lessons you’ve learned about AIDS since you began speaking out?
“There are two pieces of good news about AIDS. One is that HIV is 100% preventable. We have knowledge, skills, and resources to make it happen. The second message is don’t feel helpless about HIV. AIDS is vulnerable to information, vulnerable to places where you have a supportive community and people are willing to talk about it and help each other.”

Q: What challenges do you see in the next five years?
“I see two challenges. One is that the world may get so used to HIV and stop trying. People may say, ‘Well, AIDS is one of many problems.’ If we don’t keep up our advocacy, it could become like any other disease and the world would be willing to tolerate it. The second challenge is that we’re now getting a whole new generation that wasn’t exposed to what we know about HIV. So we can never stop teaching the basics. I hear all the time, ‘Excuse me, tell us where AIDS comes from.’”

Q: What gives you hope about meeting these challenges?
“The group that is walking with AIDS, sleeping with AIDS, they will not get tired. They are not going to keep quiet. We need to get to them, train them, empower them. They are our future saviors.”
WITH THE SIGNIFICANT RECENT EXPANSION of HIV/AIDS care programs in resource-limited settings, we may cautiously say that we are reaching “the end of the beginning” of the global AIDS pandemic. While infection rates have not yet decreased in many locations and populations, the ever-widening impact of treatment and prevention efforts is a sign that the relentless expansion that marked the beginning of the epidemic is slowing in many settings around the globe. The long “middle stage” of the epidemic and the urgent need to further expand our response now looms ahead, especially without the prospect of an HIV vaccine on the immediate horizon.

Over the last 25 years, millions of lives have been taken, but with each life lost, the flame of dedication that burns in our hearts has grown more intense. Experience has taught us that long-term success is realized not by building programs in a vertical or isolated fashion, but rather by strengthening national health care systems through our efforts and fostering greater linkages with the communities they serve. The health of the community is tantamount to the health of individuals, and we must continue to do everything in our power to support communities in overcoming the challenges arising from the devastating combination of poverty and infectious diseases like HIV.

Looking forward to the next 25 years, many challenges lay ahead. The tools we have at our disposal to address these challenges, however, will grow ever more effective and accessible. Each one of us must learn how to use these tools ethically and responsibly, and always with the aim of improving the health and well-being of all those in need. We also must ensure that progress is never limited by borders and institutions. Together we can work toward greater collaboration and partnership in all that we do. Our strength is in our numbers and our willingness to work together.

Finally, we would like to close these three volumes with one wish: that each of us routinely steps aside from our daily activities to acknowledge and learn from the work of our colleagues, whether they are well-known or unsung heroes. In so doing, we will be personally enriched and reenergized, and the quality of our work greatly improved. This is but one of the many lessons that From the Ground Up has taught us.

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476  FROM THE GROUND UP: DEVELOPING PATHWAYS AND PARTNERSHIPS
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“This photo symbolizes the union between African children in the struggle against HIV and AIDS.”

About the Artist
Aires is a presenter on the Mozambican Television children’s program “Roda Viva” (Live Wheel). He has been participating in children’s television since 2000. “Roda Viva” has given him the opportunity to travel across Mozambique learning about the experience and realities of Mozambican children. The most memorable event he covered was the launch of the campaign “Unite for Children. Unite Against AIDS”. More than 4,000 children participated in the launch. The Mozambican head of state, his wife, ministers and other government officials attended the event and he was able to meet them afterwards.