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The PIH Guide to the
Community-Based Treatment of HIV in Resource-Poor Settings

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Revised Second Edition • 2008



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Partners In Health

Program in Infectious Disease and Social Change
Harvard Medical School

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Brigham and Women’s Hospital

François-Xavier Bagnoud Center for Health and Human Rights
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About the cover

Margarette Guerrier has been an *accompagnateur* at Zanmi Lasante in Haiti for the past 18 years. Every day she delivers medications for HIV and TB to patients in her community. Margarette is their link to the clinic and their advisor, confidante, and friend. She helps people take their medicine, comforts those who are in pain, and brings reports of their medical status back to the nurses and doctors at the clinic. Thanks to Margarette and other *accompagnateurs* like her, thousands of patients are now receiving comprehensive, community-based care through Partners In Health projects. Margarette was chosen in 2005 to represent her community at the People's Health Assembly in Ecuador, where she delivered a keynote speech on the right to health care.

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This book is dedicated to the memory of Jean Gabriel fils, who died on May 28, 2006 at the age of 35 in Central Haiti, where he had lived all his life. Known widely and affectionately as “Ti Jean,” he had been our friend and colleague since Zanmi Lasante’s earliest days. As director of Zanmi Lasante’s Program on Social and Economic Rights, Ti Jean laid the foundations for hundreds of new homes for patients and others living in destitution. He also used the struggle for AIDS treatment and health care as a national and international platform from which to call for social justice and human dignity for all. We hope to carry on the work on his behalf.

Notice

This guide is intended to be a resource for physicians and other health care professionals who provide care and treatment to patients with HIV who live in resource-poor settings. Every possible effort has been made to ensure that the material presented herein is accurate, reliable, and in accord with current standards. However, as new research and experience expand our knowledge, recommendations for care and treatment will change. It is therefore the responsibility of the individual physician or other health care professional to use his/her best medical judgment in determining appropriate patient care and treatment.

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Foreword

An estimated 90 percent of the 40 million people living with HIV infection reside in countries that possess less than 10 percent of the world's assets. *The PIH Guide to the Community-Based Treatment of HIV in Resource-Poor Settings* is a comprehensive text for HIV care delivery in these very areas.

This is a really good book. The authors have considerable experience with both AIDS treatment and the delivery of general health care in resource-limited settings—and their experience shows. The guide covers the totality of HIV care, including voluntary counseling and testing (VCT); HIV prevention; antiretroviral therapy (ART); and diagnosis and treatment of opportunistic and other related infections, with particular emphasis on tuberculosis (TB) co-infection and sexually transmitted infections (STIs). Information is presented in a practical fashion, making it useful in diverse settings. Thus, recommendations for initiating and changing HIV therapy are made for settings ranging from those in which laboratory testing is limited, to those where a total lymphocyte count can be obtained, to those with access to viral load analysis. A section on data management is also included. The guidelines for HIV treatment are—appropriately—based largely on World Health Organization (WHO) guidelines; recommendations for treating opportunistic infections (OIs) and other complications of HIV infection make use of drugs and diagnostics available in those areas of the world where the guide is intended for use.

The format used is textual; a substantial list of references is provided with each chapter to support recommendations. Most importantly, many algorithms (protocols) that care providers will find extremely useful have also been included. I found these algorithms to be logical, easy to follow, and reflective of best practices.

This book is largely based on the authors' experience in Haiti; however, the challenges they faced and the lessons they learned can easily be extrapolated to other settings. Obviously, settings exist where local practices and disease patterns will require different approaches. Nevertheless, most of this guide is likely to be an important companion for those providing care to persons with HIV/AIDS in resource-poor settings.

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Preface and Acknowledgments

Why Another AIDS Handbook?

In the 25 years since the discovery of AIDS, there has been remarkable progress in our understanding of human immunodeficiency virus (HIV), the treatment of opportunistic infections, and the development of effective therapy with antiretroviral drugs. The advent of highly active antiretroviral therapy (HAART, now called ART) has caused AIDS mortality to plunge sharply in industrialized countries. Yet AIDS remains the world's leading infectious cause of adult death, and most people with HIV live and die in developing countries without ever benefiting from these scientific achievements.

A decade has passed since the XI International Conference on AIDS, held in Vancouver in 1996, entitled "One World, One Hope." At that time, delegates from the world's poorest and most heavily HIV-burdened nations found the title to be somewhere between willfully naïve and dismissive of the obvious inequalities connected to both the risk of acquiring HIV and subsequent access to diagnosis, care, and effective treatment. Many predicted that costly combination ART would not be made available to the poor.

Unfortunately, these fears proved prescient: resource-poor settings were, until recently, overlooked entirely in terms of effective treatment. In 2001, fully five years after the discovery of ART, the United Nations General Assembly Special Session on AIDS (UNGASS) finally called on donor nations for large-scale investments to make treatment available to the millions of HIV-positive people in the developing world. Since that time, new sources of multilateral and bilateral funding have committed billions of dollars to AIDS care and treatment for the sickest and neediest patients. These sources include the Global Fund to Fight AIDS, Tuberculosis and Malaria; the World Bank's Multicountry AIDS Program (MAP); and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). As these initiatives

were launched, however, clinical and operational experience in providing AIDS treatment in resource-poor settings remained extremely limited.

In Haiti, one of the world's poorest countries, Partners In Health (PIH), working with its Haitian affiliate Zanmi Lasante (ZL), has been providing ART to patients with advanced AIDS since 1998. This guide represents the experience of a team of community health workers, nurses, doctors, laboratory technicians, pharmacists, social workers, and others who developed and implemented an integrated HIV prevention and care project in rural Haiti: the HIV Equity Initiative. This is the third handbook written and field-tested by a group of health care providers affiliated with PIH and its collaborators, which include non-governmental organizations (NGOs) in Peru, Russia, Mexico, Guatemala, Rwanda, and inner-city Boston, as well as Harvard Medical School, the Harvard School of Public Health, and the Brigham and Women's Hospital in Boston, Massachusetts.

The PIH Guide to the Community-Based Treatment of HIV in Resource-Poor Settings is meant to complement existing resources by addressing the special circumstances encountered by practitioners working in impoverished settings. Because not enough AIDS specialists exist to care for the massive numbers of people living with HIV, this guide is written to help general medical practitioners—including family practitioners, internists, pediatricians, and nurses—manage HIV without the heavy reliance on diagnostic tests that guide care in the United States and in Europe. Most of all, we hope this guide will help make high-quality AIDS care possible in resource-poor settings. We argue that introducing excellent AIDS care in such settings will not only save lives but also enhance HIV prevention efforts, revive flagging morale, and advance primary health care goals.

Responding to Poverty and Infectious Disease: Three Lessons from Tuberculosis

Among the experiences that guide our philosophy on HIV care in resource-poor settings are three lessons learned in responding to another chronic infectious disease that disproportionately afflicts the poor: tuberculosis. The first of these lessons is the integration of prevention and treatment activities. In the post-antibiotic era, the prevention of TB is no longer based on sequestering people in sanatoria for years to prevent the spread of the disease. Rather, prevention of TB transmission is based on prompt diagnosis and effective treatment, because an effectively treated patient is a noninfectious one.¹ In rural Haiti, we quickly discovered that improving HIV care helped destigmatize what had been considered a fatal and “untreatable” disease. Since the introduction of ART to central Haiti, we have seen an enormous increase in demand for voluntary counseling and testing. Many studies have shown that knowing one's HIV status enhances the ability to adopt targeted prevention strategies, from both individual and programmatic perspectives. Furthermore, it is not unreasonable to argue that patients with undetectable viral loads—that is, effectively treated patients—are less infectious.^{2,3}

A second lesson learned from our experience with TB concerns the delivery of care. Across the globe, the most successful TB outcomes are seen when patients are offered community-based care.⁴ 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 a different disease, delivering ART for AIDS.

Accompagnateurs serve as the vital link between the village and the clinic, administering therapy and ensuring adherence. They identify persons who are ill but have not yet been evaluated, and they alert clinic staff to complications in patients already

receiving therapy. Moreover, 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 our patients face. Although this approach was pioneered in rural Haiti,⁵ the *accompagnateur* model has been successfully exported by PIH to slums in Peru⁶ and communities in Tomsk, Siberia⁷ for the treatment of multidrug-resistant tuberculosis (MDR TB); to inner-city Boston⁸; and, most recently, to rural Africa for AIDS therapy. Our own experience across these different sites permits us to argue that this model may be adapted to work effectively in diverse settings.

Third, and perhaps most significantly, AIDS prevention-and-care should be seen as a public good.⁹ Tuberculosis again serves as a paradigm: an airborne disease, it has long been considered a public-health issue. Worldwide, the diagnosis and treatment of TB is normally government-funded and free of charge to all who need it. AIDS prevention and treatment should similarly be considered a public good. Although many of the countries most burdened by AIDS do not have the capacity to confront this pandemic with public funds, the answer in these instances is not to further privatize the health system, or to relegate service provision to NGOs. Instead, new resources should be used to strengthen public health systems, not to set up parallel structures.¹⁰ NGOs and outside agencies are invaluable in providing technical assistance and resources, but they should not be the end users of new monies available to fight HIV. Transfers of wealth, knowledge, and technology from the private to the public sector, and from donor countries to those most heavily burdened with illness, are not only possible but necessary if we are to break the cycle of poverty and disease.

The Way Forward in Resource-Poor Settings: How to Use This Book

The HIV Equity Initiative—the program in central Haiti from which this book draws its lessons—is described in detail in

Chapter 1. We believe that community-based AIDS prevention-and-care that is integrated with public sector-based primary care is the best possible way to tackle the AIDS epidemic worldwide. In arguing that ours is a model that can be replicated elsewhere, we assume that any model will need substantial adaptation to any given local setting. To this end, we have developed algorithms that do not depend on sophisticated laboratory tests. The bulk of the protocols presented here have been developed in the absence of tools and diagnostic data such as flow cytometry, viral load, bacterial culture, special stains, or even basic pathology. Clinical algorithms alone can guide concerned clinicians in identifying many of those patients with AIDS who are in urgent need of ART or, when a definitive diagnosis is not yet available, treatment of opportunistic infections.

With a modicum of assistance, integrating HIV care with primary health services can be accomplished through what we call the “four pillars”: VCT and HIV treatment that is integrated with (1) primary health care, (2) tuberculosis treatment, (3) women’s health services, and (4) treatment of sexually transmitted infections. Indeed, our own experience leads us to believe that each of these pillars is a necessary component of any effective AIDS prevention-and-care program. Just as AIDS prevention is hampered by a lack of AIDS care, so too will attempts to offer HIV care fail if the leading opportunistic infection—tuberculosis—does not figure in the minds of those designing interventions. Similarly, a prenatal care program that offers only VCT and prevention of mother-to-child transmission (PMTCT) but is not able to treat mothers with advanced HIV disease nor to provide basic prenatal care to women, regardless of whether or not they are HIV-positive, will soon find itself attending to many orphans. These orphans will include both those whose mothers died of HIV—and who thus may be HIV-positive themselves—and those whose HIV-negative mothers died of preventable obstetric complications. Lastly, as HIV is an STI in much of the world, and because

any untreated STI can enhance the transmission of HIV,^{11,12} it is critical to design AIDS programs that are prepared to diagnose, treat, and prevent all STIs.

In undertaking complex health interventions in poor settings, deeply rooted social and economic inequities are inevitably brought to the fore. Partners In Health and its sister organizations have taken on diseases such as AIDS and MDR TB to move the public health paradigm beyond simplistic prevention strategies and instead acknowledge and address the complex realities reflected in epidemic disease. Adjuvant social services are an important aspect of care delivery in areas beset with hunger, unemployment, and lack of access to education. In our experience, such services have been critical in reinforcing prevention efforts, assuring adherence, and promoting overall well-being; however, supplying families with food and other social services has engendered sharp rebuke from those who say that such a comprehensive approach is not sustainable. That debate is not occurring within poor communities, which see the promotion of social and economic rights as long overdue. The inability of poor countries to sustain health and development interventions without continued donor financing has long been used as an indicator of the failure of such programs, rather than of the failure of the strategy of “sustainable” development itself. Given the national budgets of the world’s poorest countries, scarcely a single intervention can be maintained without ongoing donor funding. Indeed, donor funding for extensive and ongoing social programs for the most vulnerable *must* be sustained to alleviate poverty and suffering. Such funding cannot be in the form of loans, but rather must comprise grants and technical assistance that acknowledge that the crushing weight of poverty cannot be lifted by market forces alone.

Acknowledgments and a Closing Challenge

We cannot individually thank all those who helped prepare this handbook—that list would be long, and they already know our deep gratitude. We would, however, like to thank the many

organizations that worked together to launch community-based AIDS prevention and care in Haiti—in particular, the Haitian Ministry of Health and Le Groupe Haïtien d’Étude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO), which have been engaged in the struggle against AIDS from the very beginning. We look forward to many more decades of work together. Our newest partners—the Rwandan Ministry of Health, especially Drs. Agnes Binagwaho and Innocent Nyaruhirira, and Ira Magaziner and Beth Collins at the Clinton Foundation HIV/AIDS Initiative—have helped to launch Inshuti Mu Buzima (IMB, PIH’s project in Rwanda) and given us much insight into the relevance and value of the Haiti experience in Africa.

We owe our deepest thanks to Tom White, friend and benefactor of Partners In Health for the past two decades. The philanthropic leadership of Al and Diane Kaneb has enabled the launch of Inshuti Mu Buzima and many other initiatives. PIH’s Boston-based staff provides the technical expertise and moral support that facilitates the work at our sites around the world. The Division of Global Health Equity in the Department of Medicine at the Brigham and Women’s Hospital, the Program in Infectious Disease and Social Change in the Department of Global Health and Social Medicine at Harvard Medical School, and the François-Xavier Bagnoud Center for Health and Human Rights at the Harvard School of Public Health have given us academic homes throughout Harvard University; we are indebted to them all.

Our patients and *accompagnateurs* (some of them both patients as well as *accompagnateurs*) have asked that we close this preface with a challenge. In the “Cange Declaration” of 2001,¹³ a group of approximately 100 persons living with HIV and on ART launched their own challenge to all who would listen. They called on the pharmaceutical industry, decisionmakers in wealthy countries, and all those in positions of influence to act together in an altogether unprecedented manner to slow the

AIDS epidemic. “Not for us,” they added, “but for all those elsewhere in Haiti and in Africa who do not yet have access to the fruits of science.” If people living with HIV and poverty in rural Haiti can think with compassion and solidarity of, to use their words, “their sisters and brothers in Africa,” then so too can we all. It is our greatest hope that south-south collaboration between our Haitian colleagues and those working to stem the epidemic in Africa will contribute not only to the provision of care and treatment but also to the development of working solidarity among the world’s most heavily disease-burdened nations. This handbook is a testament to our patients and co-workers, and to all those living with HIV who seek to become patients and then return to their active lives in the community through the benefit of the fruits of modernity.

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Abbreviations

3TC	Lamivudine	HIV	Human immunodeficiency virus; unless otherwise stated, refers to HIV-1
ABC	Abacavir	HSV	Herpes simplex virus
AFB	Acid-fast bacilli	IDV	Indinavir
AIDS	Acquired Immune Deficiency Syndrome	IM	Intramuscular injection
ALT	Alanine aminotransferase	IMB	Inshuti Mu Buzima (Rwanda)
APV	Amprenavir	IT	Information technology
ART	Antiretroviral therapy, previously highly active antiretroviral therapy (HAART); triple therapy; “AIDS cocktail”	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous administration
ATV	Atazanavir	JCV	Jacob-Creutzfeldt virus
AZT	Zidovudine; azidothymidine; also ZDV	kg	Kilogram
BMI	Body mass index	LFT	Liver function tests
CBC	Complete blood count	LGV	Lymphogranuloma venereum
CDC	Centers for Disease Control and Prevention (United States)	LP	Lumbar puncture
CMV	Cytomegalovirus	LPV	Lopinavir
CNS	Central nervous system	m	Meter
CT	Computerized tomography	MAP	Multicountry AIDS Program (World Bank)
d4T	Stavudine	mcg	Microgram
ddI	Didanosine	MDR TB	Multidrug-resistant tuberculosis
dL	Deciliter	mg	Milligram
DOT	Directly observed therapy	mm	Millimeter
DS	Double strength, in reference to TMP/SMX (160 mg TMP and 800 mg SMX)	M&E	Monitoring and evaluation
DTR	Deep tendon reflex	MTCT	Mother-to-child transmission of HIV
E	Ethambutol, also EMB	MU	Million units
EFV	Efavirenz, also EFZ	NFV	Nelfinavir
EMR	Electronic medical record	NGO	Non-governmental organization
ESR	Erythrocyte sedimentation rate	NIH	National Institutes of Health (United States)
FTC	Emtricitabine	NNRTI	Nonnucleoside reverse transcriptase inhibitor
g	Gram	NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
GI	Gastrointestinal	NSAID	Nonsteroidal anti-inflammatory drug
H	Isoniazid, also INH	NTP	National Tuberculosis Program
Hct	Hematocrit	NVP	Nevirapine
		OI	Opportunistic infection
		PCP	<i>Pneumocystis jiroveci</i> pneumonia
		PCR	Polymerase chain reaction
		PEPFAR	President’s Emergency Plan for AIDS Relief (United States)

PI	Protease inhibitor
PID	Pelvic inflammatory disease
PIH	Partners In Health
PML	Progressive multifocal leukoencephalopathy
PMTCT	Prevention of mother-to-child transmission of HIV
PPD	Purified tuberculin protein derivative
R	Rifampin; rifampicin; also RIF
RFB	Rifabutin
RNA	Ribonucleic acid
RPR	Rapid plasma reagent, serologic test for syphilis
RTV	Ritonavir
S	Streptomycin
SQV	Saquinavir
SSRI	Selective serotonin re-uptake inhibitor
STI	Sexually transmitted infection; also sexually transmitted disease (STD)
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate; tenofovir
THZ	Thiacetazone
TMP/SMX	Trimethoprim/sulfamethoxazole, co-trimoxazole
UNAIDS	Joint United Nations Program on HIV/AIDS
UNGASS	United Nations General Assembly Special Session on AIDS, June 2001
UPS	Uninterruptible power supply
VCT	Voluntary counseling and testing
VDRL	Venereal disease research laboratory, serologic test for syphilis
VZV	Varicella-zoster virus
WBC	White blood cell
WHO	World Health Organization
XDR HIV	Extensively drug-resistant HIV
XDR TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide, also PZA
ZL	Zanmi Lasante (Haiti)

Chapter I: The Haiti Experience

I.1 The History of HIV Prevention and Care in Rural Haiti

Haiti is the poorest country in the Western Hemisphere and one of the poorest in the world, with a per capita gross national income of US\$480.¹ Not coincidentally, Haiti is also the hemisphere’s most heavily HIV-burdened country, with adult prevalence estimated at 2.2 percent.² Haiti and its neighbor, the Dominican Republic, together account for nearly three-quarters of the 230,000 people living with HIV in the Caribbean.³ Recent reports indicate, however, that the Haitian epidemic may in fact have begun to slow down; the history presented in this chapter contributed to this turning of the tide.

The introduction of HIV to Haiti occurred more than 25 years ago, largely as a result of sexual tourism from the U.S. and France. Some have termed the Haitian epidemic “generalized” because it has long been difficult to identify anything resembling discrete risk groups.^{4,5} Poverty and gender inequality remain the leading co-factors for the dissemination of HIV in Haiti. Indeed, in Haiti and in other poor countries, these forces help render existing prevention methods less effective than in developed countries, as women in settings of economic dependence have less ability to demand condom use or faithfulness of a male partner.^{6–8}

Partners In Health, working through its Haitian counterpart, Zanmi Lasante, founded its first medical center, the Clinique Bon Sauveur, in 1985 in Cange, a squatter settlement in the Central Plateau of Haiti. The clinic—now a full-service hospital—documented its first case of HIV in 1986. During the early stages of the epidemic—that is, ten years before the discovery of ART—ZL focused its efforts on AIDS prevention and education.⁹ As part of these efforts, what is now termed voluntary HIV counseling and testing was offered, free of charge, from 1988 onwards. However, clinic

workers found that very few individuals who were offered these services were inclined to accept them. Thus, these services were rarely used as a screening tool. Rather, the great majority of tests were performed simply to confirm a presumptive diagnosis of advanced HIV disease. As a result, most tests performed between 1988 and 1995 were positive.

In the absence of effective medicines, prevention efforts aimed specifically at reducing the vulnerability of women and youth to HIV infection proved central to our work in Haiti. As part of the sociobehavioral components of the AIDS program, medical staff and community health workers founded the Groupe d'Étude du SIDA dans la Classe Paysanne (GESCAP) to investigate the risk of HIV infection by surveying sexually active adults living in the area. The group's findings helped us tailor prevention efforts to increase women's agency and socioeconomic status and led to the development of an integrated women's health clinic, Proje Sante Fanm. This health clinic provides family planning, prenatal care, and treatment for STIs; all three of these concerns have now become important components of ZL's comprehensive AIDS program.

In 1992, another community-based project, Une Chance à Prendre (UCAP), was developed by ZL to make AIDS information accessible to the people of the Central Plateau. This effort focused on the prevention of HIV transmission through programs run by trained Haitian community health workers. Because most rural Haitians cannot read or write, literacy programs and alternative communication strategies were critical to UCAP's success. Local patients and activists scripted and produced *Chache Lavi, Detwi Lavi* (*Looking for Life, Destroying Life*), an AIDS prevention video based on their own life stories. Representing the first candid portrayal of AIDS and the risks that women, specifically, face due to poverty and inequality, *Chache Lavi, Detwi Lavi* is aired frequently on Haitian national television and remains an important tool in HIV prevention efforts throughout the country.

Although culturally appropriate prevention efforts have certainly contributed to the contraction of Haiti's AIDS epidemic, the burden of disease was significant by the time ZL opened a formal inpatient facility in 1993: a substantial fraction of hospitalized patients were found to be sick with complications of HIV infection. A survey of all inpatients conducted in the early 1990s found that more than 40 percent were seropositive.¹⁰ (The majority of these patients were returning from the urban slums of Haiti's capital.) Meanwhile, between 1993 and 1995, a careful study of 200 consecutive HIV diagnoses revealed that more than half of these patients had active TB.¹¹ (This fact surprised many experts from the United States, where TB is an uncommon OI among AIDS patients; however, a similar scenario was later described in sub-Saharan Africa.¹²) While TB can be treated in the absence of antiretroviral drugs, TB relapse and reinfection, as well as other OIs, frequently occurred. The overwhelmed staff at ZL did its best to manage OIs, but simply too few tools were available to stave off death; morale among the staff was at an all-time low.¹³ During this time, with no treatment yet available for AIDS, the majority of patients presenting with HIV were found to have WHO Clinical Stage III or Stage IV disease at diagnosis and died even when their OIs were treated aggressively.

As the proportion of HIV-associated admissions continued to rise, clinic workers concluded that, in the absence of effective AIDS care, HIV testing would not be sought by patients. HIV stigma remained high, and prevention programs were limited in their uptake and effectiveness.

I.2 The Introduction of Antiretroviral Therapy

In 1995, six months after the publication of the results of the influential ACTG 076 trial,¹⁴ ZL began offering zidovudine (AZT) to HIV-positive pregnant women to prevent vertical transmission of HIV. Rates of VCT uptake in the prenatal clinic skyrocketed: by the end of 1996, after AZT was made available free of charge, more than 90 percent of women offered HIV

testing accepted it. This was a novel lesson: the availability of free therapy could spur increased interest in and acceptance of testing. For the first time, the majority of serologies performed were negative, thereby opening more avenues to primary prevention among uninfected women and their partners.

In 1996, it was discovered that combination ART could slow the progress of HIV to AIDS and death and also reverse the course of AIDS to asymptomatic HIV infection. Yet the therapy cost more than US\$10,000 per patient per year and thus was not considered feasible for poor countries. In Haiti and in other high-burden poor countries, patients with advanced HIV continued to fare poorly.

In 1998, ZL obtained some of the new drugs and began treating 50 patients who had advanced AIDS and no longer responded to the treatment of OIs. This was done in much the same way AIDS care is undertaken throughout the developed world: patients were prescribed the appropriate medications, then took them at home and returned to the clinic for monthly appointments. Although all our services were free of charge to the patients, we quickly learned that they were not taking their full prescription of doses. Pill counts and missed appointments revealed levels of adherence similar to those reported in the United States—levels not nearly as high as those we achieved during a decade of experience in the community-based treatment of TB.

Toward the end of 1998, ZL made a fateful decision: from that moment forward, *accompagnateurs* would deliver ART for AIDS, using the same model of directly observed therapy (DOT) used to treat TB. The strategy of daily care delivered by community health workers proved effective.^{15–17} From 1999 to 2002, the medical staff (who at that time had no access to CD4 counts or viral load assays) used clinical algorithms to identify those patients who would not survive long without antiretrovirals, and *accompagnateurs* delivered the life-saving

treatment. Patients' remarkable response to therapy—hailed as the “Lazarus effect”—led to a dramatic decrease in AIDS-related stigma and an increase in demand for VCT.

Even with publication in the medical literature of the example of this success in Haiti, however, physicians, policymakers, and public health experts remained skeptical that AIDS treatment could be delivered in resource-poor settings. Chiefly cited was concern about the high cost of ART and the lack of infrastructure available in such settings to deliver life-long treatment, raising the specter of generating drug-resistant strains of HIV. Happily, the entry of generic formulations of ART has dramatically reduced the price of therapy. Concerns about “missing infrastructure” and developed drug resistance remain.

1.3 The Vital Role of Community Health Workers

The experiences of our health workers in Haiti and elsewhere suggest that the “missing infrastructure” may largely be a question of personnel, rather than of laboratory or medical resources. Settings boasting few physicians and nurses are often those with a large number of underutilized community health workers, and underemployed persons and traditional healers alike have expressed interest in being trained to “accompany” their neighbors living with AIDS. The involvement of these and other community-based health workers is critical if even modest treatment goals are to be met in the coming years.

Community health workers are the backbone of ZL's treatment program. *Accompagnateurs* observe the ingestion of pills, respond to patient and family concerns, and offer psychosocial support. *Accompagnateurs* also undergo training in the importance of observing therapy daily, recognizing symptoms of illness or side effects of medications, and maintaining confidentiality. Most importantly, *accompagnateurs* provide emotional support to patients and help ensure adherence to treatment, thus prolonging patient survival and minimizing

the development of drug resistance. In the future, we anticipate that patients afflicted with other chronic diseases—from diabetes to major depressive disorder—may also benefit from the engagement of community health workers and receive high-quality medical care even when no doctor is regularly present.¹⁸ See Section 3.10 for an extended discussion of PIH's *accompagnateur* model.

I.4 A Syndromic Approach to HIV Management

The HIV Equity Initiative was launched with the ability to run only very basic laboratory tests, such as hematocrit (Hct), white blood cell (WBC) count, liver function tests (LFTs), and serologic testing for HIV. The medical staff did not have access to flow cytometry for CD4 counts or polymerase chain reaction (PCR) for viral load assays. These constraints necessitated the initiation of ART for only the sickest patients as determined by a “syndromic approach”—that is, according to the clinical staging of immune suppression based on the following guidelines:

- Patients with other treatable OIs (including TB) were treated for their OIs first.
- Clinical criteria were used to identify patients most urgently in need of ART, as indicated by the following factors:
 - Absence of active TB;
 - Recurrent OIs;
 - Chronic enteropathy with wasting;
 - Otherwise unexplained and significant weight loss;
 - Severe neurologic complications attributable to HIV; and/or
 - Severe leukopenia, anemia, or thrombocytopenia.

ZL medical staff soon discovered that patients receiving ART were far less likely to require admission to the hospital than were patients with untreated HIV. In fact, the majority of

HIV-related admissions occurred among patients from beyond the catchment area served by *accompagnateurs*.

The HIV Equity Initiative in Haiti initially started 150 patients on ART and followed more than 1,500 patients. All the patients who were started on ART based on clinical criteria—in most cases, extreme cachexia and the inability to ambulate—and who were well enough to leave the hospital to begin ambulatory DOT between 1998 and 2001 are still living today.

1.4.1 Limitations of the syndromic approach

The initiation of ART based on syndromic criteria was necessary to save the lives of the sickest patients in the absence of laboratory diagnostics. However, the mortality rate was unacceptably high among patients who appeared well and for whom ART was deferred. Since November 2002, when ZL acquired the capacity to perform CD4 counts in central Haiti, a combination of syndromic management and CD4 count criteria has been used to initiate treatment. Now, patients who appear well clinically but in fact have significant immunosuppression are also offered ART.

This handbook addresses both immunologic monitoring and syndromic management of patients on ART. We have confirmed that, even in resource-poor settings, the CD4 count is a powerful tool for rapidly identifying patients with advanced but minimally symptomatic HIV disease. However, in high-burden areas without access to CD4 counts, there remains a role for the syndromic management of late-stage HIV infection.

I.5 Scaling Up HIV Prevention and Care in Central Haiti

In seeking to improve AIDS care, ZL medical staff were not only serving HIV-affected families, but also increasing their ability to identify and treat patients with other diseases—most notably TB and STIs. Expanding our capacity to prevent mother-to-child transmission of HIV enhanced the quality not only of prenatal care, but of all women's health services.

In other words, improving AIDS prevention and care led to a dramatic improvement in the quality of primary health care in general.¹⁹

In 2001, with the advent of the Global Fund to Fight AIDS, Tuberculosis and Malaria, ZL made the decision to expand its HIV prevention, testing, and treatment services to the public sector's health clinics rather than proceeding as a freestanding NGO. With large-scale HIV treatment a possibility, the government's Ministry of Health seemed best placed to expand what could now be offered as a public good.

At each of its current sites across central Haiti, ZL strengthened or re-opened inadequately functioning or closed public clinics by implementing the "four pillars" of a comprehensive AIDS strategy as described in Section 2.2: provision of HIV prevention and care services, including VCT, in the context of primary health care; aggressive case finding and supervised treatment of TB; women's health services; and aggressive case finding and treatment of all STIs. At each site, ZL medical staff relied on community health workers to provide the bulk of daily care.

By providing basic health services, essential drugs, and expanded staffing, ZL has been able to improve the quality of all services offered in the public facilities. In less than six months, daily ambulatory visits at each site skyrocketed from 10-30 patients per day to 100-300 patients per day. HIV and TB case-detection also increased dramatically at each site.

The first scale-up clinic launched—in the large town of Lascahobas, near the border of the Dominican Republic—is illustrative of later experiences at other sites. A preliminary assessment of the Lascahobas clinic in 2002 revealed it to be nearly empty in the morning and closed by noon. The staff was demoralized, having access to very little in the way of tools. As for HIV prevention and care, no services were being

offered at all—and the absence of serologic tests meant that even VCT and PMTCT of HIV were unavailable. On paper, at least, the diagnosis and care of TB was provided free of charge to patients. But in the year preceding ZL's involvement, only a dozen cases had been diagnosed in this town of over 40,000 people. (Incidence data from around Cange suggested that closer to 180 patients should have been expected to present with TB.)

Less than a year later, the Lascahobas clinic had been transformed by what was ostensibly an "AIDS project." Introducing all four pillars of the comprehensive AIDS strategy meant introducing essential drugs and a small laboratory, training and paying *accompagnateurs*, and complementing the salaries of Ministry of Health staff. The impact of these efforts was profound. Hundreds of people living with HIV came forward for evaluation and care; more than 120 of these patients were receiving supervised ART within a year. In Lascahobas, as in Cange, almost all prenatal care came to include VCT. Management of STIs was introduced. Aggressive HIV prevention activities took place within the clinic, at area churches and schools, and in the villages served by *accompagnateurs*. Close to 200 TB patients were identified and placed in the care of *accompagnateurs*. A small inpatient unit was built within four months and, in April 2003, rural Haiti's second AIDS clinic—replete with the same equipment and supplies available at l'Hôpital Bon Sauveur in Cange—was dedicated at a ceremony that drew hundreds of local well-wishers. The naysayers who argued at the time that stigma would prevent the success of such a clinic were proven incorrect,²⁰ as the AIDS clinic remains the most active component of what is now one of rural Haiti's busiest health centers.

The lessons of scale-up have shown that, rather than diverting resources, instituting comprehensive AIDS care can in fact strengthen primary health care.²¹

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Chapter 2: Initiating a Comprehensive HIV Prevention and Treatment Program: The PIH Model

2.1 Public Clinics and Primary Health Care

In settings where basic health-care systems are weak, the launching of an HIV program can and should be used to strengthen—rather than siphon resources from—primary health services and the public sector.¹ Such was the experience in Haiti, where Partners In Health, working through its Haitian counterpart, Zanmi Lasante, has scaled up HIV services in partnership with the Ministry of Health. In our new programs in Africa, too, Partners In Health is working closely with Ministries of Health and with national AIDS programs.

The public sector is best positioned to provide health care to the poorest communities. In many impoverished settings, however, public clinics stand empty or underutilized because the national health budget can provide neither a decent wage to retain health professionals in the public sector nor the tools necessary for a clinic to function. Thus, both the staff and the community become demoralized. The toll of HIV further devastates health systems by causing illness and death among clinic staff and their families and increasing the volume of extremely ill and seemingly “terminal” patients.²

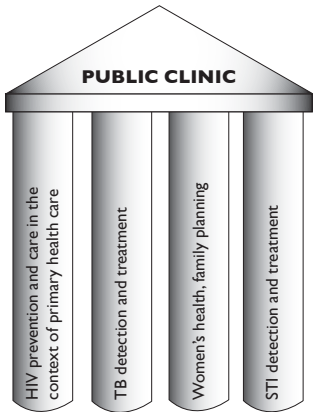
Partnerships between NGOs and the public sector that result in a positive flow of money, essential drugs, personnel, and other resources will help revitalize public clinics and improve both the uptake of HIV services and the overall health of the community.³ This synergy has long been evident to us, as the majority of Zanmi Lasante patients present for clinical care of non-HIV-specific symptoms such as cough, fever, diarrhea, or weight loss, without the specific intention to seek HIV testing.

2.2 The Four Pillars of HIV Prevention and Care

As outlined in Chapter 1, ZL’s approach to expanding HIV care in Haiti is not to provide freestanding, NGO-managed VCT and HIV treatment alone. Rather, the goal is to integrate HIV prevention, testing, and treatment with primary health care in the setting of a public clinic. There are four critical program components—or “pillars”—that serve as entry points for HIV case detection (Figure 2.1):

- 1. people seeking primary health care;
- 2. people diagnosed with tuberculosis;
- 3. women seeking women’s health or family planning services; and
- 4. people diagnosed with sexually transmitted infections.

Figure 2.1 PIH’s Four Pillars of HIV Prevention and Care



The provision of VCT within the context of primary health services constitutes the first pillar. Rapid HIV testing has facilitated the linkage between addressing basic health concerns and the provision of VCT. In this model, sometimes called provider-initiated testing, all patients seen for primary care services are offered VCT if their symptoms may be associated

with HIV or an OI. HIV test results can be presented and explained to patients on the same day the test is performed. In addition, integrating VCT into primary health care decreases the perceived stigma of AIDS because patients need not implicitly or explicitly declare that they are at risk for HIV infection when they present for care.⁴ Careful patient histories—including information about the status of the patient’s partner(s), the status of the patient’s parents, and the patient’s employment history (including any history of migration for work, domestic servitude, or commercial sex work)—are always taken in order to elucidate social and epidemiological risk factors for HIV.⁵ In addition to offering testing to patients who present with illness, risk factors, or a desire to be tested (i.e., passive casefinding), active casefinding is carried out by encouraging disclosure and the testing of children and partners, as well as through prevention and education programs at schools, churches, and community events.^{6,7}

The second pillar of ZL’s comprehensive and integrated approach is improved TB casefinding and treatment. Because TB is the most common opportunistic infection in HIV patients worldwide, all HIV patients should be screened for both active and latent TB, just as all active TB patients should be tested for HIV.^{8,9} When the two screening services are provided concomitantly, a greater number of co-infected individuals are identified, and the likelihood of improved outcomes for both diseases is increased.

The third pillar is comprehensive women’s health services, with an emphasis on family planning and safe motherhood.¹⁰ The availability of antiretrovirals and of antepartum, maternity, and postpartum care greatly enhances the uptake of HIV testing among pregnant women.¹¹

Finally, VCT should be offered to all patients presenting with STIs—the fourth pillar.¹² Numerous studies have shown that treatment of other STIs diminishes the risk of acquiring HIV.¹³

Additionally, the detection and treatment of STIs opens up an important avenue for HIV testing and prevention messages.¹⁴

The remainder of this chapter will lay out the main issues encountered in implementing this four-pillar approach.

2.3 Integration of VCT with Primary Care

It is vital to facilitate the integration of VCT within the setting of primary care services. The constraints of time and space in a busy clinic must be balanced against the need to ensure appropriate patient privacy and participation in the decision-making process.^{15,16} The reality for busy clinics in the developing world is that pre-test counseling must be brief so as to minimize disruption of the flow of patient services.¹⁷ The same practitioner—whether nurse, social worker, or physician—who sees the patient for the presenting complaint provides counseling during the same session and refers the patient directly to the lab for rapid HIV testing. The patient then returns to the referring provider to receive and discuss the test result. This streamlined approach to VCT minimizes the inconvenience to and effort required of the patient, since returning to the clinic at a later date presents considerable difficulty for many people in impoverished settings.¹⁸

If the initial rapid HIV test is positive, a second (different) rapid test is performed as confirmation. If both tests are positive, the patient is definitively identified as HIV-positive. If the two tests are discordant, a third (different) rapid test or Western Blot analysis is performed and considered the definitive result. This process is illustrated in Protocol 2.1.*

2.3.1 Post-test and ongoing counseling

Post-test counseling is critical in helping patients respond to and cope with a diagnosis of HIV.¹⁹ In order for care providers

to adapt post-test counseling to the context of their patients' lives, soliciting patients' concerns and ensuring their understanding of HIV are crucial. In the ZL program in Haiti, post-test counseling occurs at the time of diagnosis and continues during subsequent clinic appointments and home visits by nurses, social workers, physicians, and *accompagnateurs*. Community-based support ensures that patients truly understand the nature and management of their disease and realize that psychological and medical support exists to allow them a long, productive life. In PIH programs, the long-term relationships between patients, community health workers, and members of the clinic staff constitute the most effective ongoing counseling.

2.3.2 Discordant couples

If the partner of an HIV-positive patient is HIV-negative, preventing HIV transmission from the infected patient to the uninfected partner becomes an important component of care. Disclosure of HIV status to one's sexual partner(s) and children is encouraged and facilitated through counseling. However, issues of privacy, stigma, discrimination, and violence associated with HIV disclosure must be respected if the HIV-positive person chooses not to disclose his or her status.²⁰ Condoms should be promoted and provided free of charge, as their correct and consistent use during sexual intercourse decreases the risk of transmitting HIV to the uninfected partner by up to 96 percent and provides protection against other STIs and unplanned pregnancies.²¹ If couples are not consistently using condoms, they should be advised against having sex during menses or in the presence of untreated STIs. HIV-negative partners should receive routine checkups, including counseling and HIV testing as well as screening and treatment for STIs, every six months.²²

The infected person's viral load and CD4 count influence the likelihood of transmission between discordant partners.^{23–29}

* All protocols for Chapter 2 are grouped at the end of the chapter, immediately before the References.

Therefore, starting the HIV-positive partner on ART as soon as clinically indicated may significantly decrease the likelihood of infecting the HIV-negative partner.

2.4 TB and HIV Co-Infection

It is critical that HIV programs include a strong TB component, the second pillar of PIH's approach to comprehensive care. HIV infection is the most potent risk factor yet identified for the development of TB. HIV infection enhances susceptibility to TB infection; facilitates progression of latent to active TB; and increases the likelihood of treatment failure, relapse, and reinfection. Due to this biologically mediated risk and the ubiquitous and aggressive nature of TB in the developing world, TB is the most common cause of death in HIV-positive persons worldwide.³⁰

HIV-positive persons are 100 times more likely than HIV-negative individuals to develop active TB.^{31–33} Additionally, molecular studies have confirmed that HIV-positive persons are more susceptible to exogenous reinfection by a second strain of TB, even after adequate anti-TB treatment has been provided.^{34–37} The risk of poor response to TB treatment—failure, relapse, and death—is also greater among HIV-positive individuals.^{38–41} In addition to having a markedly increased risk of developing active TB, once a person who has HIV develops active TB, their progression to AIDS and death is more rapid than that of HIV-positive patients who do not have active TB.^{42–44} However, when indicated, ART can improve survival in co-infected patients and slow the progression of HIV to AIDS.⁴⁵

2.4.1 Prevention of TB in HIV-positive patients

Implementation of infection-control measures and prompt diagnosis and treatment of both latent and active tuberculosis will help prevent the development and spread of active disease in and among HIV-positive patients. To underline the importance of infection-control measures, education and outreach about tuberculosis and its prevention and treatment should be ongoing

for both patients and health-workers. In hospitals and clinics, smear-positive and MDR TB patients should be separated from HIV-positive persons without smear-positive or MDR TB. Additional measures, including natural and mechanical ventilation, ultraviolet germicidal irradiation, and use of TB-protective masks, should be undertaken as appropriate.

HIV-positive patients who present with a tuberculin skin test induration of greater than 5 mm, known household contact with active TB, or suspected anergy (CD4 below 200 cells/mm³) and who have no radiographic or clinical evidence of TB should receive chemoprophylaxis for latent TB infection: nine months of isoniazid 300 mg/day plus pyridoxine (vitamin B6) 50 mg/day.⁴⁶ In endemic areas, full (four-drug) treatment for TB should be considered if the patient has any manifestations of active TB, including cough, weight loss, night sweats, or fever.

2.4.2 Diagnosis of TB in HIV-positive patients

All HIV-positive patients should be thoroughly evaluated for TB by a review of symptoms, physical exam, tuberculin testing (i.e., PPD, TST, or Mantoux skin test), and chest radiography. Special attention should be given to signs of extrapulmonary disease such as fever, lymphadenopathy, and wasting. Any patient with respiratory symptoms should submit three sputum samples for smear microscopy. (Note that it is critical to instruct and, if possible, observe and coach the patient to produce a deep cough that generates sputum rather than just saliva. Induced sputum or aspiration of gastric aspirates prior to the first meal of the day may be considered in patients who cannot produce sputum—such as children—and in patients with a nonproductive cough.) Where available, bronchoscopy may increase the diagnostic yield.⁴⁷ Because fewer than half of active TB cases demonstrate a positive smear, culture for *Mycobacterium tuberculosis* increases the likelihood of diagnosis. However, neither culture nor smear of concentrated sputum is available in most developing-world labs. Thus, even

in the absence of bacteriologic evidence of infection, many TB cases at Zanmi Lasante are diagnosed and treated based on patient history, physical exam, and radiographic findings alone. In endemic settings, any clinical, bacteriological, or radiographic evidence of TB merits the initiation of treatment.

As a co-infected patient’s degree of immunosuppression increases, the clinical, radiographic, and microbiologic features of TB are more likely to be atypical.⁴⁸ Patients with pulmonary TB may have chest radiographs that do not demonstrate classic upper lobe findings or that even appear normal. Extrapulmonary TB—including disseminated disease with mycobacteremia—occurs with greater frequency in HIV-positive persons than in TB patients without HIV.^{49–51} For both pulmonary and extrapulmonary disease in co-infected patients, the assessment of sputum microscopy for acid-fast bacilli (AFB) is often negative.

2.4.3 Initiation of TB therapy and ART in co-infected patients

Our approach to tuberculosis management in co-infected patients is outlined in Protocol 2.2. All new cases of TB in co-infected patients should be treated per WHO guidelines. The dosing for first-line TB medications is indicated in Table 2.1. All doses are observed. Intermittent dosing of TB therapy is not recommended for HIV-positive patients. For co-infected patients who are already receiving ART, the ART regimen should be adjusted to be compatible with TB therapy.

In co-infected patients, a CD4 count, when available, should be performed prior to the initiation of TB therapy. The decision to start ART should be based on this CD4 count and on the patient’s clinical status. ZL’s practice is to consider ART for all patients with a CD4 count below 350 cells/mm³. In order to minimize drug toxicity, improve adherence, and avoid immune reconstitution reactions, ART may be deferred in co-infected patients with a CD4 count between 200 and 350

cells/mm³ until after completion of the intensive phase or the entirety of TB treatment. For patients with a CD4 count below 200 cells/mm³ or severe clinical status, ART should be initiated during TB therapy—either simultaneously or after two to eight weeks of treatment. While severely immune-suppressed patients are at greatest risk for immune reconstitution reactions,⁵² their risk of dying from either TB or another OI is very high, even in the first month of TB treatment. Thus, concern about immune reconstitution should not preclude the initiation of ART in these patients.

Table 2.1 Dosing of First-Line TB Drugs

First-line medications	Daily dose (maximum dose)
Isoniazid (H)	5 mg/kg (300 mg)
Rifampin (R)	10 mg/kg (600 mg)
Pyrazinamide (Z)	20-25 mg/kg (2.0 g)
Ethambutol (E)	15-20 mg/kg (1.6 g)
Streptomycin (S)	15 mg/kg (1.0 g)

Sources: World Health Organization. *Treatment of tuberculosis: guidelines for national programs*, 3rd ed. Revision approved by STAG, June 2004. Geneva: WHO, 2004. Bartlett JG, Gallant JE. *Medical management of HIV infection*. Baltimore, MD: Johns Hopkins University, 2005.

If a CD4 count is unavailable, co-infected patients should be treated as WHO HIV Clinical Stage III or IV for pulmonary or extrapulmonary status, respectively, and should be started on ART concomitantly or after completing the first two months of TB therapy.

Lastly, because co-infected persons have WHO HIV Clinical Stage III or IV disease and often have CD4 counts below 200 cells/mm³, all patients who have a CD4 count below 200 cells/mm³ or whose CD4 count is unknown should receive trimethoprim/sulfamethoxazole (TMP/SMX) as prophylaxis

against the development of additional OIs during the course of TB treatment.

2.4.4 Choice of TB and ART regimens in co-infected patients

Treatment of TB in patients with or without HIV should last a minimum of six months. As summarized in Table 2.2, the “intensive phase” is defined as the period during which the patient receives four drugs daily for a minimum of two months. If the patient demonstrates clinical improvement, the “continuation phase” is started, in which the patient receives two drugs daily or three times a week for four months. Again, intermittent dosing of TB therapy is not recommended for HIV-positive patients.

Many antiretroviral medications—particularly protease inhibitors (PIs) and nevirapine (NVP)—interact with rifampin (R). This interaction results in lower levels of both the antiretroviral drug³³ and rifampin, potentially generating drug-resistant HIV and TB. Because TB is such a serious infection in HIV-positive persons and because rifampin is the most potent anti-TB drug, the use of rifampin in anti-TB regimens is important. If a patient is clinically stable, has a high CD4 count, and is not yet receiving ART, treating TB first and deferring ART until the patient is no longer on rifampin is the preferred course of action. If a patient is already receiving ART or is in urgent need of ART when TB is diagnosed, a regimen containing ART agents that do not interact with rifampin should be used. The regimen of choice is two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted dose of the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV). However, efavirenz must be avoided in children under three years of age, pregnant women, and patients with a prior adverse reaction to it. When EFV cannot be used, abacavir (ABC) may be substituted; conversely, rifabutin (RFB) may be substituted for rifampin in the TB regimen.

Drug interactions with rifamycins are summarized in Appendix A. Some experts argue for cessation of R after the intensive phase and use of H and E in the continuation phase so that an ART regimen containing NVP can be initiated. However, this regimen (H and E in the continuation phase) has been associated with higher rates of treatment failure.⁵⁴

Table 2.2 TB Treatment Regimens for Patients with HIV

WHO TB diagnostic category ^a	Intensive phase regimen ^b	Continuation phase regimen ^c
I: New smear-positive or smear-negative patients	2 months of HRZE	4 months of HR
II: Previously treated patients; relapse and return after treatment default; MDR TB not suspected	2 months of SHRZE, then 1 month of HRZE	5 months of HRE
IV ^d : Patients demonstrating failure to respond to previous treatment, failure of previous treatment, or in whom MDR TB is either documented or strongly suspected	Specialized treatment for MDR TB is indicated, usually with five drugs to which the TB strain is thought to be susceptible. See Section 2.4.6 for specialized references.	

Sources: World Health Organization. *Guidelines for the programmatic management of drug-resistant tuberculosis*. Geneva: WHO, 2006; Bartlett JG, Gallant JE. *Medical management of HIV infection*. Baltimore, MD: Johns Hopkins University, 2005.

^a WHO no longer recommends the 3-drug regimen (Category III).
^b The intensive phase should be continued past two months if the patient remains smear- or culture-positive. If the patient is still smear- or culture-positive after four months, consider treatment failure and use Category IV.
^c The continuation phase can be extended to seven months (for a total of nine months of therapy) in cases that are slow to respond or if chest radiography indicates persistent cavities.
^d Modified from the WHO guidelines. Patients who have failed to improve during Category I treatment are often placed in Category II. The authors of this book believe that patients who have not responded to observed TB treatment most often have a high likelihood of MDR TB and should receive Category IV treatment.

2.4.5 Monitoring of TB in co-infected patients

As recommended by WHO, each dose of TB treatment should be directly observed throughout the duration of therapy. Monthly smear microscopy, in addition to clinical evaluation, is helpful in gauging treatment response. Ongoing clinical symptoms, cavitory disease, and/or a persistently positive sputum smear or culture after two months of treatment may reflect delayed treatment response and justify prolongation of four-drug therapy.^{55,56} At ZL clinics, sputum-smear microscopy is performed for all smear-positive patients after two months of treatment; the use of four drugs is extended for any patient who is still smear-positive at that time. Subsequent monthly smear microscopies determine the duration of the intensive phase for these patients. Patients with a positive smear in the fourth, fifth, or sixth month of treatment should be considered TB treatment failures.

Poor clinical response to TB treatment may be the result of treatment failure, especially in the case of a persistently positive smear (due either to the presence of drug-resistant TB or to poor patient adherence to anti-TB therapy); paradoxical worsening (immune reconstitution syndrome), particularly when fevers and shortness of breath become more prominent during treatment; or occurrence of an additional OI while the patient is receiving effective anti-TB therapy. All patients with poor clinical response and/or persistent positive smear microscopy after the intensive phase of treatment should be assessed for possible TB treatment failure, including evaluation of adherence; drug susceptibility testing, if available; and consideration of a TB regimen change if MDR TB is suspected.

Immune reconstitution syndrome in patients with pulmonary TB is characterized by clinical and radiographic worsening, often with high fever, dyspnea, or adenopathy.⁵⁷ This syndrome is associated with recrudescence of CD4 T-cells and increased host response as a consequence of ART. The syndrome can occur two weeks to several months after the initiation of therapy and is more common in patients with very low CD4 counts and

disseminated TB. For mild to moderate immune reconstitution reactions, provide nonsteroidal anti-inflammatory drugs (NSAIDs) and close observation. In patients with severe pulmonary symptoms, prednisone (1 mg/kg/day for one to two weeks, tapering the dose over a two- to four-week period) may be indicated, especially if the patient has TB in the central nervous system.⁵⁸

In patients with TB meningitis, intracranial TB or immune reconstitution can cause worsening of the neurologic deficits. In patients who experience worsening of neurologic deficits due to immune reconstitution, it is reasonable to stop ART and continue TB treatment and steroids until the central nervous system process is controlled. In general, HIV patients have a higher rate of adverse reactions to both TB and non-TB medications than do those without HIV disease.⁵⁹ Among co-infected patients, peripheral neuropathy may occur in more than 50 percent of those who are receiving H and the antiretroviral drug stavudine (d4T).^{60,61} (See Section 3.6.6 and Protocol 3.10 for additional discussion of peripheral neuropathy.) Pyridoxine at a dose of 50 mg/day should be administered concurrently with H to help prevent neuropathy.

Notably, a markedly increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome, is associated with the use of thiacetazone (THZ) in HIV-positive patients; this antituberculous drug should therefore not be used in co-infected individuals.⁶²

2.4.6 MDR TB and HIV

In certain geographic areas, HIV is a risk factor for MDR TB. Understanding the regional prevalence of MDR TB and co-infection with HIV is thus important in the management of HIV treatment. Strains of MDR TB are, by definition, resistant to H and R and therefore more difficult to treat.

Acquired resistance is caused by incomplete or inadequate treatment of TB. While patients' nonadherence to their prescribed regimen is often invoked as the principal cause of acquired resistance, unreliable drug supplies, inadequate TB programs, physician error, and malabsorption (particularly among HIV-positive patients) are also likely culprits.^{63–65} Patients with primary resistance are those who directly contracted a resistant strain of TB. Among HIV-positive patients, nosocomial transmission poses a particular threat for the spread of primary resistance.^{66–68}

If a patient has suspected or confirmed MDR TB, please refer to the WHO's *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*⁶⁹ and *The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis*.⁷⁰

2.4.7 Coordination of HIV and TB programs

Delivering HIV care through national TB programs (NTPs) has both advantages and disadvantages. The advantages include utilization of an established TB-control infrastructure, including DOT services; management of the two diseases by a single provider; and the employment of a joint approach between NTPs and national AIDS programs. Disadvantages include the potential for overwhelming TB services by introducing large numbers of patients; a possible increased risk of TB transmission among patients seeking care through the program; and the need for TB physicians to gain specialized knowledge in HIV management.⁷¹

Regardless of the disadvantages, TB and HIV programs must coordinate care in order to maximize diagnoses, continuity of care, utilization of TB and HIV health services, and positive outcomes. Both TB and HIV services should ideally be integrated into primary care services.

2.5 Women's Health and PMTCT of HIV

The provision of comprehensive women's health services constitutes the third pillar of PIH's approach to integrated programming. By the end of 2007, women of childbearing age represented half of the 30.8 million adults living with HIV/AIDS worldwide.⁷² In regions where antiretroviral prophylaxis is not readily available, rates of MTCT of HIV range from 25 to 40 percent.⁷³ Programs to prevent MTCT will have the greatest impact if the vulnerability of the whole family is taken into account. Ideally, HIV prevention and care, including PMTCT, should be integrated with primary health care and women's health services.

2.5.1 Family planning

Family planning and PMTCT go hand-in-hand: clinical visits for one are an ideal time to address the other. If a female patient is found to be HIV-positive, the patient (ideally, the couple) should be counseled about birth spacing and contraception. Both barrier and hormonal methods should be discussed.

At the ZL clinics in Haiti, all presenting women of childbearing age receive family planning counseling. Contraceptive methods available to these patients include oral contraceptives, depot medroxyprogesterone acetate (Depo-Provera®), levonorgestrel (Norplant®), and male and female condoms. All women desiring to use oral contraceptives should also be given and counseled to use condoms, especially since PIs, rifamycins, and NNRTIs may decrease the effectiveness of oral contraceptives.^{74–76} During the initial and subsequent clinic visits, all women are counseled regarding proper usage and possible side effects of their chosen method(s) of contraception. For those receiving depot medroxyprogesterone acetate, subsequent clinic visits should be scheduled up front to avoid interruption of the medication.

2.5.2 Care of HIV-positive pregnant women

If a pregnant woman is found to be HIV-positive, it is critical to preserve and improve the mother's health as well as to decrease

the risk of transmission of the virus to the infant. HIV-positive pregnant women should receive medical care and extended social support, including an assessment of the family's living situation; nutritional assistance; and testing of any children and sexual partner(s). If the mother's immunologic state is deemed poor based on CD4 monitoring or clinical status, three antiretroviral medications should be started as soon as possible per Protocol 2.3. Alternatively, if the mother is not ill, or if her CD4 count is above 350 cells/mm³, ART can be deferred until the 28th week of gestation, at which point it should be administered for PMTCT.

Nutritional supplementation should be provided to pregnant women beginning at the 12th week of gestation and continuing through the pregnancy. This supplementation should be in the form of a daily multivitamin containing B1 (20 mg), B2 (20 mg), B6 (25 mg), niacin (100 mg), B12 (50 mcg), C (500 mg), E (30 mg), and folic acid (0.8 mg). This regimen has been found to reduce the risk of fetal death, severe preterm birth, small size for gestational age, and low birth weight among children of HIV-positive women.⁷⁷ Because vitamin A has been shown to increase the risk of MTCT of HIV, particularly in women who take it during breastfeeding,⁷⁸ nutritional supplements that include vitamin A should not be given.

The presence of STIs, anemia, high viral load, and low CD4 count have all been associated with increased rates of HIV transmission from mother to child and should be addressed accordingly.^{79–82} Obstetric risk factors for transmission include prolonged rupture of amniotic membranes, vaginal rather than elective cesarean delivery (in particular, among women not receiving ART), chorioamnionitis, and obstetric complications.^{83–85} Thus, the provision of obstetrical services should be improved concurrently with the scale-up of ART if maternal mortality and vertical transmission of HIV are to be decreased.

Prenatal testing, prenatal care, and appropriate screening and treatment for STIs are clearly linked to better outcomes. However, of all known factors, high maternal viral load is the strongest predictor of vertical HIV transmission. Specifically, the risk of MTCT is increased 2.4-fold for every log increase in viral load at the time of delivery.⁸⁶ Antiretroviral therapy is thus the most important intervention for PMTCT.

2.5.3 General recommendations on the use of ART in pregnant women

The use of maternal ART has led to perinatal transmission rates of less than 2 percent.^{87,88} The literature regarding choice of ART during pregnancy, labor, and delivery continues to evolve rapidly. The landmark ACTG 076 study used a three-part AZT monotherapy regimen—antepartum and intrapartum for the mother, postpartum for the newborn—and reduced MTCT rates from 26 percent to 8 percent.⁸⁹ Since that trial, a number of other studies have attempted to determine whether shorter courses of monotherapy for the mother and/or infant, or combinations of ART, have equal or greater efficacy.⁹⁰ Efficacy has been shown for regimens involving AZT alone, AZT and lamivudine (3TC), NVP alone (single-dose to mother and infant), AZT with single-dose NVP, and AZT and 3TC with single-dose NVP.^{91–101} In wealthy countries, the current standard of care for PMTCT is triple-drug maternal ART.¹⁰² In a multivariate analysis, adjusting for maternal viral load and duration of therapy, the odds-ratio of MTCT for women receiving potent triple therapy compared with AZT monotherapy was 0.27, supporting the benefit of using three drugs.¹⁰³ Furthermore, data from PACTG 367 demonstrated that the use of two or more drugs is superior to monotherapy.¹⁰⁴

In addition to lowering the risk of MTCT, combination therapy also diminishes the mother's risk of developing drug resistance. After the use of single-dose NVP for PMTCT, strains of HIV resistant to NNRTIs have been found (at least temporarily) in just under 50 percent of babies and a little more than 50

percent of women.^{105–107} The clinical significance of this finding with regard to future pregnancies and future management of maternal and pediatric disease is unknown.

2.5.4 Recommended ART regimens for PMTCT

Decisions regarding maternal ART should be made based on the timing of presentation for care and maternal indications for therapy. Women who are already receiving ART at the time of conception should continue on the same regimen unless it includes EFV, in which case NVP or a PI should be substituted. Section 2.5.5 presents additional information about ART toxicity during pregnancy.

Per Protocol 2.3, newly identified HIV-positive pregnant women with maternal indications for ART (that is, either clinical symptoms or a CD4 count below 350 cells/mm³) should immediately start combination therapy with three antiretroviral drugs. The most widely available regimen is AZT, 3TC, and NVP. AZT has the longest track record for use by pregnant women and is a preferred component in all regimens. Where available, a PI is preferable to NVP, given the latter's association with hepatotoxicity (see Section 2.5.5).

HIV-positive women who present after the 28th week of gestation and have not yet received ART should be started on treatment as soon as possible, even before the results of CD4 testing are available; LFTs should be closely monitored. Women who present in labor and have not yet received ART should receive single-dose NVP.^{108,109} In addition, based on reports of developed NVP resistance, any woman who has previously received any NVP for PMTCT is now also given one week of AZT and 3TC.¹¹⁰ The ZL protocol recommends the continuation of AZT and 3TC for two weeks after the postpartum cessation of NVP.

Recommendations for the management of HIV-exposed infants are presented in Protocol 2.4. All HIV-exposed infants are given

AZT syrup for one week. If the mother did not receive ART prior to the 36th week of gestation, the infant should also receive single-dose NVP, and AZT should be continued for a total of six weeks. If the mother is suspected of having resistant virus, alternative drug combinations may be considered for the infant. Infant protocol is determined by the available information about the mother's prior exposure to antiretrovirals, viral load, and presence or absence of resistance mutations.

2.5.5 ART toxicity during pregnancy

Cohort studies of HIV-positive pregnant women given ART (specifically, AZT and 3TC) have demonstrated little in the way of maternal or fetal toxicity. However, several antiretroviral agents and combinations should be used with caution or avoided during pregnancy. The use of EFV in pregnant monkeys has been associated with abnormalities in their offspring;¹¹¹ a single case of myelomeningocele has also been reported in a human infant exposed to EFV *in utero*.^{112,113} Generally, pregnant women and women of childbearing age who are not using contraception should not be given EFV. If a woman becomes pregnant while receiving an EFV-containing regimen, NVP or a PI should be substituted. While this particular use has not been studied, EFV can possibly be given in the third trimester, as the development of the infant's neural tube occurs during the first trimester.

NVP has been associated with an increased risk of hepatotoxicity in women with a CD4 count above 250 cells/mm³; thus, a regimen containing AZT, 3TC, and NVP may not always be recommended for PMTCT in women with high CD4 counts.^{114–117} However, NVP is the most widely available nonteratogenic third agent in resource-poor settings and in ZL clinics is used in the first-line regimen for ART and PMTCT regardless of maternal CD4 count. A study from Brazil demonstrated minimal toxicity from this approach.¹¹⁸ When NVP-based triple therapy is given to women with a CD4 count above 250 cells/mm³, close monitoring of LFTs—one week after

the initiation of ART and then every two weeks subsequently or if symptoms develop—is strongly recommended. Another reasonable alternative is to initiate AZT at the 28th week of gestation, with the addition of maternal NVP at labor and after birth for the infant.¹¹⁹

The use of d4T and didanosine (ddI) in combination is associated with increased mitochondrial toxicity during pregnancy and should be avoided.^{120–122} In addition, tenofovir (TDF) should not be used during pregnancy due to concerns about osteopenia in infants and a general lack of safety data.¹²³

2.5.6 Mode of delivery

Elective cesarean sections prior to rupture of membranes can reduce MTCT in HIV-positive women who are not receiving ART.^{124,125} For women receiving ART, however, cesarean sections do not decrease the risk of MTCT. Data from PACTG 367 indicate that transmission rates are significantly lower when multi-agent therapy is being administered and when maternal plasma HIV RNA levels are lower; rates do not differ significantly according to mode of delivery.¹²⁶ Cesarean sections should therefore be reserved for women who are likely to have a detectable viral load at the time of labor—that is, those women who are not receiving effective ART or who demonstrate nonadherence during pregnancy—and women who have an obstetric indication for a cesarean section. This stipulation is particularly important given that women with HIV infection may be at increased risk of complications after a cesarean section.^{127,128}

2.5.7 Breastfeeding and MTCT risk

The rate of MTCT of HIV through breastfeeding can be as high as 0.7 percent per month.¹²⁹ In breastfeeding populations, 30 to 50 percent of MTCT is attributable to breastfeeding.¹³⁰ Although the U.S. Centers for Disease Control and Prevention (CDC) has recommended since 1986 that women with HIV infection avoid breastfeeding,¹³¹ breastfeeding remains heavily

implicated in fueling ongoing vertical transmission in resource-poor settings. The PETRA study (in which AZT and 3TC were given during pregnancy only) revealed that most of the impact of preventive ART was negated when infants breastfed for 18 months, with comparable rates of transmission among interventions and placebo.¹³² Risk of transmission via breastmilk has been found to be dependent on factors such as maternal viral load, maternal immune status, and infant feeding patterns as well as on the presence of infant oral candidiasis or maternal breast pathologies such as mastitis or fissure.^{133–135}

There is fierce debate over the role of breastfeeding in resource-poor settings, where the availability of infant formula and potable water is limited. However, obtaining formula and improving water sources is less complicated than administering lifelong care to HIV-infected infants. The provision of clean water also has a positive impact on the health of the mother, the family, and the community at large. We believe that the provision of clean water and aggressive diarrheal prevention constitute an incontrovertible, actionable link between evidence-based primary care and HIV programs. Similarly, the medical management of diarrheal diseases and close monitoring of growth and nutritional status are central to all child survival programs, whether or not infants have HIV. Given these considerations, recommending formula-feeding for infants born to HIV-infected mothers makes sense both practically and ethically.

While we strongly recommend that HIV-infected women not breastfeed their infants, we recognize that certain circumstances, such as fear of HIV status disclosure or unmitigable lack of access to potable water, may result in women continuing to breastfeed. As part of comprehensive HIV care, evaluation of the social and economic barriers that might lead to such a decision is encouraged.

UNICEF and other organizations recommend exclusive breastfeeding for six months, as some studies have demonstrated increased MTCT through mixed (i.e., breast and formula) feeding. However, studies have found that 75 percent of HIV infections from breastfeeding occur during the first six months.¹³⁶ In addition, if early weaning is indeed promoted and nutritional supplementation is not provided, the infant is at high risk for diarrhea and severe malnutrition.

In our 13 years of experience in providing infant formula, fewer than five percent of HIV-positive women have elected to breastfeed. For women who choose to breastfeed, weaning at six months is encouraged, and nutritional support is given during the weaning period. Because malnutrition, mastitis, and breast lesions are all associated with increased risk of HIV transmission through breast milk, a multivitamin supplement (containing vitamins B, C, and E) as well as basic instructions on the prevention of mastitis and breast lesions should be provided to all breastfeeding women.^{137,138} Single-dose NVP for the mother during labor and for the infant within 72 hours of birth has been associated with a sustained reduction in the transmission of HIV in breastfed babies through 18 months of age.¹³⁹ Studies to determine if triple-drug maternal ART can reduce the risk of viral transmission to infants who continue to breastfeed are currently ongoing.

2.6 Diagnosis and Treatment of STIs

Aggressive diagnosis and treatment of STIs are important for overall health promotion, as well as for the prevention of HIV transmission, and constitutes the fourth pillar of PIH's comprehensive approach to integrated programming. Untreated STIs—particularly untreated genital ulcer disease—increase the risk of HIV transmission tenfold.¹⁴⁰ The presence of any STI increases the shedding of HIV in the genital tract; the treatment of STIs decreases viral shedding.^{141,142}

2.6.1 Cervicitis and pelvic inflammatory disease

In women, *Neisseria gonorrhoea* and *Chlamydia trachomatis* may cause cervicitis. The complications of untreated cervicitis include pelvic inflammatory disease (PID) and tubo-ovarian abscess. If untreated, these infections can lead to scarring of the fallopian tubes, which increases the risk of ectopic pregnancy. Aggressive surveillance and treatment of STIs are thus important not only for decreasing HIV transmission, but also for reducing pregnancy-related deaths.

Because STIs are often asymptomatic (particularly in women), ZL medical staff improve case detection by relying not only on self-reported symptoms, but also on algorithms incorporating context-specific epidemiological risk factors elucidated through local research.¹⁴³⁻¹⁴⁵ Risk assessment algorithms are useful as a screening tool and are especially helpful in settings where confirmatory testing is not available. As may be true in many resource-poor settings, the risk factors identified by ZL (as outlined in Protocol 2.5) are tied not only to a woman's age and number of sexual partners but also to economic stressors. The risk factors included in Protocol 2.5 are specific to women in rural Haiti; health providers in other settings should identify context-specific (local) risk factors for cervical infection. Note that, in the absence of laboratory testing, ZL recommends that all pregnant women receive empiric treatment for chlamydial infection and gonorrhea.

Per Protocol 2.6, all women presenting with lower abdominal pain should undergo a pregnancy test, a speculum exam with cervical gram stain or DNA probe to assess for cervicitis, and a bimanual exam to assess for PID, tubo-ovarian abscess, or ectopic pregnancy.¹⁴⁶ Women with symptoms of vaginal discharge should receive empiric treatment for STIs per Protocol 2.7. However, the majority of women with STIs are asymptomatic; thus, as mentioned, screening should extend beyond the syndromic approach. Active tracing and treatment

of the patient's sexual partner(s) should be provided as a routine part of care.

2.6.2 Urethral discharge

Men reporting urethral discharge or dysuria should be carefully examined for evidence of discharge; swabs should be obtained for gram stain or PCR testing (where available). Active tracing and treatment of the patient's sexual partner(s) should be provided as a routine part of care. The most common pathogens causing male urethral discharge in Haiti are *Neisseria gonorrhoea* and *Chlamydia trachomatis*. Because chlamydia and gonorrhea may be asymptomatic in women, once a man is diagnosed with an STI, his partner(s) should receive empiric treatment for the infection. Protocol 2.8 gives the recommended course of management for urethral discharge.

2.6.3 Vaginitis

It is important to routinely ask all women presenting for care (including those who do not at first mention such symptoms) as to whether or not they are experiencing vaginal discharge or vulval itching or burning. If symptomatic, the patient should be evaluated for vaginitis, which is caused by bacterial vaginosis, trichomoniasis, or candidiasis. Diagnosis of vaginitis is made based on exam findings, wet mount microscopy, and pH and KOH tests per Protocol 2.7; empiric treatment can also be considered without a pelvic exam or in the absence of laboratory evaluations.

In pregnant women, bacterial vaginosis has been associated with increased risk of preterm labor, premature rupture of membranes, late miscarriage, and MTCT of HIV. Treatment of asymptomatic vaginal infections during pregnancy has been shown to reduce preterm delivery by 50 percent.¹⁴⁷ All pregnant women, whether symptomatic or asymptomatic, should thus be screened for vaginal infections and treated as necessary.

2.6.4 Genital ulcers

The diagnosis and treatment of genital ulcers are of particular importance for decreasing the risk of HIV transmission between discordant partners. While some genital ulcers present with pain, others are relatively asymptomatic. As a routine part of the medical history, the practitioner should ask every patient if he or she has noticed bumps, sores, or ulcers on the genitalia. Worldwide, the causative organisms for genital ulcers vary greatly. In Haiti, the most common cause of a painless genital ulcer is syphilis.

Chancroid is another common form of genital ulcers. Unlike syphilis, chancroid presents with painful single or multiple ulcers and, often, enlarged inguinal nodes. Herpes simplex virus (HSV) can also present as painful ulcers, appearing as multiple, small vesicular lesions. There is no cure for HSV. Patients with HSV, especially HIV-infected patients suffering from chronic herpes outbreaks, should be offered acyclovir for symptom relief and suppressive therapy. Granuloma inguinale (also called donovanosis) presents as large, painless, nodular and spreading ulcers not associated with lymphadenopathy. Lastly, lymphogranuloma venereum (LGV) causes a painless ulcer at the genital site of inoculation and then spreads, involving the inguinal or perirectal lymph nodes (so-called "tropical bubo"); such nodes are tender and may eventually suppurate. If buboes are present, they should be drained by needle aspiration through healthy skin. If suppuration occurs, TB should be ruled out by performing AFB analysis on the purulent discharge. Long-term sequelae of LGV include rectovaginal fistula, proctocolitis, and elephantiasis of the genitals due to lymphatic obstruction. Decisions regarding treatment for syphilis, chancroid, HSV, granuloma inguinale, or LGV should be based on local epidemiology per Protocol 2.9.

2.6.5 Screening for latent syphilis

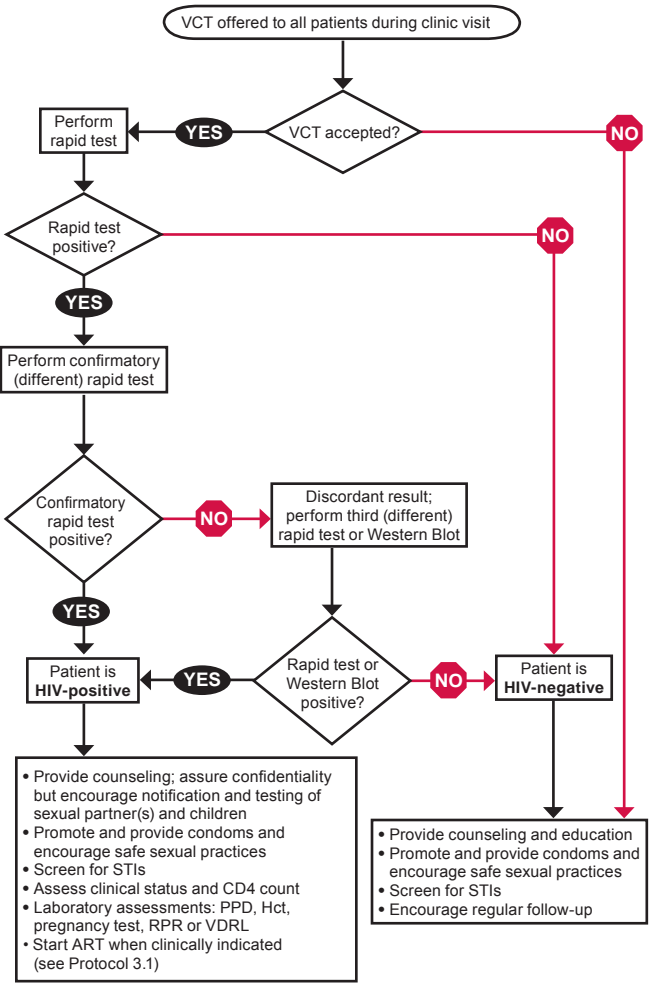
All patients who present for VCT, pregnancy testing, or STI screening should receive a serologic test for syphilis. While

false-positives are not uncommon, in resource-poor settings where syphilis is endemic and access to confirmatory testing is limited, all patients who have a positive serologic test should be treated for latent disease. The patient’s sexual partner(s) should be referred for testing and treatment.

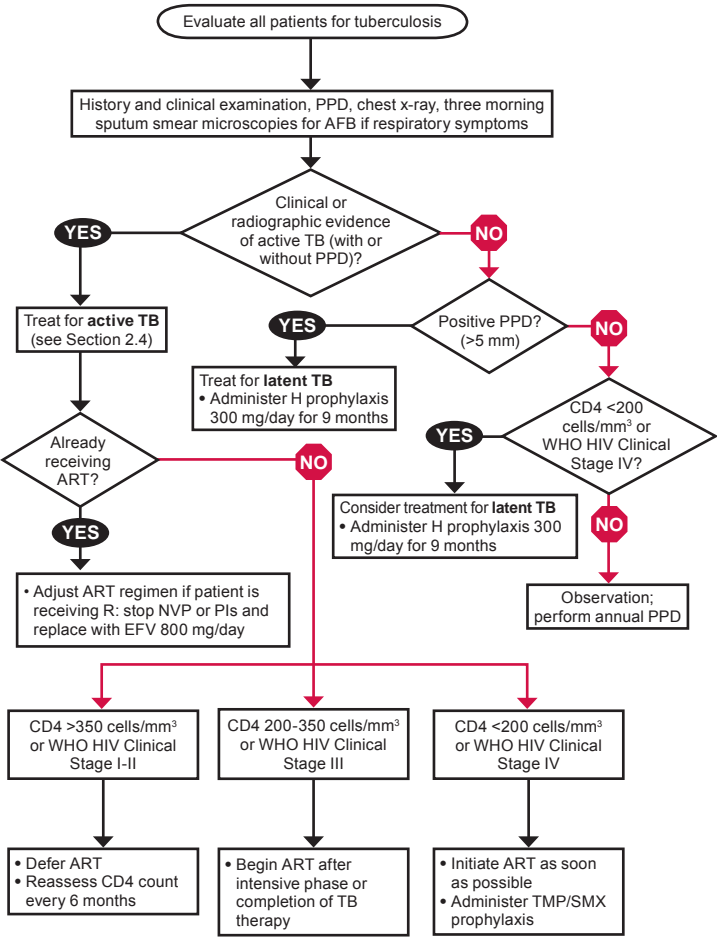
2.7 Conclusion

In Haiti, the ZL medical staff have found that the “four pillars” approach facilitates the identification of the majority of HIV-positive patients in need of care and provides a comprehensive structure for the promotion of primary health. Within the context of comprehensive health services that are available to all members of the community, a great number of HIV patients can be efficiently identified and started on any necessary therapies.

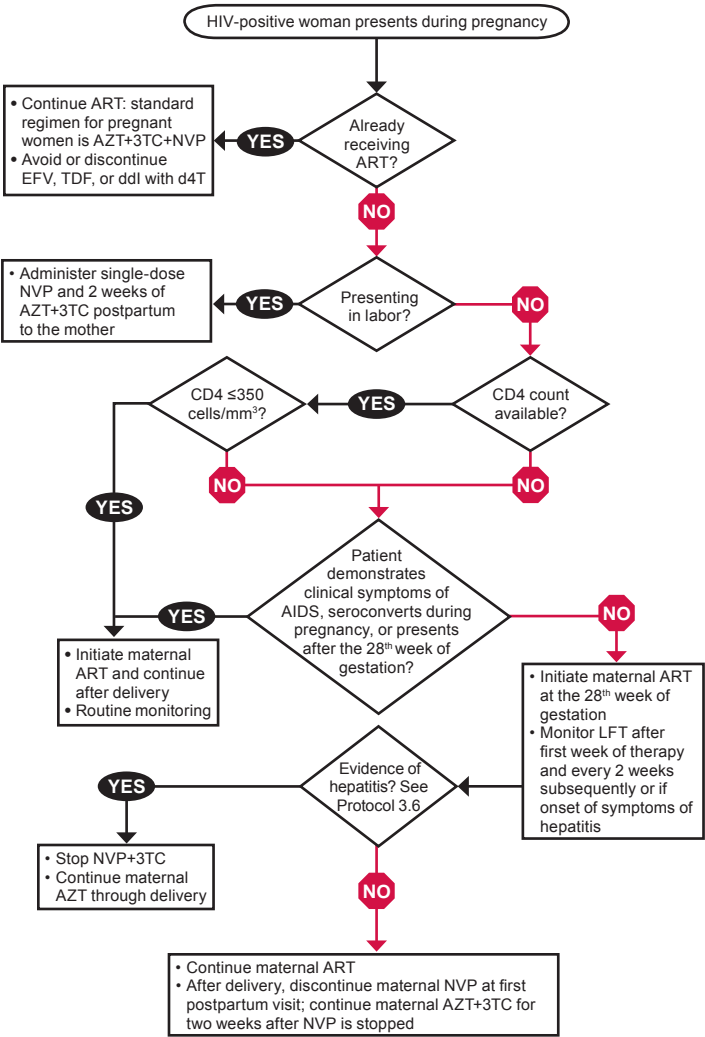
Protocol 2.1 Provider-Initiated HIV Counseling and Testing for Adults and Adolescents



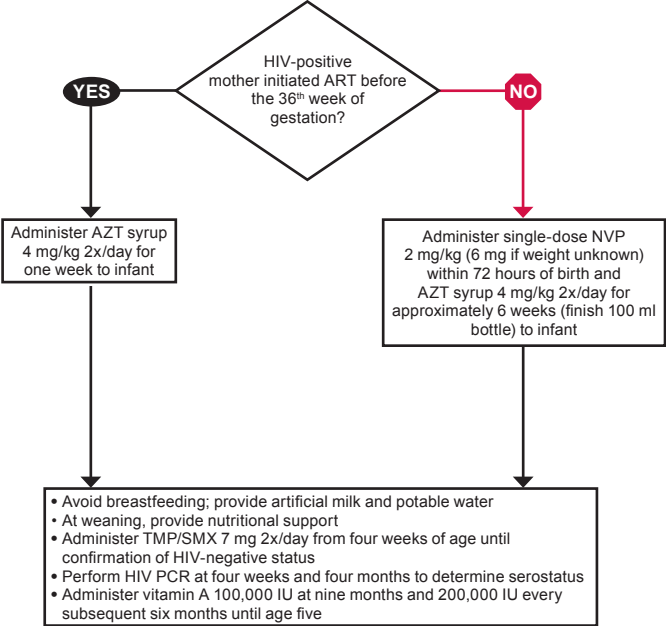
Protocol 2.2 Approach to TB Management in HIV-Positive Patients



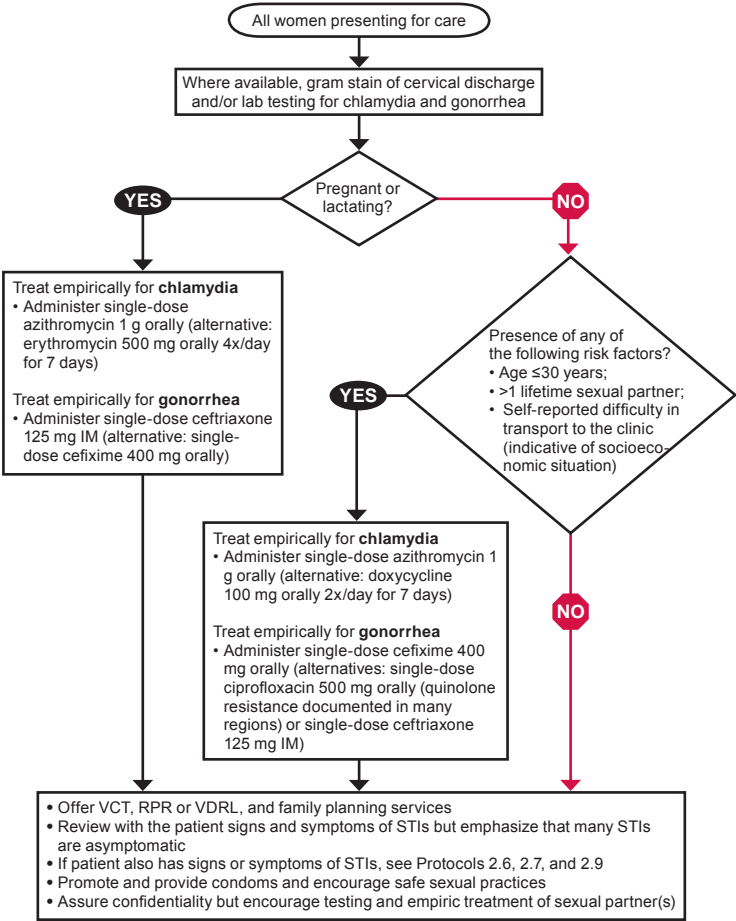
Protocol 2.3 Management of HIV-Positive Pregnant Women to Prevent Mother-to-Child Transmission



Protocol 2.4 Management of Infants Born to HIV-Positive Mothers

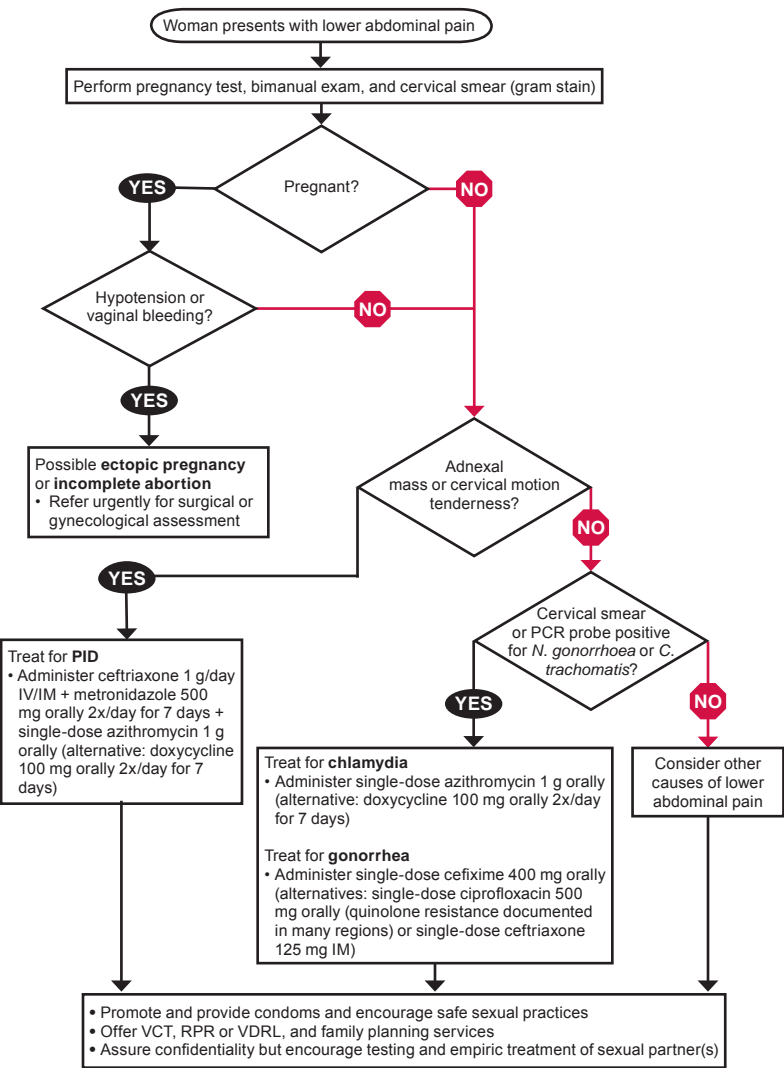


Protocol 2.5 Epidemiologic Screening and Treatment of Chlamydia and Gonorrhea in Women

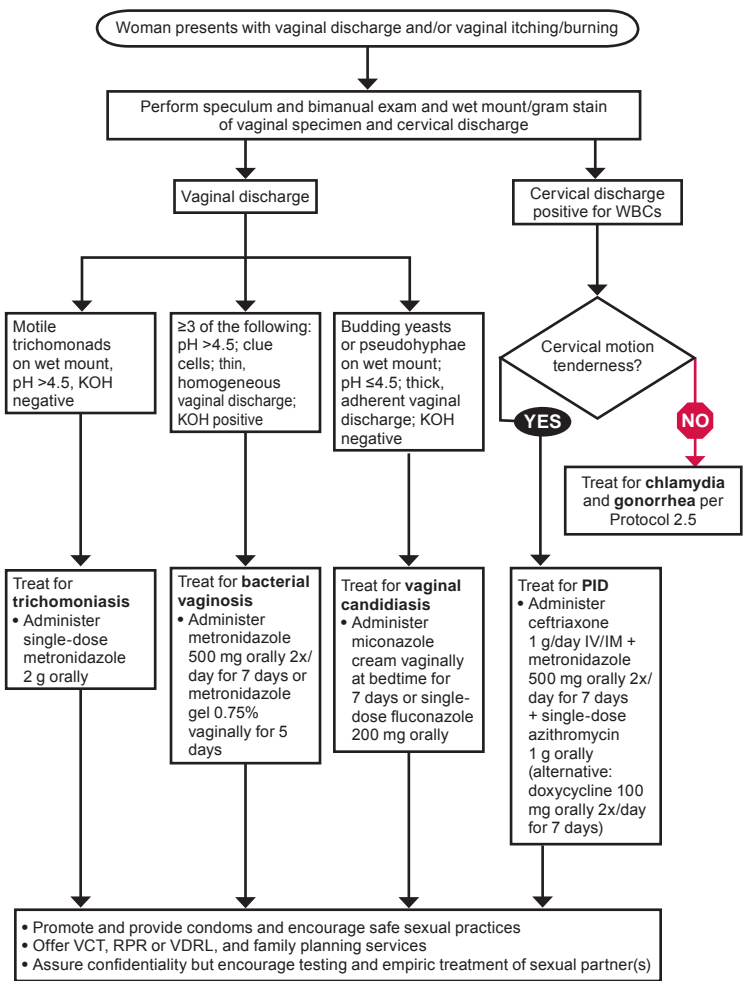


Risk factors indicated in this protocol are specific to women in rural Haiti. Health workers in other settings should adjust this protocol to reflect local risk factors for cervical infection.

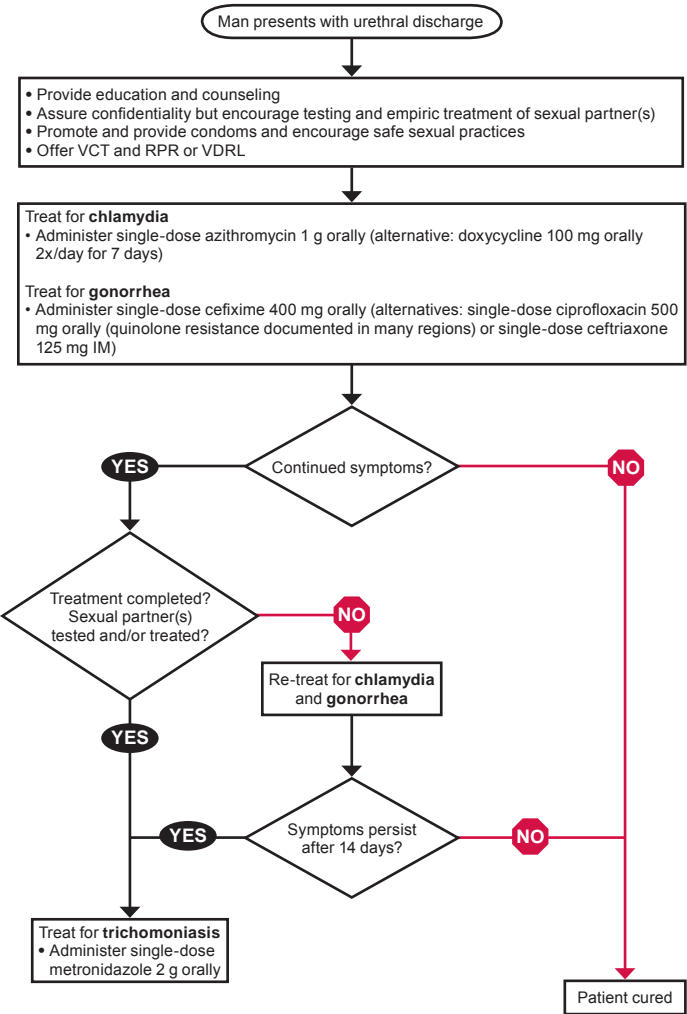
Protocol 2.6 Management of Lower Abdominal Pain in Women



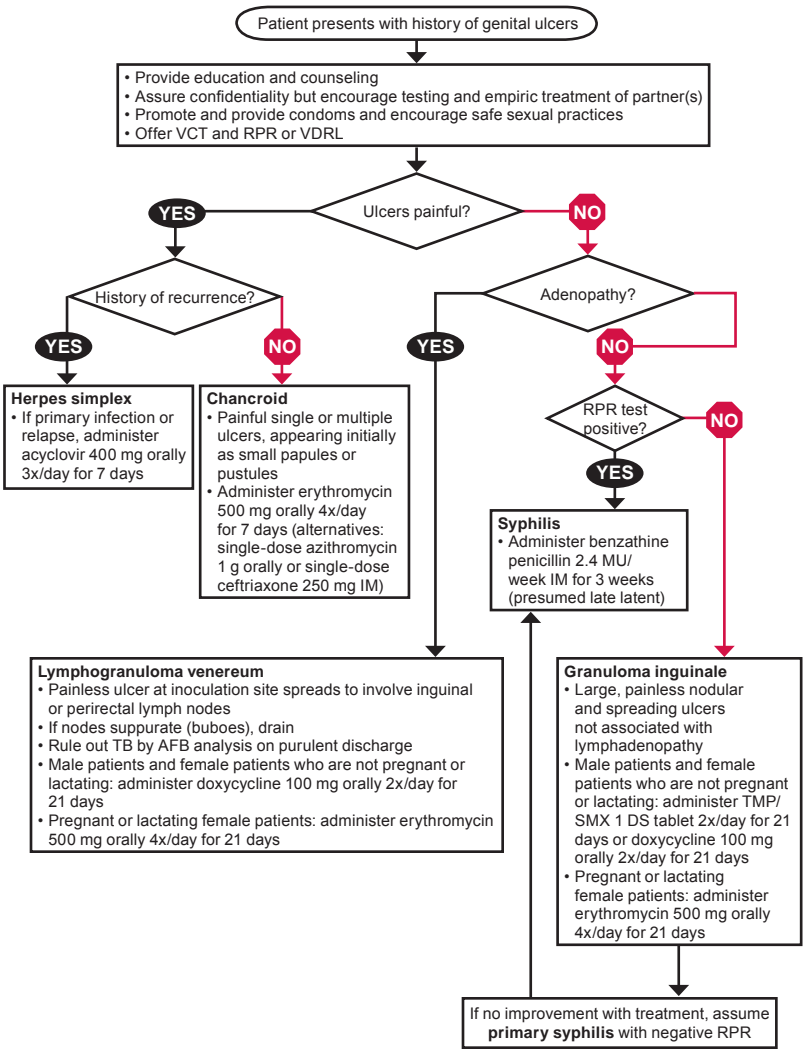
Protocol 2.7 Management of Vaginal Discharge



Protocol 2.8 Management of Urethral Discharge



Protocol 2.9 Management of Genital Ulcers



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Chapter 3: Guidelines for the Management of HIV-Positive Patients

This chapter presents the treatment guidelines and protocols developed by PIH for the management of HIV in rural Haiti and now Africa. It discusses the provision of basic health care, the prevention and treatment of opportunistic infections, and the use of ART for adults and children with AIDS. The recommendations in this section are intentionally broad so as to allow for the clinical management of HIV and its related complications in settings with limited laboratory capacity. While expanding access to modern diagnostics should be a goal of global AIDS control, the absence of such diagnostics should not preclude the implementation and scale-up of comprehensive HIV programs. In fact, much of the care of HIV patients can be undertaken based on clinical assessment alone.

3.1 Initial Evaluation of a Newly Diagnosed HIV-Positive Patient

All patients diagnosed with HIV should undergo a detailed history, clinical examination, and assessment of their social and economic circumstances. Patients in resource-poor settings often experience poor nutritional status, inadequate housing, and limited access to clean water, all of which increase the HIV-positive person's susceptibility to opportunistic infections, especially TB, and waterborne organisms such as salmonella and cryptosporidium. At PIH's programs in Haiti and Rwanda, a social worker, nurse, doctor, or community health worker visits the home of all newly diagnosed persons to assess the overall situation of the patient and his or her family.

During the new patient's initial physical examination, the presence of AIDS-related complications should be carefully evaluated. In particular, per Section 2.4, the presence or absence of TB must be determined prior to assessing the patient's immunologic status and deciding whether or not, and

when, to start ART. All newly diagnosed HIV patients routinely undergo a tuberculin test, a chest radiograph, and, if a cough is present, three consecutive microscopic examinations of sputum for acid-fast bacilli. Lastly, an erythrocyte sedimentation rate (ESR) is often performed in the workup, as a low rate may be helpful in excluding TB; an elevated ESR can be associated with TB, cancer, and even advanced AIDS.

Additional laboratory exams include a pregnancy test for all women of childbearing age, a serologic test for syphilis, complete blood count (CBC) (or Hct alone) and hepatic transaminase enzymes if available, and a pelvic exam that includes screening for gonorrhea and chlamydia. When possible, a Pap smear for the screening of cervical cancer should be performed on all HIV-positive women at the time of diagnosis and yearly thereafter. All newly diagnosed patients should also have their CD4 count measured. If CD4 count technology is not available, assessing the patient's stage of disease according to WHO standards may be helpful. See Appendices B and C for the WHO's staging criteria for HIV infection.

The initial encounter with a newly diagnosed patient should also include an assessment of his or her need for and receptiveness to counseling. Counseling of patients and their sexual partners, as well as screening of patients' family members and social contacts, is undertaken based on the consent of the patient. In addition, women of childbearing age are referred for family planning, and all couples are counseled on the use of condoms per Sections 2.3.2 and 2.5.1.

3.2 When to Start Antiretroviral Therapy

As discussed in Chapter 1, in 1998 ZL began administering ART in Haiti based on patients' clinical status alone. Since CD4 testing has become available in central Haiti, initiation of treatment has been guided by CD4 count as well as by the clinical status of the patient. The WHO has also used

both clinical staging and total lymphocyte count as surrogate markers for immune suppression. Under the WHO guidelines, the total lymphocyte count is calculated by multiplying WBC count per high-powered field by the patient's percentage of lymphocytes. Protocol 3.1* provides an overview of both the laboratory and syndromic approaches to initiating ART; for a discussion of when to initiate ART in HIV-positive pregnant women, also see Sections 2.5.2 through 2.5.5 and Protocol 2.3.

3.2.1 Recommendations based on CD4 count

Based on evidence from clinical trials, the U.S. Department of Health and Human Services (DHHS) and the European Guidelines agree that all HIV-positive adults with a CD4 count below 200 cells/mm³ should be started on ART. Thus, when a CD4 count is in fact available, 200 cells/mm³ should be the minimum standard for initiating ART.

Other studies suggest that patients with a CD4 count below 350 cells/mm³ also benefit from ART. In Haiti and Rwanda, as in many HIV-endemic countries, more aggressive pathogens such as TB and salmonella are associated with high morbidity and mortality among HIV-positive patients. Therefore, at PIH projects, the decision to initiate ART is based on this more conservative guideline of 350 cells/mm³. (See Section 2.4.3 for a discussion of ART initiation in TB co-infected patients.)

Lastly, a small subset of persons with CD4 counts above 350 cells/mm³ may merit ART based on symptoms that indicate failure to thrive or persistent recurrent OIs.

* All protocols for Chapter 3 are grouped at the end of the chapter, immediately before the References.

3.2.2 Recommendations based on clinical staging and limited laboratory capacity

In settings where CD4 count technology is not yet available, the patient's total lymphocyte count may be used as a proxy for CD4 count as discussed above. However, measuring total lymphocyte count is a labor-intensive process and requires either expertise in microscopy or a cell counter; therefore, the most practical alternative to CD4 testing is clinical staging. The WHO recommends ART for all patients with Adult Clinical Stage III or Stage IV disease, irrespective of total lymphocyte count, and for patients with Stage II disease when the total lymphocyte count is less than 1,200 cells/mm³.¹

3.3 Recommendations for ART in Adults

Antiretroviral regimens consist of at least three drugs—in general, two NRTIs and a third agent, either an NNRTI or a PI.

In 2001 the WHO introduced the concept of first- and second-line ART regimens. The choice of two NRTIs and one NNRTI was designated the first-line regimen. The choice of an NNRTI as the third agent was based on the greater potency of this particular class over the PIs that are temperature-stable (indinavir (IDV) and nelfinavir (NFV)). The most effective PIs are those combined with ritonavir (RTV)—the “ritonavir-boosted” PIs—which depend on a cold chain. Due to this logistical complexity, the use of a ritonavir-boosted PI as the third agent has been relegated to second-line status. (Note that, at the writing of this manual, a new heat-stable formulation of ritonavir-boosted lopinavir (LPV/r) is not yet available in most resource-poor settings; however, numerous groups are advocating for concessional pricing of this agent.) See Figure 3.1 for the drugs constituting the first- and second-line regimens; Appendix D presents dosing and interaction information for each drug.

3.3.1 First-line regimens

The two NRTIs generally used as first-line drugs are 3TC and either AZT or d4T (which are antagonistic and should not be prescribed together). Zidovudine can cause or worsen anemia in settings where malnutrition or other chronic diseases such as TB and malaria are endemic. On the other hand, while d4T may be safer as an initial therapeutic agent for anemic patients, it has been associated with higher rates of neuropathy and lipodystrophy. While lowering the d4T dose may prevent progression of these side effects, AZT may be a better long-term option once anemia is controlled. 3TC is used in all first-line (and many second-line) regimens because it is the best-tolerated antiretroviral drug and has no significant drug-drug interactions. Moreover, the 184 mutation that develops with 3TC may result in a virus that is in fact less fit than the native (wild-type) virus.

Abacavir, ddI, or TDF can also be paired with 3TC to form the nucleoside backbone of the ART regimen. However, ddI is less well tolerated than other NRTIs. Abacavir and TDF are very potent drugs and generally well tolerated, but generic equivalents are not available at the time of this writing. Thus, these medications remain very expensive for inclusion in first-line therapy, and they are recommended for second-line use.

Due to its safety profile in pregnant women, its generic availability, and its low cost, NVP is the most common third agent in first-line therapy. As described in Section 2.5.5, however, several studies and recent data from the manufacturer suggest that women with a CD4 count above 250 cells/mm³ experience a much higher risk of hepatitis from NVP than either men or women with low CD4 counts. Thus, women with a CD4 count above 250 cells/mm³ who are receiving NVP should have their LFTs monitored one week after initiation of therapy and every two weeks subsequently (or earlier and more frequently if symptoms of hepatitis occur).²

Figure 3.1 Components of the ART Regimen

First-line regimens:
2 NRTIs and 1 NNRTI

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs) Efavirenz (EFV) Nevirapine(NVP)	Nucleoside Reverse Transcriptase Inhibitors (NRTIs) Zidovudine (AZT) ^a Lamivudine (3TC) Stavudine (d4T) ^{a,b} Didanosine (ddI) Abacavir (ABC) AZT/3TC AZT/3TC/ABC Tenofovir (TDF) ^c	Protease Inhibitors (PIs) Indinavir (IDV) Ritonavir (RTV) Saquinavir (SQV) Nelfinavir (NFV) Lopinavir/Ritonavir (LPV/r)
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^a AZT and d4T are antagonistic and should never be used together.
^b The combination of d4T and ddI has been shown to have increased toxicity and should be avoided if possible.
^c TDF is a nucleotide reverse transcriptase inhibitor but is typically grouped with the nucleoside reverse transcriptase inhibitors.

Efavirenz is indicated as the third agent for patients who are intolerant of NVP (due to rash or hepatitis). Additionally, patients who are being treated for TB with a regimen containing rifampin should receive EFV instead of NVP, as described in Section 2.4.4, as levels of both NVP and R are lowered in the presence of the other drug. Concomitant administration of EFV will not alter the blood level of R, and increasing the EFV dose to 800 mg/day will counter the effect that R has on the blood level of EFV. Note that EFV is teratogenic and should not be prescribed for women who are pregnant or not practicing birth control.

The most common first- and second-line antiretroviral regimens as recommended by the WHO are summarized in Table 3.1.

Table 3.1 Recommended First- and Second-Line ART Regimens for Adults and Adolescents

Regimen	Components		
	NRTI	NRTI	NNRTI or PI
First-line regimen	AZT or d4T	3TC	NVP or EFV
Second-line regimen	TDF	ABC, 3TC, or AZT/3TC	LPV/r

3.3.2 Emergence of antiretroviral drug resistance
Adherence to therapy is a key factor in preventing the development of drug-resistant strains of HIV. Studies with currently available drugs have shown that adherence rates must be very high in order to achieve suppression of viral replication. In one study, more than half of the patients who took less than 95 percent of their ART doses had detectable viral loads, indicating active viral replication during the study period; many other studies have shown similar results.^{3–8} While newer drugs with lower pill burdens and improved pharmacokinetics may lessen the need for near-perfect adherence, the currently available data highlight the importance of stringent adherence to ART.

There is no evidence to suggest that the emerging burden of viral resistance to ART will be worse in developing countries than in wealthier countries, and such concerns should not be used as arguments against providing life-saving therapy to those who need it. Rather, concerns regarding the emergence of viral resistance should encourage HIV programs to develop comprehensive strategies for the delivery of care. As discussed in Section 3.10, every HIV treatment program should develop a full range of locally relevant strategies to enable and improve adherence. As ART becomes widely available, the WHO and its partners intend to collect reliable, updated information on

the prevalence of drug-resistant strains among treated and untreated subjects.⁹

3.3.3 When to suspect treatment failure

Patients receiving ART may eventually reach a point where they experience treatment failure: clinical worsening despite receiving ART. Treatment failure generally occurs as a result of inadequate levels of ART in a patient's bloodstream,¹⁰ usually due to poor treatment adherence or drug malabsorption. The low levels of ART allow the HIV virus to replicate and select for mutations that confer drug resistance.¹¹ Once mutations in the virus have conferred resistance to an ART drug, viral replication will recur and, over time, CD4 cells will once again start to be destroyed, resulting in worsening immune suppression. Detection of virologic replication while on ART is thus the gold standard for determining treatment failure.

Assessing the patient's adherence to the prescribed ART regimen is the first and most important step in evaluating possible treatment failure.¹² The next step is to carefully rule out other possible causes of clinical worsening, including immune reconstitution syndrome (see Section 3.9.7) or the presence of OIs (particularly extrapulmonary TB) or chronic diarrhea, which may result in malabsorption of ART.

The most sensitive test to determine whether or not ART is resulting in suppression of viral replication is a viral load assay. When such assays are available, viral load should be measured every three to six months during treatment.¹³ An increase in viral load of greater than 1 log while the patient is on ART is suggestive of treatment failure.

In practical terms, however, because surveillance of viral load is not available in most resource-poor settings,¹⁴ evaluation of treatment failure must start with a thorough history and a physical examination to assess for signs of clinical progression of disease.¹⁵ Treatment failure may be considered based on

clinical features such as weight loss, fever, adenopathy, or the onset of a new OI. Immunologic criteria may also be used to evaluate treatment failure: the WHO has established a 50 percent decrease in CD4 count from the peak count registered or a drop below the pre-ART baseline as reasonable criterion. Protocol 3.2 outlines an algorithmic approach to assessing the clinical and immunologic response of patients receiving ART.

3.3.4 Second-line regimens

In resource-poor settings, the resistance pattern of a patient who is failing therapy will most likely not be known; however, it is reasonable to assume that the following mutations will be present: the N103 mutation, which confers resistance to both NVP and EFV; the 184 mutation, which confers resistance to 3TC; and multiple NRTI mutations that confer resistance to AZT and d4T. Because a high cross-resistance between AZT and d4T is manifested when one of these drugs is used in the first-line regimen, including the other drug in a second-line regimen is not recommended.¹⁶

Based on the aforementioned mutations and as indicated in Table 3.1, the WHO recommends the use of an empiric second-line regimen consisting of TDF as the nucleoside backbone; ABC, 3TC, or an AZT/3TC combination as the second agent; and the potent combination of LPV/r as the third agent. Protocol 3.3 presents an algorithm for determining the necessity of switching to second-line treatment.

3.4 Management of Pediatric HIV

HIV can be transmitted from HIV-infected mothers to their offspring during pregnancy, at the time of delivery, or during breastfeeding. As discussed in Section 2.5.4 and illustrated in Protocol 2.4, in order to minimize the chances of transmission near the time of delivery, all infants born to HIV-infected mothers should receive AZT prophylaxis for one to six weeks and possibly single-dose NVP, depending on the mother's ART

history and time of presentation. In addition, PIH programs recommend and train HIV-positive mothers to use formula-feeding. Bottles and fuel for boiling water are provided, and mothers are counseled on the use of oral rehydration solution and the importance of seeking clinical care at the first suspicion of diarrheal disease. See Section 2.5.7 for a comprehensive discussion of breastfeeding and MTCT risk. Where clean water cannot be assured, some programs recommend exclusive breastfeeding for six months to balance the benefits of breastmilk and the prevention of diarrheal disease against the risk of HIV transmission.

All infants born to HIV-positive mothers should receive monthly medical follow-up, complete immunizations, and nutritional support. Beginning at four weeks of age and continuing until the infant's HIV-negative status can be confirmed, all HIV-exposed infants should receive daily TMP/SMX prophylaxis (7 mg 2x/day) to prevent *Pneumocystis jiroveci* pneumonia (PCP) and bacterial infections.¹⁷ All HIV-exposed infants should receive 100,000 IU of vitamin A at nine months of age and 200,000 IU every subsequent six months until the age of five.^{18,19}

3.4.1 Diagnosing HIV in infants

Maternal antibody to HIV may be present in infants until 18 months of age; infants may therefore record a false-positive HIV antibody test up until clearance of these maternal antibodies. This period of uncertainty as to whether or not the infant is HIV-infected can be fatal. Studies have shown that babies who acquire HIV *in utero* or immediately postpartum and who have high viral loads at birth are at a greater risk of dying during their first year of life than infants infected through breastfeeding.²⁰

Improving access to virological testing—an effective method for diagnosing HIV in infants under 18 months of age—has received increased interest over the past several years. Virologic detection of the presence of either DNA (at one month of age) or RNA (at four months of age) in an infant's blood can

confirm his or her serostatus. For HIV-infected infants, an early definitive diagnosis can be life-saving. ZL uses HIV-1 RNA tests from samples collected on filter paper (dried blood spots). The blood is obtained via heel prick; once dried on the filter paper, the spots are noninfectious and stable at room temperature for many months and can be sent to a testing laboratory. ZL clinical staff have found the blood spot assay to be a feasible method for early diagnosis of HIV in children living in resource-poor settings. Protocol 3.4 illustrates the virologic approach to the diagnosis of HIV infection in infants.

In areas where HIV antibody testing is the only available option, PIH recommends that all infants born to HIV-infected mothers receive routine antibody testing at birth, 6 months, 12 months, and 18 months of age; these infants should also be closely monitored for clinical indicators of infection.

3.4.2 Starting ART in infants and children

If HIV infection is suspected in infants younger than 18 months of age and virologic diagnosis is not available, WHO staging criteria (see Appendix C) and CD4 count or percent, if available, may be sufficient criteria to initiate therapy. Note that clinical diagnosis of these infants remains uncertain because many of the syndromes indicated—especially recurrent bacterial infections, growth failure, and tuberculosis—are frequently seen in HIV-negative infants in the developing world. For all infants under 18 months of age in whom ART is initiated based solely on clinical criteria, HIV serum antibody should be measured after 18 months; ART should be continued only in those infants who have a positive antibody test.

The classification of immune suppression in HIV-exposed children under five years of age is optimally assessed by percentage of CD4 cells of all T-lymphocytes (all CD3-positive cells) rather than by absolute CD4 count.²¹ Protocol 3.5 summarizes the approach to deciding when to initiate ART in children.

3.4.3 Choice of pediatric ART regimens

The choice of first-line ART for children follows the same general principles as for adults, but with additional considerations regarding available formulations and certain pharmacokinetic factors. First-line NRTIs generally used for children are 3TC and either AZT or d4T. The third agent is typically an NNRTI, usually NVP. The recommended first- and second-line pediatric ART regimens are summarized in Table 3.2. Once a child weighs more than 10 kilograms, it is possible to administer tablets and capsules, which are cheaper and simpler to procure and store than syrup formulations. Appendix E presents dosing information for the most commonly available formulations of pediatric ART.

Table 3.2 Recommended First- and Second-Line ART Regimens for Children

Regimen	Components		
	NRTI	NRTI	NNRTI or PI
First-line regimen	AZT or d4T	3TC	NVP or EFV ^a
Second-line regimen	ABC	3TC or AZT/3TC	LPV/r

^a The bioequivalence for EFV in children under three years of age has not been determined. Thus, for co-infected children under three years of age who are receiving R, ABC should be used as the third agent instead of EFV.

For children co-infected with TB, ART is generally deferred until after at least two months of TB therapy, or (if possible) until TB treatment is completed. Delaying ART avoids adverse drug interactions with rifampin and helps limit the number of medicines a child must take at any one time. In children above three years of age who are receiving rifampin as part of concomitant TB treatment, the third ART agent should be EFV instead of NVP. The bioequivalence for EFV in children under three years of age has not been determined, however; HIV/TB co-infected children under three years of age who are receiving R should receive ABC as the third antiretroviral agent. Note that known perinatal exposure to NVP also warrants

consideration in determining an appropriate pediatric ART regimen.

3.5 Monitoring Treatment Response

Clinical improvement is the most important indicator to monitor in judging a patient’s response to ART. In general, weight gain and the absence of symptoms indicative of OIs are sufficient clinical markers for assuming a positive response to therapy.

Patients should be seen in clinic monthly, at which time they should be assessed for their adherence to medications; their need for social assistance and nutritional support; and their risk of transmitting HIV, including transmission through pregnancy or to new sexual partners. The patient’s CD4 count and/or viral load, if available, should be checked every three to six months. Screening of all family members and social contacts should also be conducted on a biannual basis.

Common side effects of ART, as discussed in the next section, should be monitored clinically. Basic laboratory tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and CBC are useful. Other helpful tests include those for glucose, amylase, lipase, and lactic acid. When such tests are available, CBC and differential and a full chemistry panel, including renal and hepatic parameters, should be performed one month after the initiation of therapy and every six months subsequently; tests should be performed more frequently if a patient exhibits symptoms of ART toxicity.

In children, growth and height should be monitored using standard curves. Doses should be adjusted regularly based on weight gain. Development is also assessed during the monthly clinic visit. Routine testing and follow-up are otherwise the same as for adults.

3.6 Management of Adverse Reactions to Treatment

During the course of HIV management, numerous side effects of ART and of medications for OIs may be encountered.^{22,23} Most of the adverse reactions associated with HIV treatment are not life-threatening, though they may impede patient adherence to therapy and should thus be managed aggressively.^{24,25} Early diagnosis and prompt discontinuation of the offending agent(s) can help prevent rare but deadly reactions. Once identified, the management of all adverse reactions associated with HIV treatment can be undertaken using simple algorithms adjusted to individual circumstances. Table 3.3 identifies possible adverse reactions to medications used in HIV management. The subsequent pages, and Protocols 3.6 through 3.14, present brief summaries and diagnostic and management algorithms for the treatment of the most common adverse reactions.

3.6.1 Hepatotoxicity

Hepatotoxicity is defined as a three- to five-fold elevation of serum transaminase enzymes above the normal limit. Risk factors for ART-induced hepatotoxicity include female gender and chronic hepatitis.²⁶ While all NNRTIs and PIs can cause hepatitis, the antiretroviral agent most commonly associated with this reaction is NVP. In one study, 12.5 percent of patients receiving NVP had abnormal liver enzymes, while 1.1 percent of all patients receiving the drug had clinically significant hepatitis.^{27,28}

Hepatitis usually occurs within the first 12 weeks of initiating ART. Most patients with NVP-induced hepatitis are asymptomatic; however, some may complain of poor appetite, nausea, vomiting, abdominal discomfort, malaise, or jaundice. For men and children, transaminases should be measured one month after starting therapy and every three months thereafter.²⁹ For women (especially those with a CD4 count above 250 cells/mm³ who are initiating a NVP-containing ART regimen), liver function should be checked after one week of therapy and every two weeks subsequently, or more frequently if any symptoms of hepatitis occur.

If hepatitis is diagnosed either clinically or as indicated by the patient's LFTs being five times greater than normal, all ART should be stopped. Once transaminases have returned to normal or symptoms have resolved, a new ART regimen should be started. The same two NRTIs may be continued, but NVP should not be re-introduced.³⁰ An EFV-containing regimen may be tried, as EFV is in the same class of drugs as NVP but is much less likely to cause hepatitis. See Protocol 3.6 for a management algorithm for hepatotoxicity.

3.6.2 Rash

Rash may occur in response to ART or to the medications used for the prevention or treatment of OIs. The HIV-related medications that are most likely to cause rash are TMP/SMX, NVP, and ABC (see Section 3.6.3 for a discussion of ABC-associated rash). The rash caused by either NVP or TMP/SMX usually presents shortly after medication is initiated.³¹ While the majority of HIV medication-induced rashes are not life-threatening, prompt evaluation is necessary to rule out the presence of more severe reactions. The types of rash due to HIV-related drugs may range from mild photosensitivity to life-threatening Stevens-Johnson syndrome, a severe presentation in which the rash is associated with fever, malaise, serositis, and involvement of mucous membranes.³²

Table 3.3 Adverse Reactions Associated with ART and with Medicines for Opportunistic Infections

Adverse reaction	Possible offending agent(s), time of presentation, potential severity, differential diagnosis
Hepatotoxicity Protocol 3.6	<ul style="list-style-type: none"> • Possible offending agents: NVP, Pls, TMP/SMX, H, R, Z • Time of presentation: with NVP, usually within first 12 weeks of therapy; with Pl, TMP/SMX, or H, anytime during therapy • Severity: may be life-threatening • Differential diagnosis: granulomatous hepatitis from TB; viral hepatitis A, B, C; CMV
Rash Protocol 3.7	<ul style="list-style-type: none"> • Possible offending agents: NVP, TMP/SMX • Time of presentation: usually early (first 1-3 months) in therapy • Severity: can be mild but may be severe, including Stevens-Johnson syndrome • Differential diagnosis: eosinophilic folliculitis, ABC hypersensitivity
Abacavir hypersensitivity Protocol 3.7	<ul style="list-style-type: none"> • Offending agent: ABC • Time of presentation: usually during first year of therapy • Severity: possible life-threatening anaphylaxis upon rechallenge • Differential diagnosis: anaphylaxis to other agents
Anemia, leukopenia Protocol 3.8	<ul style="list-style-type: none"> • Possible offending agents: AZT, TMP/SMX • Time of presentation: during first year of therapy • Severity: rarely life-threatening • Differential diagnosis: HIV-associated cytopenias, TB, malaria, nutritional deficiency, chronic parasitic infestation
Central nervous system disturbance Protocol 3.9	<ul style="list-style-type: none"> • Possible offending agent: EFV • Time of presentation: early in therapy • Severity: not life-threatening • Differential diagnosis: cerebral malaria, chronic meningitis (TB, cryptococcal, neurosyphilis), HIV dementia, nutritional deficiencies (especially pellagra)
Peripheral neuropathy Protocol 3.10	<ul style="list-style-type: none"> • Possible offending agents: NRTIs (especially d4T, ddI), H • Time of presentation: during first year of therapy • Severity: symptoms may be severe, although not life-threatening • Differential diagnosis: HIV-associated neuropathy, vitamin (B1, B6, B12) deficiencies, diabetes mellitus

Adverse reaction	Possible offending agent(s), time of presentation, potential severity, differential diagnosis
Myopathy Protocol 3.11	<ul style="list-style-type: none"> • Possible offending agents: NRTIs (especially d4T, ddI, AZT) • Time of presentation: middle to late in therapy • Severity: rarely severe • Differential diagnosis: HIV-associated myopathy
Nephrolithiasis (kidney stones) Protocol 3.12	<ul style="list-style-type: none"> • Possible offending agent: IDV • Time of presentation: anytime during therapy • Severity: not life-threatening • Differential diagnosis: pyelonephritis
Pancreatitis Protocol 3.13	<ul style="list-style-type: none"> • Possible offending agents: d4T, ddI (especially in combination) • Time of presentation: middle to late in therapy • Severity: may be life-threatening • Differential diagnosis: gallstones or alcoholic pancreatitis, peptic ulcer disease, cholecystitis
Dyslipidemia, hyperglycemia	<ul style="list-style-type: none"> • Possible offending agents: Pls • Time of presentation: late in therapy • Severity: not life-threatening • Differential diagnosis: new onset diabetes mellitus
Lipodystrophy	<ul style="list-style-type: none"> • Possible offending agents: NRTIs (especially d4T, ddI) • Time of presentation: late in therapy • Severity: cosmetic effects only
Lactic acidosis, hepatic steatosis Protocol 3.14	<ul style="list-style-type: none"> • Possible offending agents: NRTIs (especially d4T, ddI) • Time of presentation: late in therapy • Severity: may be life-threatening • Differential diagnosis: sepsis, hepatitis

Stevens-Johnson syndrome is most commonly associated with NVP and may also be associated with LFT abnormalities and eosinophilia. If a severe reaction is diagnosed, medications should be stopped immediately and supportive care provided until the patient has improved. Once a severe rash has occurred, the offending agent should not be used again.³³ See Appendix F for more details about specific rashes and Protocol 3.7 for a management algorithm.

3.6.3 Abacavir hypersensitivity

A specific rash is associated with ABC hypersensitivity and may also present with nausea, vomiting, diarrhea, fever, shortness of breath, or hypotension.³⁴ The initial presentation of the ABC rash may not be as serious as the rash provoked by NVP. However, if an ABC rash has occurred, anaphylaxis is possible upon rechallenge with ABC.³⁵ Thus, once ABC is stopped due to rash, it should not be used again.³⁶ Any patient receiving ABC who reports a rash should be evaluated immediately. If hypersensitivity is diagnosed, stop ART and provide supportive care, including aggressive hydration and blood pressure support if needed. Once the patient is hemodynamically stable, ART may be resumed; as noted above, the patient should never receive ABC again. Protocol 3.7 gives management information for ABC hypersensitivity.

3.6.4 Anemia and leukopenia

Drug-induced bone marrow toxicity can decrease blood cell production, which leads to anemia or leukopenia.^{37,38} Less commonly, the production of all blood cells is suppressed, resulting in pancytopenia. Suppression of cell counts can be associated with ART (in particular, with AZT) or with HIV itself. All patients' WBC count and hematocrit should be checked at baseline, one month after initiation of therapy, and every three to six months thereafter. Drug-induced bone marrow suppression should be considered in cases of new-onset leukopenia (WBC count below 3,000 cells/mm³) and/or new-onset anemia after initiation of ART. Alternative causes of abnormalities—including endemic and opportunistic infections—should be ruled out. TMP/SMX-associated anemia may improve with the administration of folinic acid supplementation. Note that malaria and TB, in particular, are associated with anemia. If leukopenia or anemia is severe and no other causes are identified, replace AZT with another NRTI, typically d4T.³⁹ Protocol 3.8 gives a management algorithm for anemia and leukopenia.

3.6.5 Central nervous system disturbance

Efavirenz may be associated with dizziness, sleep disturbance, memory loss, and difficulty concentrating.⁴⁰ In general, these symptoms are mild and abate within a few weeks of initiating therapy. Most patients can tolerate these symptoms without requiring a change in ART regimen. Similarly, AZT may cause headaches; but, again, symptoms are mild and will resolve with continued therapy.⁴¹ Of course, any new onset of more serious central nervous system (CNS) disturbances should prompt evaluation for other causes of these symptoms, including OIs. See Protocol 3.9 for a management algorithm for CNS disturbances.

3.6.6 Peripheral neuropathy

Peripheral neuropathy may be associated with HIV itself or be triggered by vitamin deficiencies connected with malnutrition. In particular, pyridoxine deficiency may be worsened by the administration of isoniazid for the treatment of active or latent TB. Damage to peripheral nerves can also be caused by direct mitochondrial toxicity from NRTIs, especially from d4T and ddI.⁴² Patients report burning, numbness, hyperesthesia, and difficulty walking due to pain; symptoms are most pronounced in distal extremities, usually in a stocking-glove distribution.⁴³ While these symptoms are enough to warrant a presumptive diagnosis, peripheral neuropathy may be confirmed on physical exam by the presence of decreased sensation to light touch and diminished deep tendon reflexes (DTRs) at the ankle.

Mild neuropathy may be managed either by correcting vitamin deficiencies or by the use of mild NSAIDs. However, because neuropathy is often irreversible,⁴⁴ a report from the patient of significant pain should prompt the discontinuation of the offending agent, usually d4T or ddI; AZT or 3TC may be substituted. While tricyclic antidepressants are often recommended, they have little effect and are not widely available in resource-poor settings. Nutritional support is likely to be

more beneficial to patients in such settings. See Protocol 3.10 for a management algorithm for peripheral neuropathy.

3.6.7 Myopathy

Damage to muscles (myopathy) may be seen alone or within a constellation of mitochondrial toxicity syndromes such as lactic acidosis and peripheral neuropathy. Myopathy is most frequently associated with the NRTIs AZT, d4T, and ddI.⁴⁵ Patients with myopathy may present with myalgias, muscle aches or tenderness, and elevated creatine kinase.⁴⁶ If symptoms are mild, ART should be continued and other causes of myopathy (including infection and toxicity from other medications) ruled out.⁴⁷ If severe, the offending agent should be replaced with 3TC or ABC, which are less likely to cause myopathy. Refer to Protocol 3.11 for a management algorithm for myopathy.

3.6.8 Nephrolithiasis (kidney stones)

The deposit of indinavir crystals in the kidney due to inadequate hydration may result in renal calculi.⁴⁸ Such kidney stones present like other calculi, with colicky abdomen, flank pain, dysuria, or hematuria.⁴⁹ The stones are not radio-opaque; therefore, clinical diagnosis (via supporting laboratories, if available) is adequate.⁵⁰ Once kidney stones have developed, hydration and analgesia are the mainstays of treatment.⁵¹ Indinavir may be continued if adequate hydration is provided;⁵² however, an NNRTI or a different PI is typically substituted. See Protocol 3.12 for a management algorithm for kidney stones.

3.6.9 Pancreatitis

Life-threatening chemical pancreatitis may be induced by ddI and d4T, particularly when these two drugs are used in combination.⁵³ Symptoms include abdominal pain, anorexia, nausea, vomiting, malaise, and fever.⁵⁴ To confirm the diagnosis, pancreatic function tests (in particular, lipase and amylase) may be performed. If pancreatitis is suspected or confirmed, ART should be discontinued and supportive care provided until symptoms resolve. Stavudine and ddI should not be restarted or given to any patient with a prior history of pancreatitis,

regardless of etiology.⁵⁵ See Protocol 3.13 for a management algorithm for pancreatitis.

3.6.10 Dyslipidemia and hyperglycemia

Lipid abnormalities have been observed after long-term use of PIs and EFV.⁵⁶ While elevated cholesterol may result, it remains unclear whether such elevation will cause significant problems in countries where malnutrition is endemic and diets are generally low in fat.

Worsening diabetes control, diabetic ketoacidosis, and even new-onset diabetes mellitus have all been observed after prolonged use of PIs.^{57,58} For patients on PIs, blood sugar should be monitored every three months;⁵⁹ more frequent testing is recommended for pregnant women. Antiretroviral therapy should not be changed unless hyperglycemia and dyslipidemia are refractory to management.^{60,61}

3.6.11 Lipodystrophy and lipotrophy

Lipodystrophy is manifested as fat redistribution, often with disproportionate accumulation in the abdomen, dorso-cervical fat pad (“buffalo hump”), and breast, with somewhat less accumulation in the face and extremities. This syndrome most frequently occurs with long-term NRTI exposure, typically involving d4T.⁶² Even if ART is modified or discontinued, physical changes are rarely reversible.⁶³ A change in therapy may be warranted, however, if the cosmetic disturbance is so severe that the patient stops taking his or her medications. In addition, for patients with lipids present in centrifuged plasma or who have risk factors for heart disease, including smoking or diabetes, TDF or ABC should be used in place of d4T.

3.6.12 Lactic acidosis and hepatic steatosis

Lactic acidosis is a potentially fatal complication of ART, thought to be caused by cellular toxicity due to NRTI-associated inhibition of mitochondrial DNA synthesis.⁶⁴ Secondary to

lactic acidosis, droplets of unmetabolized fat can build up in the liver, resulting in hepatic steatosis.

Lactic acidosis is rare—1.3 cases per 1000 person-years of NRTI exposure⁶⁵—and occurs months after the initiation of NRTIs. Risk factors for lactic acidosis and hepatic steatosis include obesity, female gender, and prolonged use of NRTIs.⁶⁶ Lactic acidosis may be suspected if a patient initially has a positive response to ART but then experiences symptoms such as general malaise, weakness, nausea, vomiting, abdominal pain, bloating, weight loss, myalgias, or hepatomegaly. However, in countries where TB, malaria, and hepatitis are endemic, these common illnesses should be ruled out before a diagnosis of lactic acidosis is presumed.

Laboratory abnormalities indicative of lactic acidosis include elevated lactic acid levels and possibly transaminitis and/or elevated amylase and lipase levels.⁶⁷ If lactic acid levels are not available, a diagnosis should be made based on clinical presentation and supported by laboratory evidence of transaminitis and/or anion gap acidosis. A patient is said to have an anion gap acidosis if: $\text{Na}^+ - [\text{Cl}^- + \text{HCO}_3^-] > 16 \text{ mmol/L}$.

Given the potential severity of lactic acidosis, early detection of this unexplained constellation of symptoms without other etiology may be sufficient to prompt empiric regimen change.⁶⁸ If symptoms are severe, ART should be stopped and supportive care maintained until symptoms improve. Administration of hydration, thiamine, and pyridoxine may be beneficial.

The most commonly implicated agents in lactic acidosis are d4T, ddI, and, less commonly, AZT; 3TC and ABC have rarely been implicated.⁶⁹ If the patient has experienced lactic acidosis while on a d4T-containing regimen, the new ART regimen can include AZT but should not include ddI (which has a toxicity profile similar to that of d4T).⁷⁰ The substitution of ABC for the offending agent is less likely to provoke recurrence of

lactic acidosis than if AZT is used. See Protocol 3.14 for a management algorithm for lactic acidosis.

3.7 Post-Exposure Prophylaxis

Although occupational exposure to HIV accounts for only a small burden of transmission, offering health-care workers adequate protection against infection is important. Programs should provide gloves, soap and water or hand sanitizer, disposable needles, and proper waste disposal containers for sharps and other hazardous materials. All workers at health care facilities, including custodial staff, should be trained in universal precautions and the proper use, storage, and disposal of needles.

The risk of contracting HIV from exposure to blood or body fluids depends on the type of exposure and the quantity of fluid to which the person is exposed. Pooled data from several prospective studies of health care personnel suggest that the average risk of HIV transmission is approximately 0.3 percent after a percutaneous exposure to HIV-infected blood and approximately 0.09 percent after a mucous membrane exposure.⁷¹

Appropriate first-aid measures should be taken immediately if a staff member is exposed to a patient's blood or other body fluids. Fluid contact with intact skin carries the lowest exposure risk. Only thorough washing of the affected area is needed; HIV testing and ART are not warranted. For percutaneous needle or surgical instrument injuries, the injury site should be washed briskly with soap and water. For mucous membrane exposure, appropriate flushing procedures should be undertaken. A supervisor should be available to assess the level of exposure and risk and determine the appropriate course of follow-up. VCT should be offered as appropriate.

If necessary, post-exposure prophylactic ART should be administered to the victim within 72 hours (and ideally within

2-3 hours) of exposure. If significant exposure is determined to have occurred, the victim should be offered hepatitis B immunoglobulin and the hepatitis B vaccine series, and antiretroviral prophylaxis should be considered. Although some providers recommend two-drug prophylaxis in cases where risk is thought to be lower, three-drug prophylaxis is generally believed to be the most effective regimen for preventing HIV transmission in these cases. If the source patient is known to have HIV and is on ART, that patient's ART regimen should be taken into consideration. If the possibility of resistance to ART is suspected and the victim's exposure is high-risk, second-line ART should be employed as post-exposure prophylaxis. Otherwise, the exposed victim can be started on a standard regimen of AZT, 3TC, and NVP for 28 days.

Health-care workers taking prophylaxis should immediately receive baseline CBC and liver function and renal function tests; these procedures should be repeated two weeks after prophylaxis is initiated. In general, if the source patient is confirmed to be HIV-negative, prophylaxis can be stopped immediately. If the source patient is confirmed to be HIV-positive, or if the source patient's HIV status is unknown, repeating the antibody testing or the testing of the victim's plasma HIV viral load prior to stopping prophylaxis is warranted. HIV testing for the victim should occur after 12 weeks and again at 6 months.

Post-exposure prophylaxis should also be given to victims of sexual assault and rape. Being the receptive partner of vaginal or anal intercourse incurs an HIV transmission risk of up to 10 percent per episode, depending on a variety of factors.⁷² As with occupational exposure, baseline HIV testing should be performed prior to the initiation of therapy. Patients should also be offered psychological counseling and support and, if appropriate, a pregnancy test and emergency contraceptives.

Additionally, we recommend empiric treatment for chlamydia and gonorrhea.

Protocol 3.15 outlines approaches to post-exposure prophylaxis for victims of occupational exposure or sexual assault.

3.8 Prophylaxis Against Common Opportunistic Infections

In resource-poor settings, *Mycobacterium tuberculosis* contributes most heavily to the morbidity and mortality associated with HIV; under certain circumstances, however, other infections also merit prophylaxis.

3.8.1 Treatment of latent TB infection

HIV is the most powerful known risk factor for the reactivation of latent TB infection. To avoid the serious complications that may develop from active TB, treatment of latent TB in HIV-positive patients is essential. Multiple studies have demonstrated dramatic risk reductions with isoniazid prophylaxis. A placebo-controlled trial conducted in Haiti in 1993 demonstrated an 83 percent reduction in the risk of developing active TB in HIV-infected patients who had a positive PPD and received isoniazid prophylaxis.⁷³

Protocol 2.2 and Section 2.4.4 present the algorithms for diagnosing and treating co-infected patients. Before initiating treatment of latent disease, it is essential to rule out the presence of active TB, per Section 2.4.2. Once active TB has been excluded, treatment for latent infection should be initiated immediately. Isoniazid is the most common drug for this purpose as it is inexpensive, relatively nontoxic, and well studied. The medication can be administered either daily or twice weekly and should be continued for at least nine months. (Due to the risk of liver toxicity, the two-month regimen of rifampin and pyrazinamide that had been previously recommended is no longer recommended for either HIV-positive or HIV-negative patients.) During treatment, patients should undergo monthly follow-ups to check for side effects and signs of hepatitis. If

possible, baseline ALT, AST, and bilirubin should be obtained, especially for patients with a history of liver disorder or who are taking other potentially hepatotoxic medications. If LFTs are elevated above five times the normal value, medication should be stopped. Patients who develop symptoms of peripheral neuropathy should be given pyridoxine along with H if they have not already been receiving it.

3.8.2 Prophylaxis against *Pneumocystis jiroveci* pneumonia and invasive bacterial infections

Pneumocystis jiroveci pneumonia⁷⁴ remains a major problem for HIV-infected patients who are not receiving or not responding to ART. Recent reports from many developing countries have shown that PCP comprises a significantly greater percentage of cases of pneumonia than previously thought.^{75–77} Furthermore, initiation of treatment only after PCP has reached an advanced stage may account for the high mortality rates associated with pediatric PCP in the developing world.⁷⁸ Patients who are not receiving prophylaxis and who have a CD4 count below 200 cells/mm³ are nine times more likely to develop PCP within six months than those receiving prophylaxis.⁷⁹

Patients who live in resource-poor settings also have a higher incidence of invasive bacterial infections that can be prevented by the prophylactic use of TMP/SMX. Prophylaxis against bacterial infections and PCP is recommended for all HIV-infected patients with a prior history of *Pneumocystis* pneumonia, a CD4 count below 200 cells/mm³, a history of oral candidiasis, or active TB in areas without access to CD4 count. In places where advanced disease is suspected and toxoplasma serostatus is unknown (or CD4 count unavailable), using double-strength formulations of TMP/SMX is preferred for the added benefit of toxoplasmosis prophylaxis. PCP prophylaxis can typically be stopped once patients maintain a CD4 count above 200 cells/mm³ for six months. It is unclear when to stop PCP prophylaxis in settings where CD4 counts are not available, but it is likely that patients with evidence of sustained clinical

improvement (at least one year) in HIV disease without evidence of other OIs could also stop secondary prophylaxis.

3.9 Common AIDS-Related Complications

Infectious diseases are a major cause of death in poor countries, even among people who do not have HIV. Thus, when evaluating an HIV patient in a resource-poor setting, a broad differential of infectious diseases must be kept in mind rather than simply focusing on the classically described OIs. Some common infections seen in resource-poor settings are outlined in Appendix G; additional details for specific syndromes are given in the following sections.

3.9.1 Diarrheal syndromes

Diarrhea is common in resource-poor settings, especially where access to clean water is unreliable.^{80–82} As mentioned before, chronic diarrhea may be an indication for starting ART.⁸³ Common diarrhea-causing bacterial infections (such as that caused by *Salmonella typhi*) may be more aggressive and/or invasive in HIV-infected patients.⁸⁴ Diarrhea may also be the presenting feature of other systemic illnesses, especially in children. Management of diarrhea in HIV-infected patients depends on the severity of disease, the acuteness of the diarrhea, and the degree of immunosuppression (Table 3.4).⁸⁵ Management approaches to acute and chronic diarrhea are summarized in Protocols 3.17 and 3.18.^{86–88} Adequate hydration with either oral rehydration solution or intravenous fluid resuscitation is essential.⁸⁹ For acute diarrhea, systemic illnesses such as malaria must first be ruled out. If the patient is very ill, the care provider should not wait for culture results before initiating empiric therapy.

Table 3.4 Differential Diagnosis of Diarrhea by CD4 Count

Any CD4 count	CD4 <200 cells/mm ³
<ul style="list-style-type: none">• <i>Mycobacterium tuberculosis</i>• Enteric viruses• <i>Salmonella</i> spp• <i>Shigella</i> spp• <i>Campylobacter</i> spp• <i>Escherichia coli</i>• <i>Clostridium difficile</i>• <i>Giardia lamblia</i>• <i>Entamoeba histolytica</i>• <i>Strongyloides stercoralis</i>• Any systemic illness, e.g., TB and malaria, especially in children	<ul style="list-style-type: none">• <i>Mycobacterium tuberculosis</i>• <i>Mycobacterium avium</i> complex• <i>Cryptosporidium parvum</i>• <i>Cyclospora cayentanensis</i>• <i>Isospora belli</i> (CD4 <100 cells/mm³)• <i>Microsporidia</i> spp (CD4 <50 cells/mm³)• Cytomegalovirus (CD4 <50 cells/mm³)

Source (Tables 3.4–3.6): Sande MA, Volberding PA, eds. *The medical management of AIDS*. 5th ed. Philadelphia, PA: W.B. Saunders and Company, 1997.

3.9.2 Pneumonia, cough, and shortness of breath

Although persons with HIV are at increased risk for coagulopathies and pulmonary emboli⁹⁰ and may have cardiomyopathy, pericardial effusion, or clinical congestive heart failure,⁹¹ when patients complain of dyspnea it is most commonly an acute or subacute infectious process of the lung.^{92,93} Tuberculosis is the most common pulmonary complication in this population. Note, however, that TB typically presents with chronic rather than acute shortness of breath under these circumstances. Table 3.5 summarizes the differential diagnosis of infectious pulmonary syndromes.

In resource-poor settings, evaluation of shortness of breath may be limited to a detailed clinical examination, sputum examination, and basic chest radiograph. If available, computerized tomography (CT) scanning of the chest and echocardiography may be useful. The ability to specifically diagnose the pathogen causing an OI may be limited; thus, recognizing common clinical and radiographic patterns is critical for the prompt implementation of appropriate therapy. Infectious etiologies can be segregated by immunologic state and presentation.⁹⁴ Clinical evaluation and management of

patients with shortness of breath is outlined in Protocol 3.19. Protocol 3.20 presents an evaluation algorithm for chest radiography.

Table 3.5 Differential Diagnosis of Pulmonary Syndromes by CD4 Count

Any CD4 count	CD4 <200 cells/mm ³
<ul style="list-style-type: none">• <i>Mycobacterium tuberculosis</i>• Bacterial pneumonias, including <i>Streptococcus pneumoniae</i> and <i>Haemophilus</i> spp (influenzae and non-typable)• Viral illnesses	<ul style="list-style-type: none">• <i>Mycobacterium tuberculosis</i>• <i>Pneumocystis jiroveci</i>• Fungal pneumonias: <i>Cryptococcus neoformans</i>, <i>Histoplasma capsulatum</i>• Cytomegalovirus (CD4 <50 cells/mm³)

3.9.3 Herpes infections

The infection commonly known as zoster is caused by the varicella-zoster virus (VZV), a member of the herpes virus family. Most people with VZV are infected as children, when the virus presents as chicken pox. The virus remains dormant within the body, living in the nerve root ganglion. When a person’s immune system is compromised, VZV can reactivate and cause the clinical syndrome known as shingles, which presents as a rash with a dermatomal distribution beginning with pain and developing into a papulovesicular eruption that later scabs and crusts. In some cases, the rash may spread across two or more dermatomes (disseminated varicella), at times encompassing the whole body. While uncommon, disseminated varicella can be seen in patients with HIV and is more serious than the common zoster infection.

Zoster is common among HIV-positive patients, even those with preserved CD4 counts; it is frequently a presenting diagnosis that prompts HIV testing.⁹⁵ Disseminated, recurrent, or chronic zoster, accompanied by neurologic complications, is more common at low CD4 counts. In areas where CD4 counts are not available, these complications should prompt the initiation of PCP prophylaxis.⁹⁶

Herpes simplex is also more common among HIV-infected patients, presenting as a painful cluster of vesicles. Lesions may be peri-oral or genital. Chronic, ulcerative lesions and frequent recurrence are associated with advanced immunosuppression.⁹⁷

An approach to managing herpes infections is summarized in Protocol 3.21.^{98,99}

3.9.4 Candidal infections

Candidal infections occur frequently in patients with HIV.¹⁰⁰ These infections are often a worrisome sign of immunosuppression and signify the need to initiate *Pneumocystis* prophylaxis. In resource-poor settings—especially those without CD4 monitoring capacity—candidal infections may also signify the need to start ART.

Candida albicans is the most common cause of candidal infections, although in patients with HIV the non-*albicans* species—which may be resistant to common antifungal agents—are more common.¹⁰¹ The oropharynx and esophagus are common sites of candidal infection. Patients often present with whitish plaques and painful or difficult swallowing.^{102,103} An approach to managing oropharyngeal and esophageal candidal infections is summarized in Protocol 3.22. Vulvovaginal candidiasis can be quite severe in women with HIV, often presenting with vaginal discharge and itching; please refer to Section 2.6.3 and Protocol 2.7.¹⁰⁴

3.9.5 Neurologic complications

Neurologic complications of HIV disease can be successfully managed using a diagnostic method based on clinical presentation.¹⁰⁵ First, mass lesions, meningitis, and other OIs must be ruled out. The most important clinical distinction is to determine whether the presentation represents focal neurologic changes suggestive of a mass lesion, meningitis, or nonfocal or global mental status changes.¹⁰⁶ Imaging of

the brain may be difficult to obtain in resource-poor settings; therefore, a careful clinical exam—including an examination of the retina for papilledema—is critical, as are any specific neurologic findings.¹⁰⁷

Protocols 3.23, 3.24, and 3.25 summarize the approach to managing HIV-positive patients who present with neurologic symptoms.^{108–110} In addition to the diagnoses reported here, patients should be evaluated for drug side effects, psychiatric illness, and systemic illness (including hypoxia, sepsis, uremia, acid-base disturbance, and hepatic encephalopathy).^{111,112}

3.9.5.1 Focal neurologic changes and deficits suggestive of mass lesions

All patients presenting with a change in mental status, new onset of seizures, neurologic findings, or neck stiffness should be urgently evaluated.¹¹³ Clinical examination should determine whether or not the patient has a focal neurologic deficit or evidence of increased intracranial pressure, either of which may indicate the presence of a mass lesion. If a lumbar puncture (LP) is performed, the presence of mass lesions increases the risk of herniation. This risk is very small and should be weighed against the benefits of the diagnostic information gained by performing the LP.

There are multiple causes of CNS mass lesions in patients with HIV.¹¹⁴ In countries where TB is endemic, tuberculoma may occur at any CD4 count and is likely the most common cause of a mass lesion. Toxoplasmosis (more common) and CNS lymphoma may occur in patients with CD4 counts below 100 cells/mm³. Less commonly seen is a mass lesion from *Cryptococcus neoformans*, which usually causes meningitis.^{115–117} Therapy should be directed towards the most likely underlying pathogen. The following findings support the empiric treatment of tuberculosis, the most common pathogen:

- An LP that demonstrates elevated lymphocytes and protein;

- Focal neurologic findings and CD4 counts above 100 cells/mm³; and/or
- Evidence (i.e., chest x-ray and/or PPD) of tuberculosis in another site.

If tuberculosis is excluded, toxoplasmosis should be treated (and may also be treated concomitantly). CNS lymphoma is often a diagnosis of exclusion if the patient does not respond to TB and toxoplasmosis treatment. Definitive diagnosis of CNS lymphoma may be made by flow cytometry of the spinal fluid or by brain biopsy. Corticosteroids should be prescribed if there is evidence of mass effect, provided that the risk of overwhelming systemic infection does not outweigh the anti-inflammatory benefits. Anti-seizure prophylaxis should also be considered.¹¹⁸

3.9.5.2 Meningitis

Once mass effect has been clinically excluded, a lumbar puncture should be performed on any HIV-positive patient experiencing neurologic complications. Meningitis is a common syndrome among HIV patients. As with other OIs, the pathogen causing meningitis can be classified with respect to the CD4 count at which it is likely to occur (Table 3.6).^{119,120}

Because TB is the most common OI in resource-poor settings and can occur at any level of immune suppression, it is also a common cause of meningitis among HIV-positive persons.¹²¹ As tuberculous meningitis can cause basilar meningitis, it may present with abnormalities in the cranial nerve exam; however, tuberculous meningitis can also have a chronic, nonspecific presentation. Tuberculosis is very difficult to diagnose by spinal fluid smear or culture; care should be taken to examine the patient for other findings consistent with TB.

Bacterial meningitides—including *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Haemophilus influenzae*—can occur and present acutely at any CD4 count. Meningitis

from *Cryptococcus neoformans*, an endemic fungus in many areas of the world, is common in many heavily HIV-burdened countries.

Table 3.6 Differential Diagnosis of Meningitis by CD4 Count

Any CD4 count	CD4 <50 cells/mm ³
<ul style="list-style-type: none">• <i>Mycobacterium tuberculosis</i>• Bacterial meningitis, including <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>Neisseria meningitidis</i>, and <i>Listeria monocytogenes</i>• Neurosyphilis	<ul style="list-style-type: none">• <i>Mycobacterium tuberculosis</i>• <i>Cryptococcus neoformans</i>, <i>Histoplasma capsulatum</i>

3.9.5.3 Global mental status changes

If the presentation of a patient experiencing neurologic complications is negative for focal deficit or symptoms of meningitis, global mental status changes or psychiatric issues should be taken into account. After careful consideration of all neoplastic and infectious causes of mental status changes, several further diagnoses must be explored. Table 3.7 presents a helpful conceptual framework developed by the HIV/AIDS Bureau of the Health Resources and Services Administration of the U.S. Department of Health and Human Services.

In the advanced stages of HIV, neuropsychiatric complications often arise in patients who are not receiving ART. These complications include dementia, minor cognitive-motor disorder, and subclinical cognitive-motor impairment.¹²² HIV dementia correlates with the level of HIV in the central nervous system¹²³ and is also related to low body mass index (BMI), low CD4 counts, and anemia. Clinical signs of dementia are listed in Table 3.8.¹²⁴

3.9.6 Psychiatric complications

As in any population suffering from chronic illness, HIV-positive patients often experience mental health problems.¹²⁵ In order to determine if a change in mental status stems from a pre-existing medical or psychiatric disorder or is caused by

HIV or an OI, any acute or chronic change in mental status must be evaluated immediately.

Table 3.7 Differential Diagnosis of Acute and Chronic Mental Status Changes During the Course of HIV Infection

Direct effect of HIV on brain tissue and function <ul style="list-style-type: none">AIDS Dementia Complex: Occurs late in AIDS course. Can occur in 20-30% of all AIDS patients with CD4 <100 cells/mm³. Treatment is ART. Imaging shows atrophy and nonspecific white matter changes.AIDS mania: Seen in late stages. Treatment is ART. Must be differentiated from bipolar disease. Opportunistic infections that cause generalized neurologic symptoms <ul style="list-style-type: none">Encephalitis: CMV, VZV, HSV, JCV, PML Impact of systemic illness on brain function Endocrine or metabolic disturbances which affect brain function Effects of antiretrovirals and other medical and psychiatric treatments on brain function Pre-existing neurologic or psychiatric disorders Neurologic and psychiatric disorders that arise after HIV infection Persistent or intermittent substance use or withdrawal states

Tables 3.7–3.9 adapted from: Forstein M. Psychiatric problems. In: O'Neill JF, Selwyn PA, Schietinger H, eds. *A clinical guide to supportive and palliative care for HIV/AIDS*. United States Department of Health and Human Resources, Health Resources and Services Administration, 2003:207–52.

Table 3.8 Clinical Signs and Symptoms of HIV Dementia

Type of impairment	Manifestations
Cognitive	<ul style="list-style-type: none">Impaired concentration and attentionImpaired verbal memory (e.g., word finding)Mental slowingDifficulty with calculationsImpairment of visuospatial memoryLack of visuomotor coordination (e.g., eye movement abnormalities)Difficulty with complex task sequencing <p>Late:</p> <ul style="list-style-type: none">Global cognitive impairmentMutism
Motor	<ul style="list-style-type: none">Unsteady gait or ataxiaLoss of balanceSlowed fine motor speedTremorsChange in handwritingHyperactive DTRsWeakness <p>Late:</p> <ul style="list-style-type: none">SeizuresDecorticate posturingMyoclonusSpastic weaknessFrontal release signs
Behavioral	<ul style="list-style-type: none">Psychomotor retardation (slowed speech or response time)Personality changes <p>Late:</p> <ul style="list-style-type: none">HallucinationsDelusions
Affective	<ul style="list-style-type: none">Apathy, loss of interest in friends or othersIrritabilityMania

Depression is a common reaction to the diagnosis of a life-threatening and historically stigmatizing disease such as AIDS. Economic stressors and social upheaval, which may worsen once the patient falls ill, are often the very factors that put individuals

at risk for HIV infection in the first place. Depression can be debilitating and should never be discounted as a “normal” reaction to diagnosis or progression of disease.¹²⁶ Rather, depression should be treated with counseling and selective serotonin re-uptake inhibitors (SSRIs) or other antidepressants, when available. Anxiety is also common among HIV-positive patients and should be treated after biological causes have been ruled out. Other mental health disorders that are not more common in HIV-positive persons—such as schizophrenia and bipolar illness—should also be considered and treated accordingly.¹²⁷

Psychosocial issues affecting HIV-positive patients and their families are often overlooked by providers but should in fact be addressed as part of a comprehensive treatment plan.^{128,129} Although Table 3.9 divides the occurrence of these issues into early, middle, and late phases, any of these issues may present during any stage of disease progression.

Table 3.9 Psychological and Psychosocial Issues

<p>Early after HIV diagnosis</p> <ul style="list-style-type: none">• Adjusting to new diagnosis of HIV seroconversion; acute vs. chronic adaptational responses (fear of imminent death, guilt over infecting others, exacerbation of existing psychiatric conditions, acute suicidal ideation)• Disclosure to others; informing intimate contacts, partners, children• Adopting safer sexual behaviors• Accessing medical and psychiatric care• Defining those involved in the care of the patient <p>Middle phase</p> <ul style="list-style-type: none">• Adjusting work and family needs to physical and emotional impact of illness• Learning about the nature of the illness and the potential treatments• Adherence to medication• Decisions about working and providing for family• Maintaining relationships and managing normal developmental issues in the context of the uncertainty of the progression of illness• Dealing with untoward effects of illness and/or treatment (fatigue, medication side effects, etc.) <p>Late phase</p> <ul style="list-style-type: none">• Planning for care of family members• Decisions about end of life and preparations for death

3.9.7 Immune reconstitution syndrome

Immune reconstitution syndrome refers to a paradoxical worsening of a patient’s clinical status that can occur after the initiation of ART.¹³⁰ The worsening of symptoms is due to improved function of the patient’s immune system, resulting in the system’s ability to mount an inflammatory response to infectious pathogens and neoplasms.¹³¹ Immune reconstitution syndromes have been reported in patients with *Mycobacterium avium* complex,¹³² TB,¹³³ *Cryptococcus neoformans*,¹³⁴ cytomegalovirus (CMV),¹³⁵ PCP,¹³⁶ and a host of other AIDS-related malignancies.¹³⁷ The differential diagnosis of a new ART patient who presents with worsening symptoms should include an adverse reaction to a drug, a new or previously unrecognized OI, and failure of OI therapy. Once other causes of worsening symptoms have been ruled out, management of patients almost always includes continuation of ART, treatment directed at the specific OI affecting the patient’s immune system, and the occasional use of anti-inflammatory agents. Care should follow the approach outlined in Protocol 3.26.¹³⁸

3.9.8 Dermatological conditions

Problems of the skin and mucous membranes may affect up to 90 percent of HIV-infected people and can occur at all stages of the disease. Mucocutaneous reactions may be associated with the virus itself, immunologic effects of the disease, OIs, or the medications used to treat HIV. All patients who present with cutaneous mucous membrane problems should be questioned as to the duration of the problem; the presence of itching, pain, bleeding, discharge, lumps, or sores; and their recent sexual history. Patients should also be questioned as to whether their partner(s) or family members have similar symptoms. Appendix F presents an overview of dermatological conditions common among HIV-infected patients.

3.10 Adherence: Community-Based Care and the *Accompagnateur* Model

The availability of health care that is free to everyone in the community greatly increases the patient's and his or her family's utilization of services. This not only enables the entire family to be engaged in their own health care but also permits close surveillance of a patient's social contacts, who are at increased risk for HIV and TB. The comprehensive support provided to all patients, regardless of whether they are yet receiving ART, helps prevent the loss of HIV-positive patients to follow-up. At ZL, even if HIV-positive patients are not receiving directly observed ART or prophylactic therapy, a community health worker performs routine visits to assess the ongoing needs of the household and to monitor health problems in the family.

As discussed in Section 3.3.2, adherence to antiretroviral medications is critical for optimizing clinical outcomes and preventing the emergence of drug resistance; this is one reason ZL clinical staff rely on the technique of directly observed therapy of ART. DOT takes place in the patient's home, where *accompagnateurs* are responsible for administering all TB- and HIV-related medications as well as medications for any other chronic diseases, such as hypertension or psychiatric disorders. Visits by *accompagnateurs* take place once or twice a day, to accommodate the schedules of both the patient and the *accompagnateur*. The performance of *accompagnateurs* should be closely supervised and assessed on a regular basis to ensure that proper DOT is taking place.

Daily visits and observation of ingestion of medicines ensures that patients adhere to their treatment and also affords an opportunity for *accompagnateurs* to provide support, monitor for symptoms of adverse reactions to ART and/or HIV-related complications, answer questions about medications and their side effects, and stress secondary prevention messages. Although patients are seen monthly at a ZL health clinic, most HIV patients develop a close relationship with their

accompagnateur that reflects both a supportive friendship and a resource connecting them even more closely to their medical care.

The ZL program would not have been successful without *accompagnateur*-supervised DOT. Arguments have been raised in the medical, public health, and policy literature against the use of *accompagnateurs* and DOT, citing concerns such as patient confidentiality and autonomy and the costs of salaried community health workers.¹³⁹ To date, neither argument has proved to be an impediment for PIH's programs.¹⁴⁰ Stigma against infected patients has not prevented them from accepting members of their community as treatment supervisors, and *accompagnateur* salaries represent only a minor component of programmatic costs. In addition, the *accompagnateur* model generates jobs in areas where unemployment is often high. While the feasibility of providing life-long DOT has been questioned, ZL medical staff have sustained DOT for a decade with no indications to suggest that continuation will prove unacceptable or unfeasible. In fact, by preventing treatment failure that carries with it increased mortality and morbidity, the need for complicated salvage regimens, and costly inpatient care of chronic terminal cases, DOT is likely to have significant long-term benefits as well as short-term rewards.¹⁴¹

Patients on ART who are nonadherent should be counseled about the risk of treatment failure and of the development of drug-resistant disease. Care providers should attempt to understand and address nonadherence and noncompliance within the larger context of economic hardship in which most patients in resource-poor settings live. Home visits and careful socioeconomic assessment can often reveal the broad range of factors contributing to the patient's nonadherence; these factors may include increased economic or nutritional hardship, the illness of a family member, medication side effects or intolerance,¹⁴² or domestic violence. In conjunction with the patient, a multidisciplinary team of health professionals,

educators, and social workers should strive to identify and remediate the patient’s hardship factors and improve the patient’s ability to remain engaged in her or his health care. In the ZL program, for example, transportation stipends and free health services for any ongoing complaints help to minimize the number of missed appointments. Other forms of support include education regarding TB and HIV; social worker services; nutritional support; and housing, educational, financial, and employment assistance as necessary. Rather than considering these interventions to be enablers or incentives, patients recognize them as critical components of ZL’s comprehensive approach to addressing underlying risk factors for disease.

3.11 Keeping HIV Patients Healthy: A Comprehensive Socioeconomic Approach

Although the “four pillars” approach to HIV treatment and care provides an excellent foundation for keeping HIV patients healthy, our work would be ineffective without mechanisms to address patients’ long-term socioeconomic needs. HIV spreads quickly along the social fault lines of poverty and gender inequality,¹⁴³ and social and economic stressors fuel the epidemic. The exchange of sex for food, money, or security; the need to migrate for work; and the forced displacement or dislocation of people are well-established risk factors for HIV.^{144,145} Moreover, socioeconomic factors also play a role in the development of OIs, as outlined in Table 3.10. Similarly, lower socioeconomic status is associated with an increased risk of bacterial pneumonia and TB in HIV-positive patients.^{146–149} Thus, the provision of socioeconomic support to impoverished patients and their families is an integral part of any HIV prevention-and-care package.

Table 3.10 Examples of Socioeconomic Risk Factors for Opportunistic Infections

Risk factor	Possible opportunistic infection(s)
Unclean water source	Diarrhea, typhoid, parasitic infections
Inadequate housing	Respiratory infections such as bacterial pneumonia and TB
Lack of screens or mosquito netting	Malaria
Unpaved floor, lack of shoes	Helminthic infections
Inadequate diet	Malnutrition and further immunosuppression

To help determine the need for socioeconomic support, ZL and PIH staff have developed a list of individual, family, and community factors that affect HIV infection risk. These socioeconomic factors are assessed at clinic visits and recorded as part of the patient’s medical record as well as investigated during home visits. Clinic staff and social workers use these assessments to target interventions such as home-building projects, nutritional supplementation, and microfinance and microenterprise initiatives for the neediest patients and their families. The factors that Zanmi Lasante staff assess in rural Haiti include:

- Family structure and environment: marital status; number of children alive and deceased; presence of orphans; history of violence or abuse; history of infidelity; history of exchange of sex for money, goods, drugs, gifts, food, etc.;
- Housing situation: condition of home, number of people living in house or per room, home ownership (rented or owned), type of roof (tin, banana leaf, thatch), type of floor (cement, dirt), availability of a latrine, number of windows, availability of beds and other basic furniture;
- Overall nutritional status: number of meals eaten per day or week, types of food/nutrients available,

source(s) of food (farmed, purchased at market, received from food program);

- Access to potable water: source (open stream, pump, protected source), distance to source, storage containers; and
- Overall economic situation: occupation, educational attainment, history of domestic servitude, history of migration for work, history of displacement, history of detention or imprisonment, land ownership, radio ownership.

While the relative importance of any these factors will vary from project site to project site, their underlying theme of vulnerability will no doubt hold true in most resource-poor settings.

3.11.1 Housing

Adequate housing is critical for HIV-positive persons, as overcrowding and poor ventilation may contribute to the spread of infectious pathogens, especially TB. Homelessness is not uncommon among HIV-positive patients, due to either abject poverty or rejection by the family. Inadequate housing may cause additional stigma and pose further challenges to patients' ability to adhere to treatment. Finally, a basic principle of social justice holds that all humans have a right to adequate protective shelter. For these reasons, ZL staff assess the housing status of all persons diagnosed with HIV. Housing assistance is then provided as needed.

3.11.2 Nutritional support

Adequate nutrition is a critical element in the management of HIV-positive patients. In addition to itself causing malnutrition,¹⁵⁰ HIV immune suppression is exacerbated by poor nutritional status. Without nutritional support, patients, especially those already suffering from baseline hunger, can become trapped in a vicious cycle of malnutrition and disease.^{151,152}

Recent studies have shown that malnutrition at the time of starting ART is significantly associated with decreased survival.¹⁵³ Given that malnutrition is endemic in most resource-poor settings, the provision of food supplementation during the course of HIV treatment is as important as the provision of ART. Staples such as rice and beans are sufficient, but a protein source should be included whenever possible. Protocol 3.27 outlines an algorithm for assessing a patient's need for nutritional support.

While serum albumin can be monitored to assess nutritional status, weight gain is one of the most important and straightforward clinical indicators of treatment success and is correlated with treatment outcomes.¹⁵⁴ The patient's weight and height should be recorded at intake and followed monthly. To ensure reliability, weight should always be checked using the same scale. All patients who fail to gain weight should be assessed for caloric deficiencies, drug intolerance, and the presence of OIs, particularly TB, that could contribute to weight loss.¹⁵⁵

3.11.3 Clean water

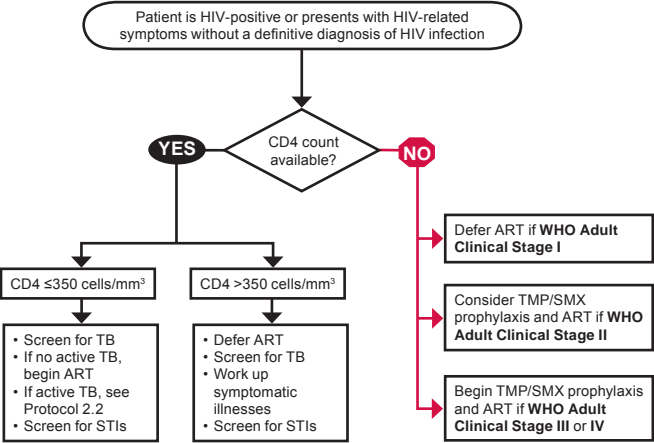
HIV-positive patients without access to clean water are at risk for a variety of common and opportunistic pathogens.^{156,157} These pathogens can be difficult to eradicate and can contribute to dehydration, malnutrition, and worsening of immune function.¹⁵⁸ Home visits are a good opportunity to assess water sources and water treatment options. Communities with high rates of waterborne illness should be considered for water treatment projects; patients and families can also be taught to boil water prior to drinking. Care should be taken, however, not to place undue financial burden for fuel costs on already stressed families; rather, the focus should be on community-wide solutions to potable-water needs. Interventions are especially critical if formula-feeding is encouraged for PMTCT, since diarrheal illness is a major cause of death in infants who are not breastfed during the first two years of life. Household-

level interventions should be considered for PMTCT and other “priority” patients.

3.12 Conclusion

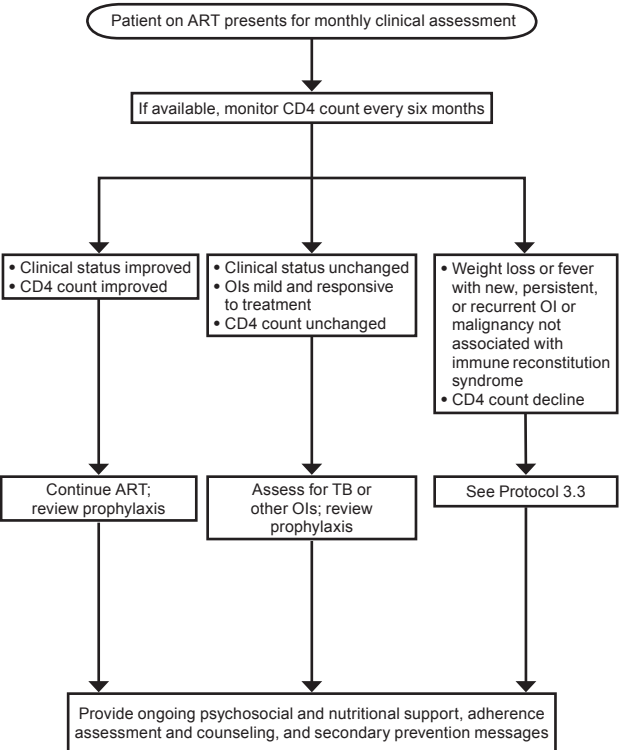
HIV infection presents a complicated array of medical and psychosocial management issues. Many lives can be saved if treatment of AIDS and its related OIs proceeds even in the absence of laboratory and radiological resources. Whether initiating ART or assessing the community water supply, much of the care of HIV patients can be performed at local health clinics and within the community. The more HIV care that can be delivered at the local level, the greater the number of patients who will be reached with ART and other life-saving interventions.

Protocol 3.1 Initiation of ART in HIV-Positive Adults and Adolescents

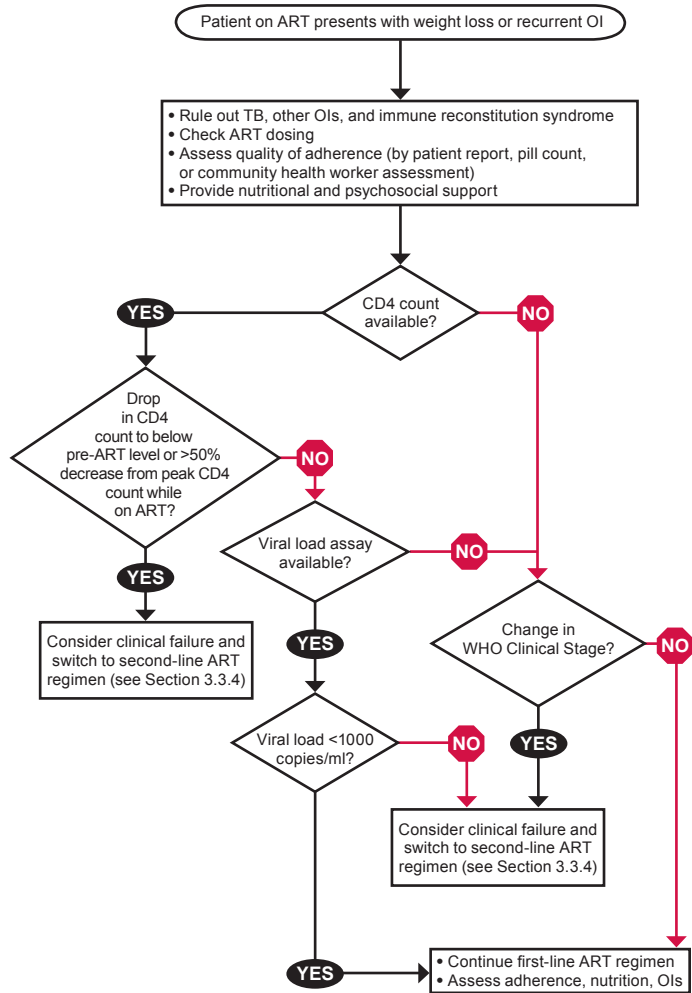


See Appendix B for the WHO guidelines on clinical staging of HIV disease in adults and adolescents.

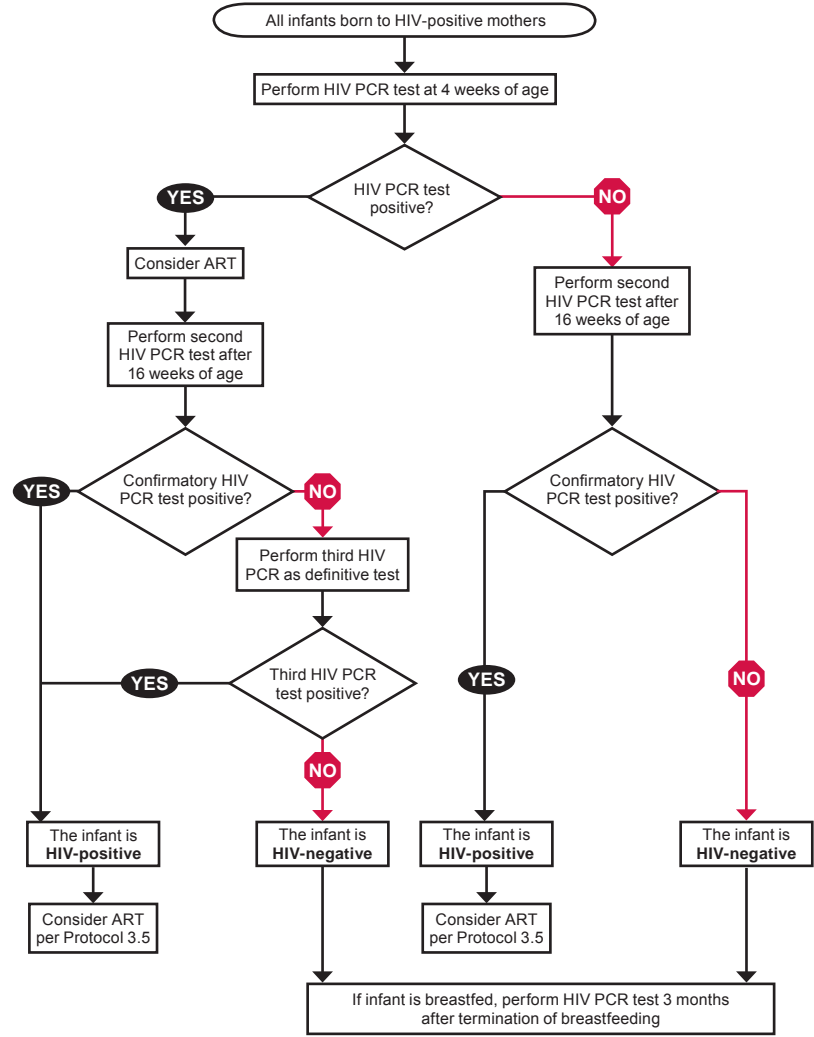
Protocol 3.2 Immunological and Clinical Monitoring of Response to ART



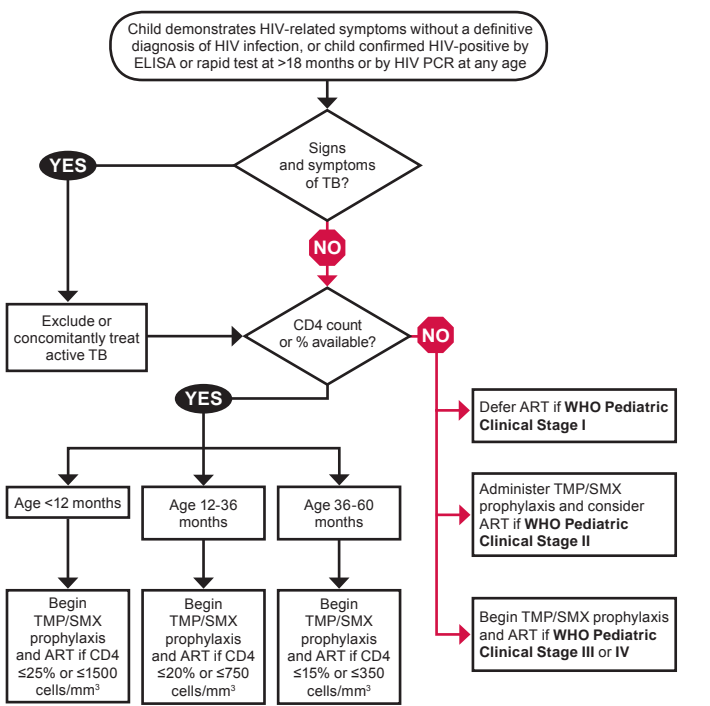
Protocol 3.3 Switching to Second-Line ART Regimens



Protocol 3.4 Virologic Diagnosis of HIV Infection in Infants Born to HIV-Positive Mothers

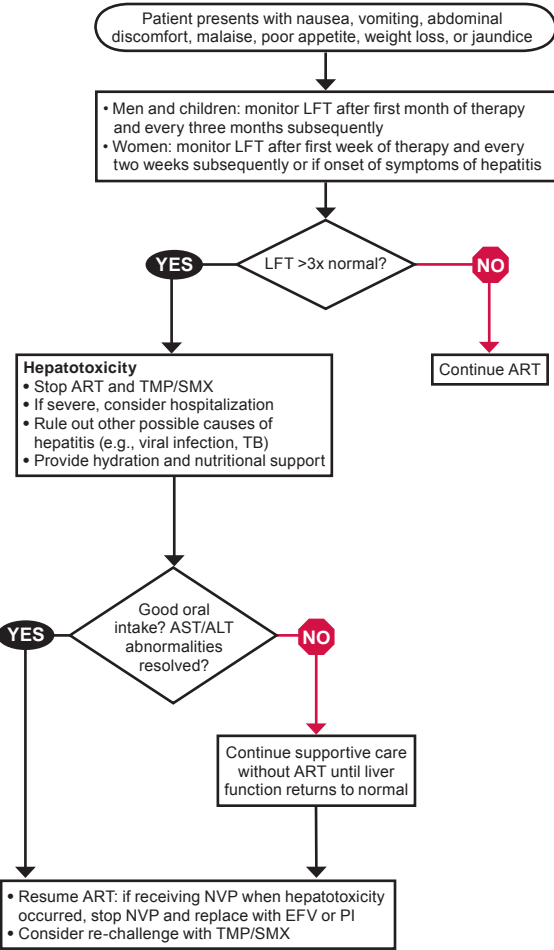


Protocol 3.5 Initiation of ART in HIV-Positive Children Under Five Years of Age

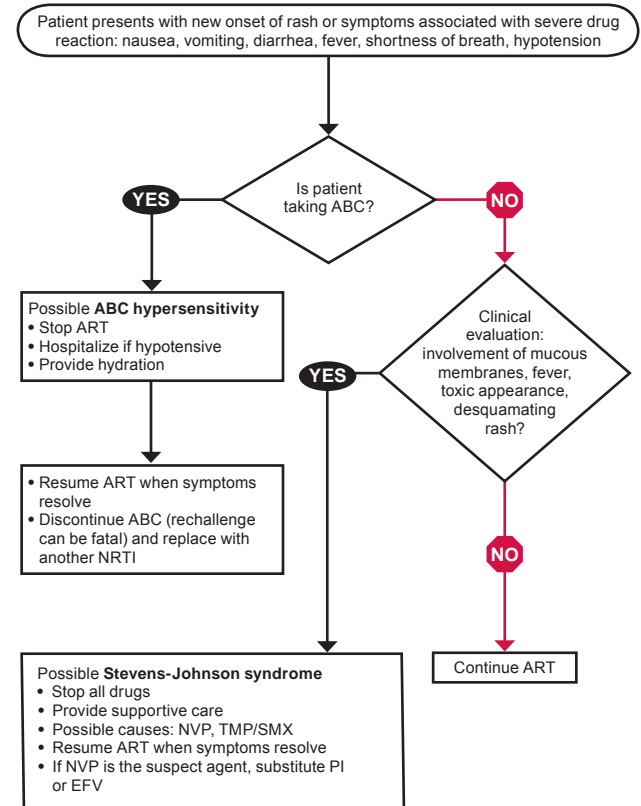


See Appendix C for the WHO guidelines on clinical staging of HIV disease in infants and children.

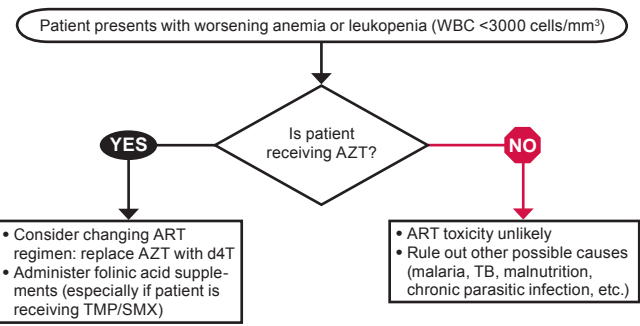
Protocol 3.6 Management of Hepatotoxicity in Patients Receiving ART



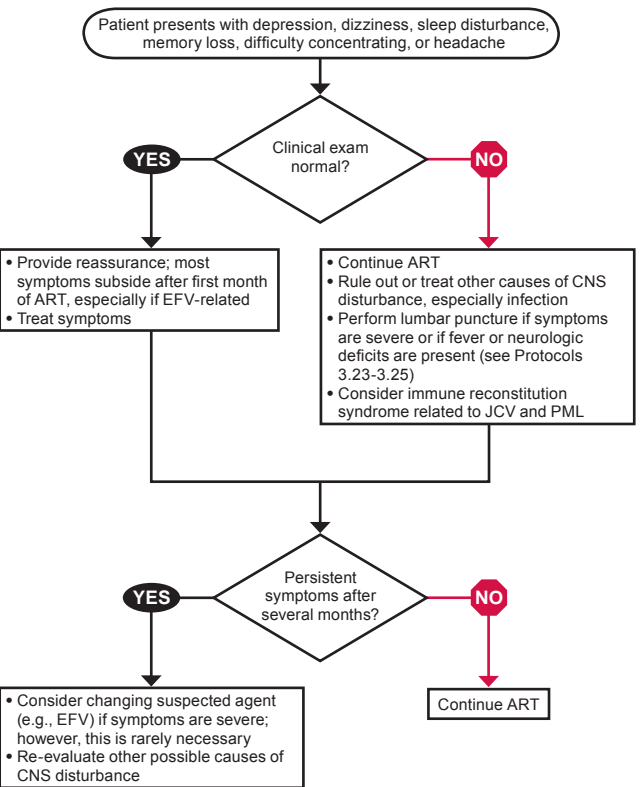
Protocol 3.7 Management of Rash and ABC Hypersensitivity in Patients Receiving ART



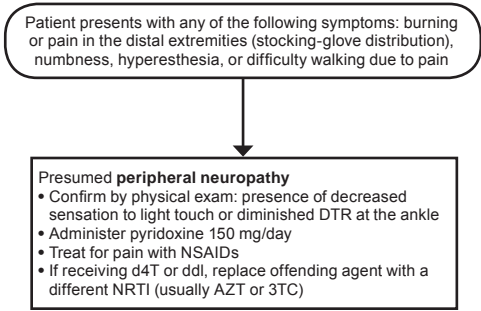
Protocol 3.8 Management of Anemia and Leukopenia in Patients Receiving ART



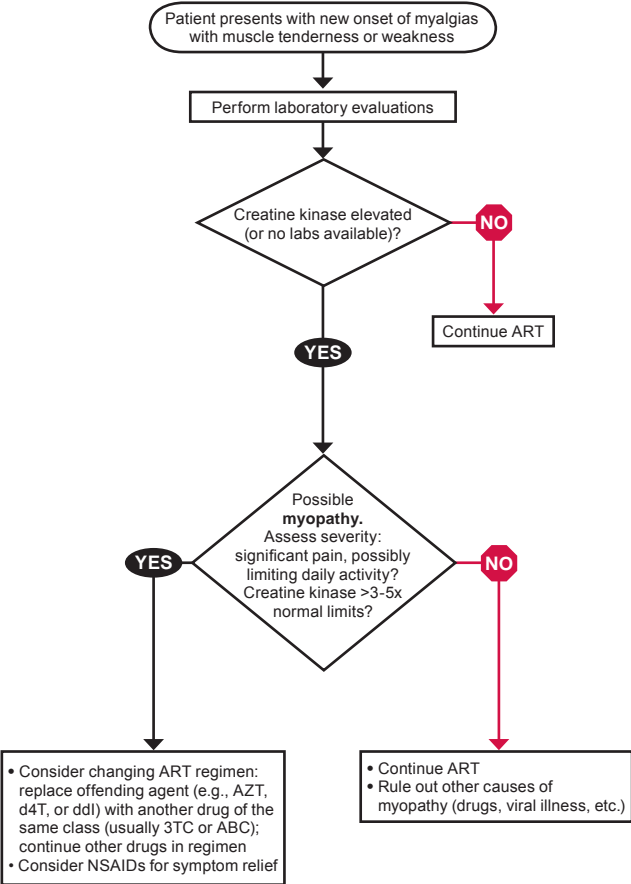
Protocol 3.9 Management of Central Nervous System Disturbance in Patients Receiving ART



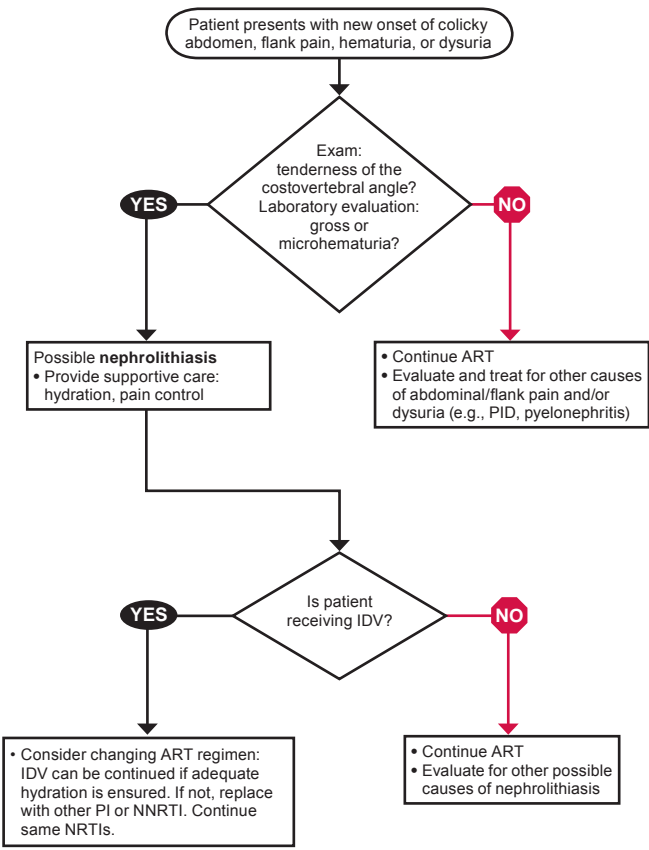
Protocol 3.10 Management of Peripheral Neuropathy in Patients Receiving ART



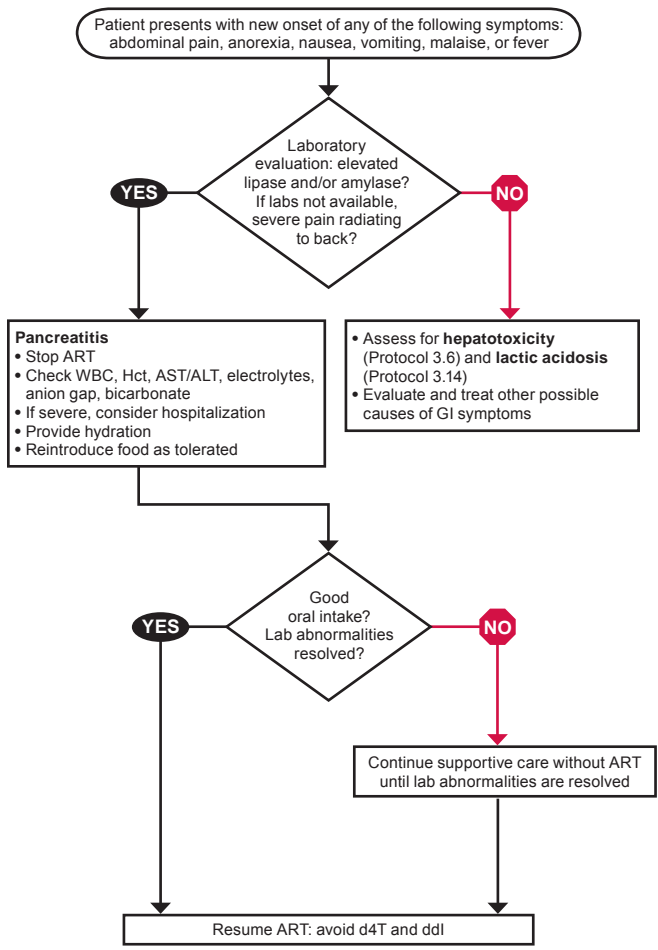
Protocol 3.11 Management of Myopathy in Patients Receiving ART



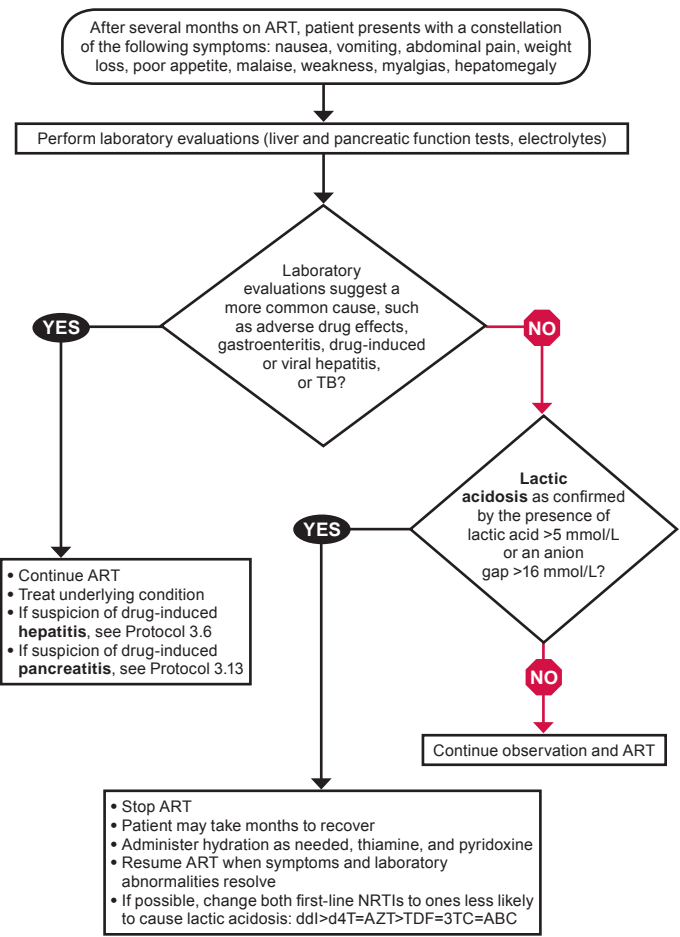
Protocol 3.12 Management of Kidney Stones in Patients Receiving ART



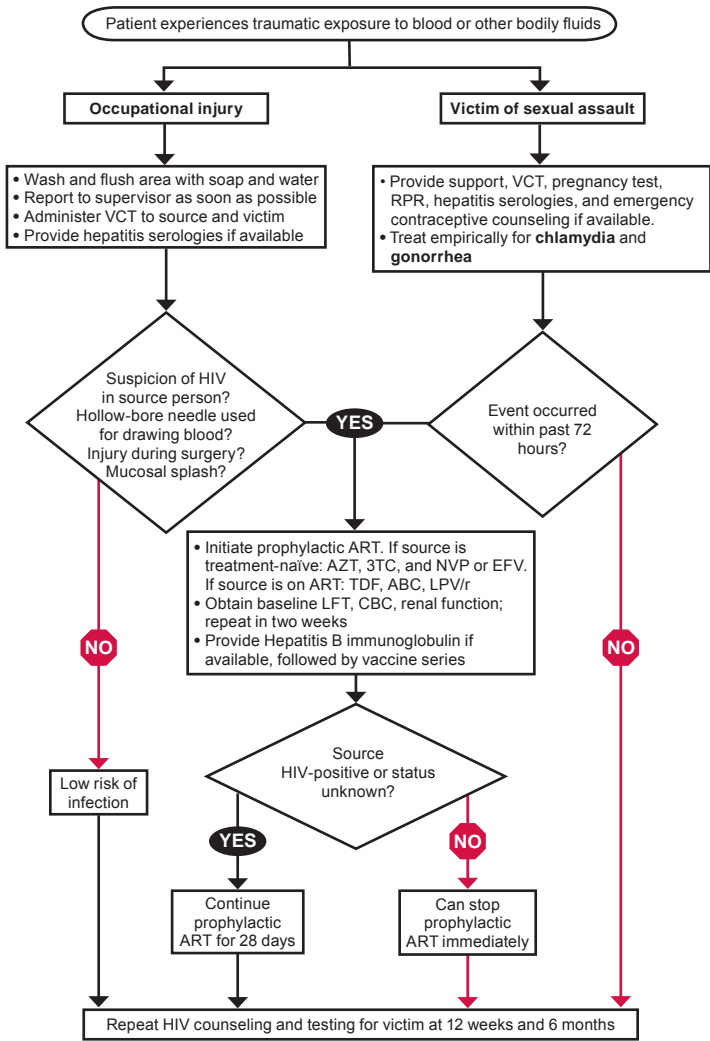
Protocol 3.13 Management of Pancreatitis in Patients Receiving ART



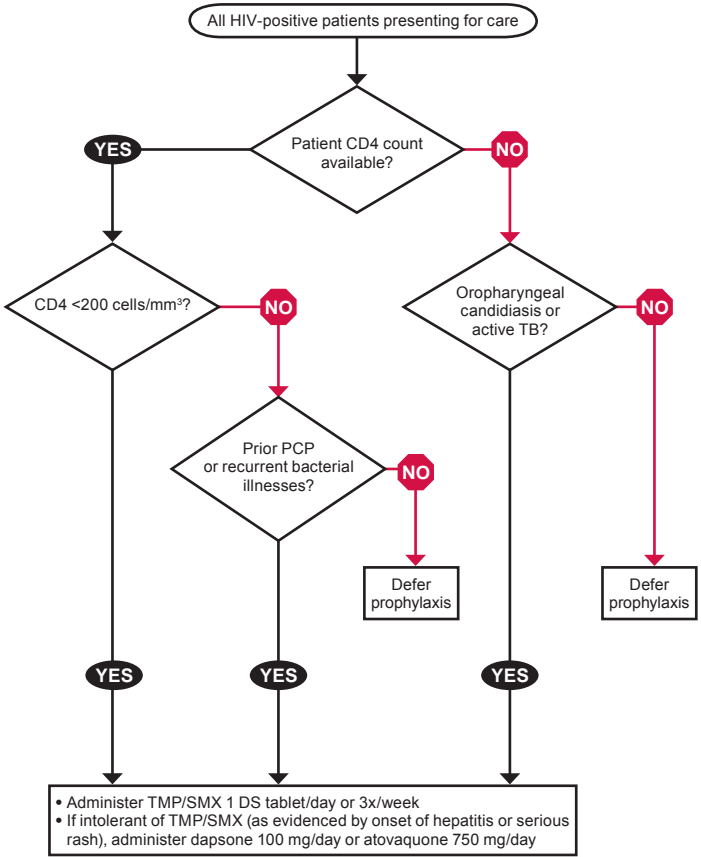
Protocol 3.14 Management of Lactic Acidosis in Patients Receiving ART



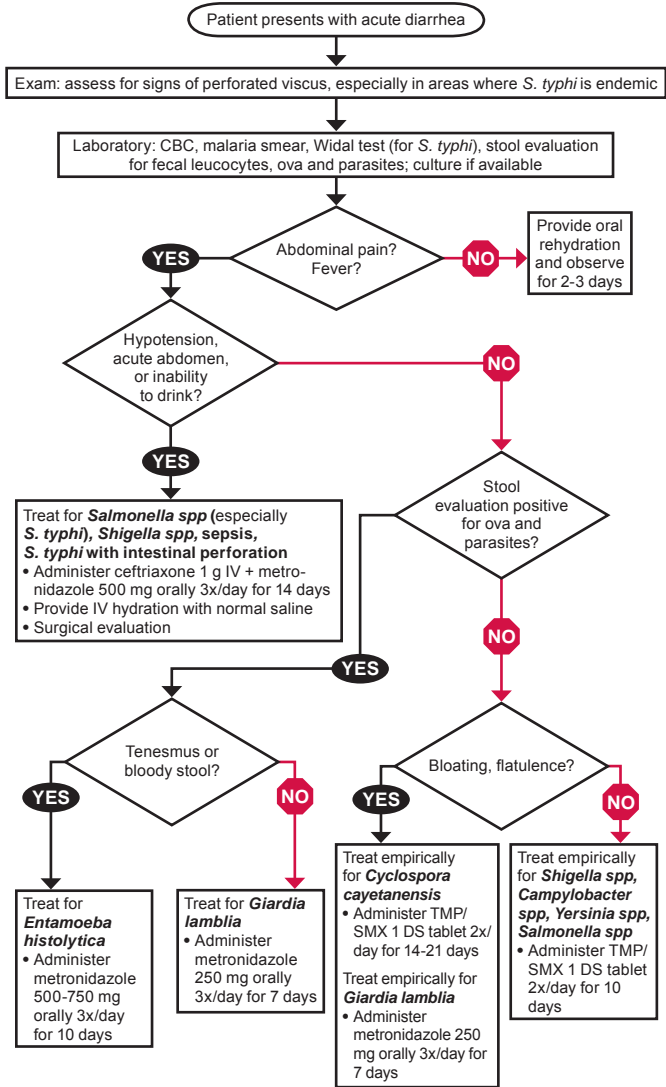
Protocol 3.15 Post-Exposure HIV Prophylaxis for Victims of Occupational Injury or Sexual Assault



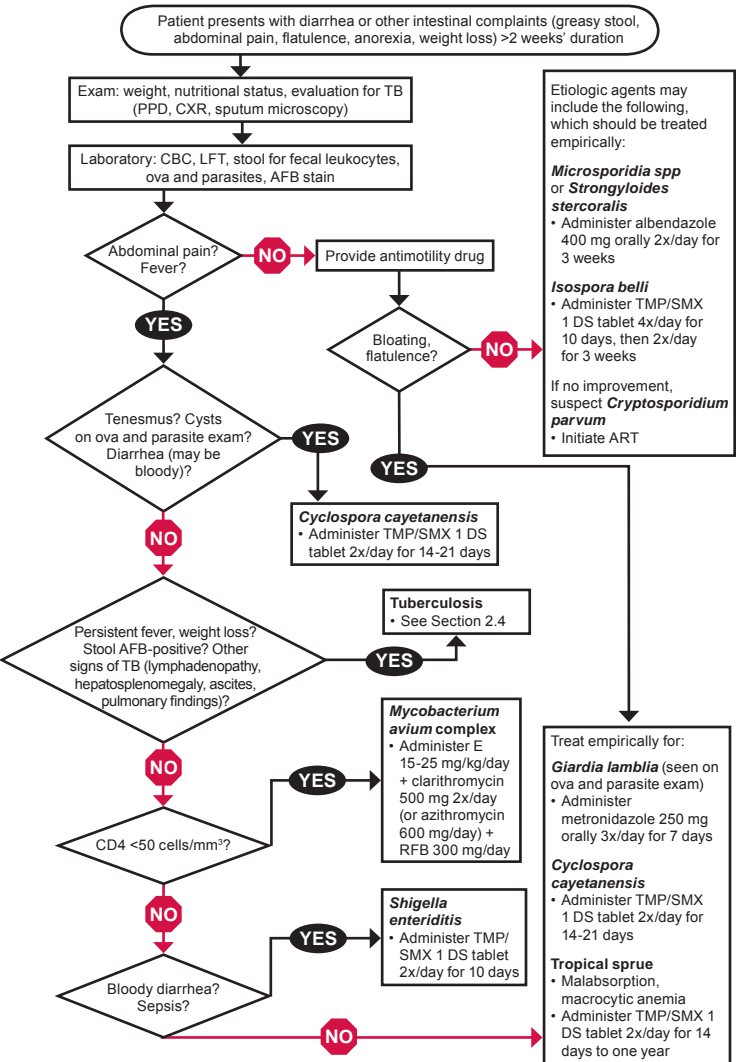
Protocol 3.16 Prophylaxis Against PCP and Invasive Bacterial Infections in HIV-Positive Patients



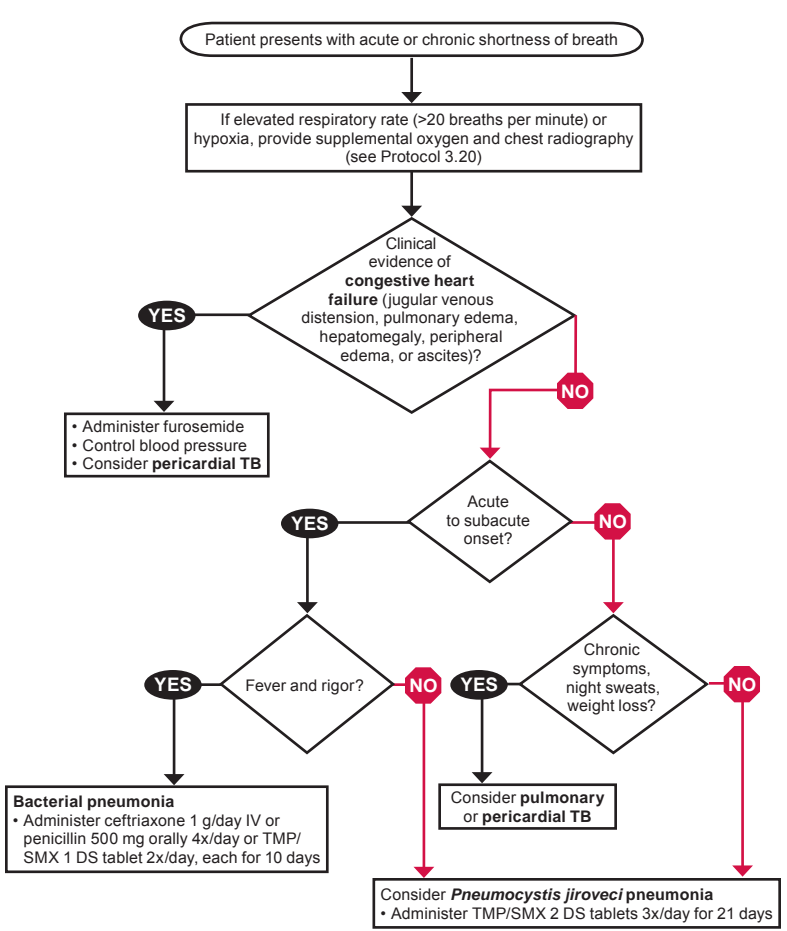
Protocol 3.17 Approach to Acute Diarrhea in HIV-Positive Patients



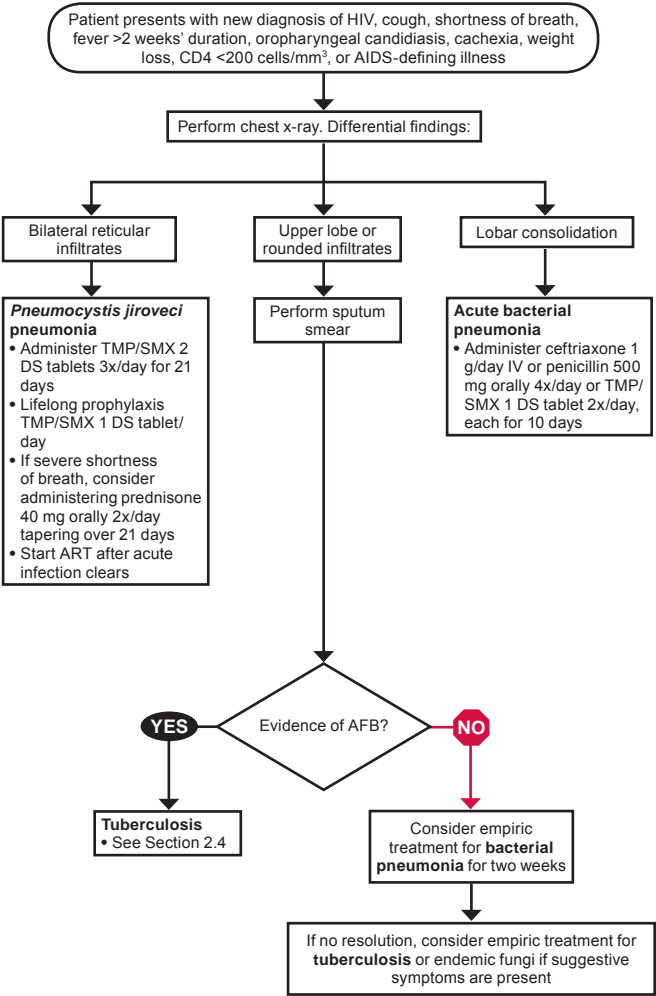
Protocol 3.18 Approach to Chronic Diarrhea (>2 Weeks) in HIV-Positive Patients



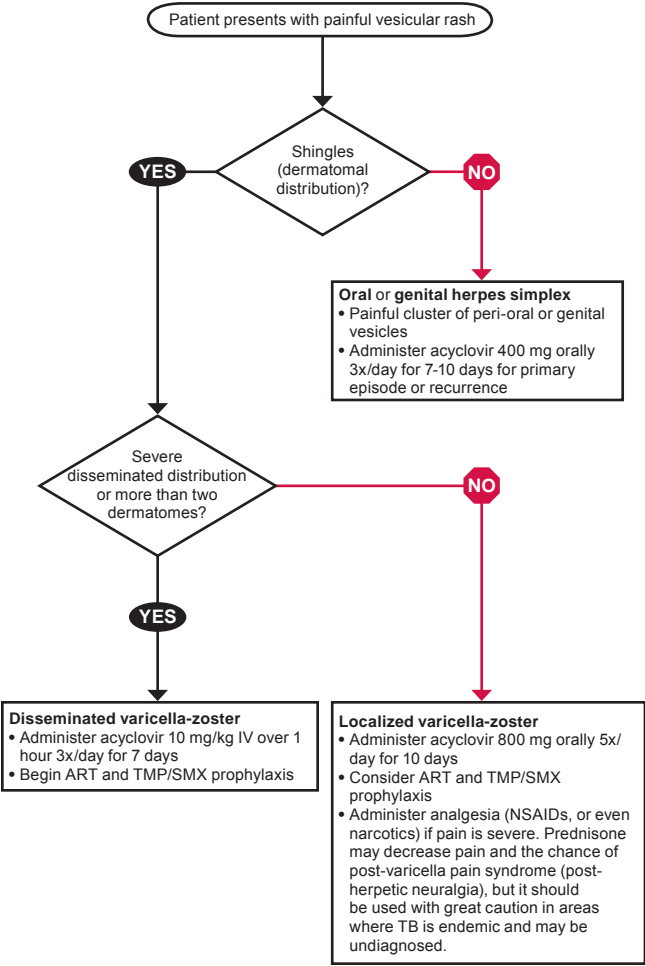
Protocol 3.19 Management of Shortness of Breath in HIV-Positive Patients



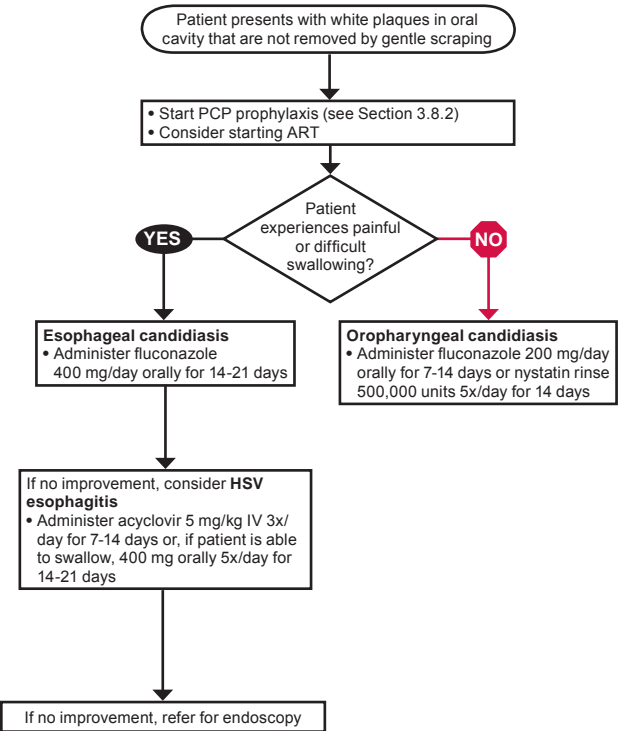
Protocol 3.20 Evaluation of Chest X-Ray Findings in HIV-Positive Patients



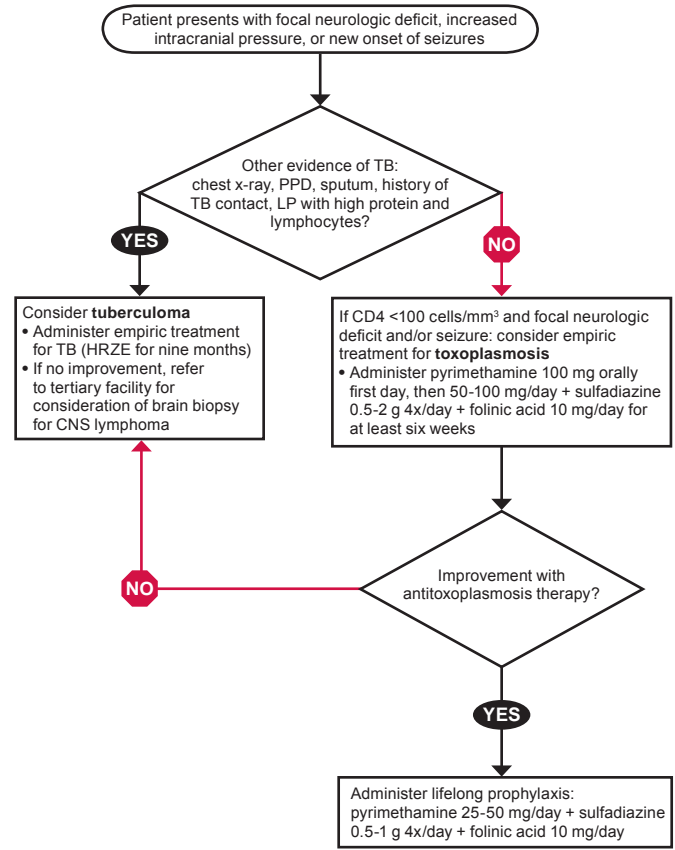
Protocol 3.21 Management of Herpetic Rash in HIV-Positive Patients



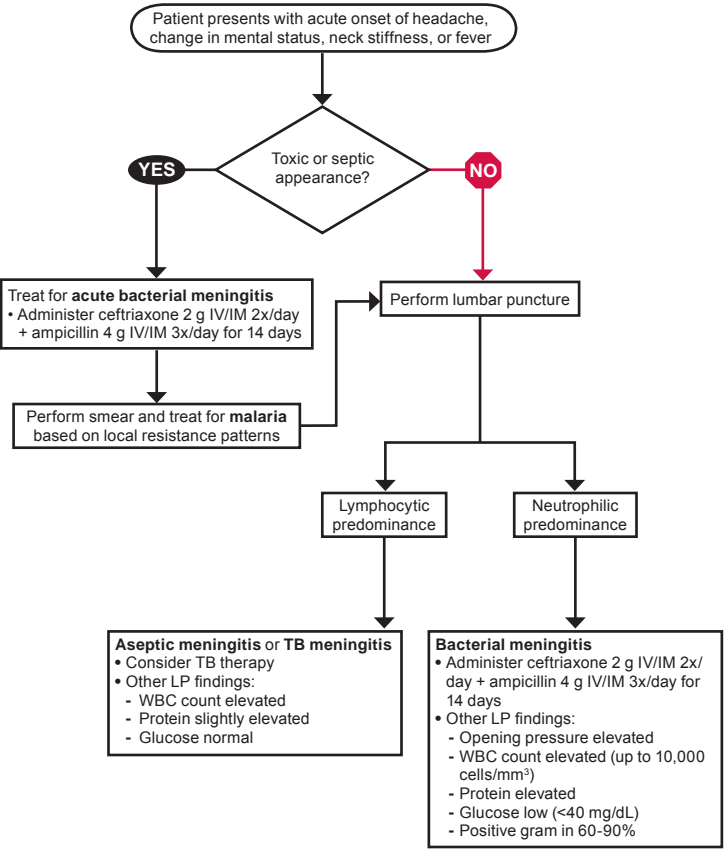
Protocol 3.22 Management of Oropharyngeal and Esophageal Candidiasis in HIV-Positive Patients



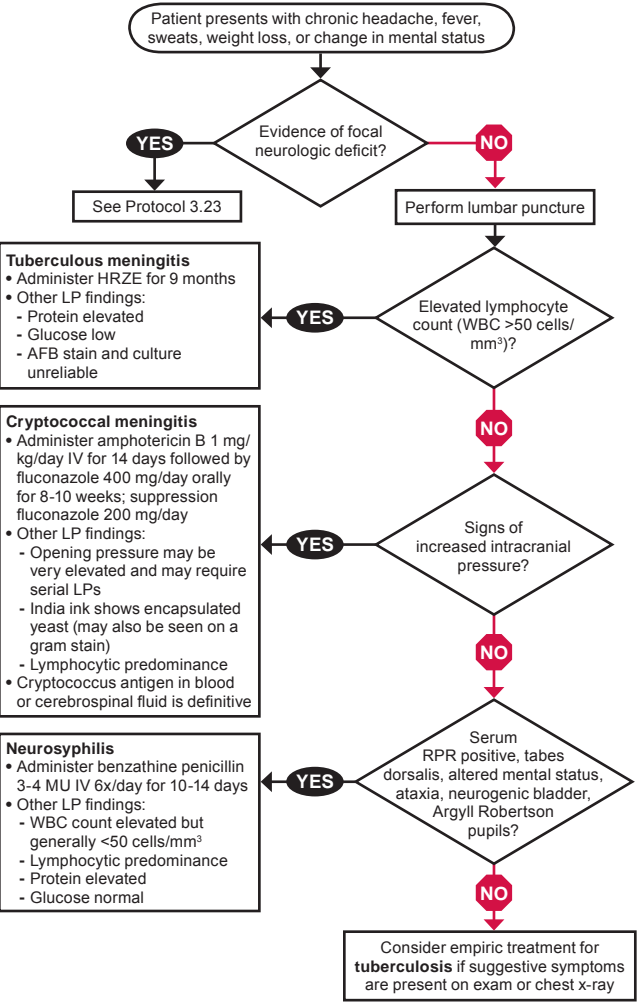
Protocol 3.23 Management of Focal Neurologic Changes in HIV-Positive Patients



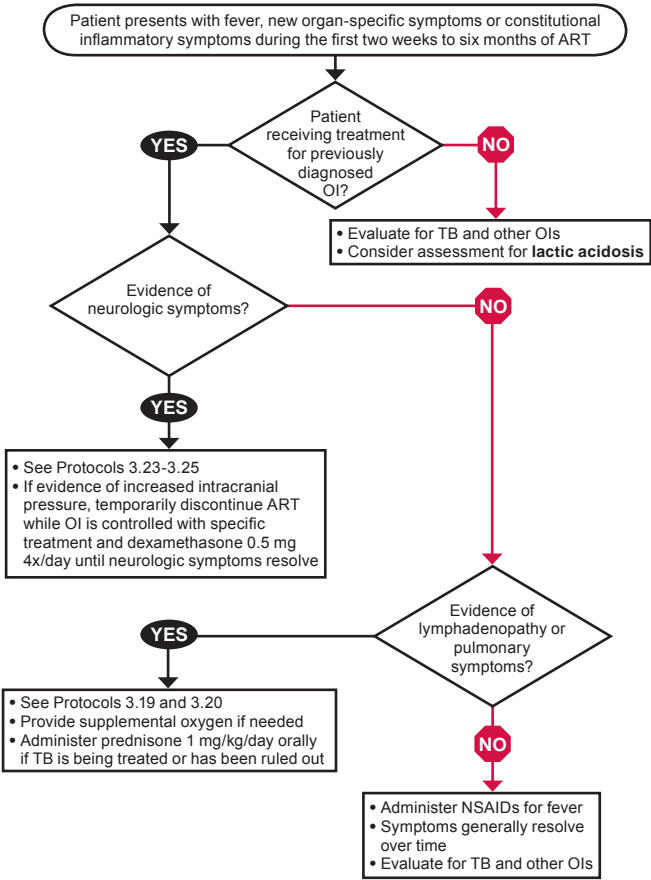
Protocol 3.24 Management of HIV-Positive Patients with Suspected Acute Meningitis



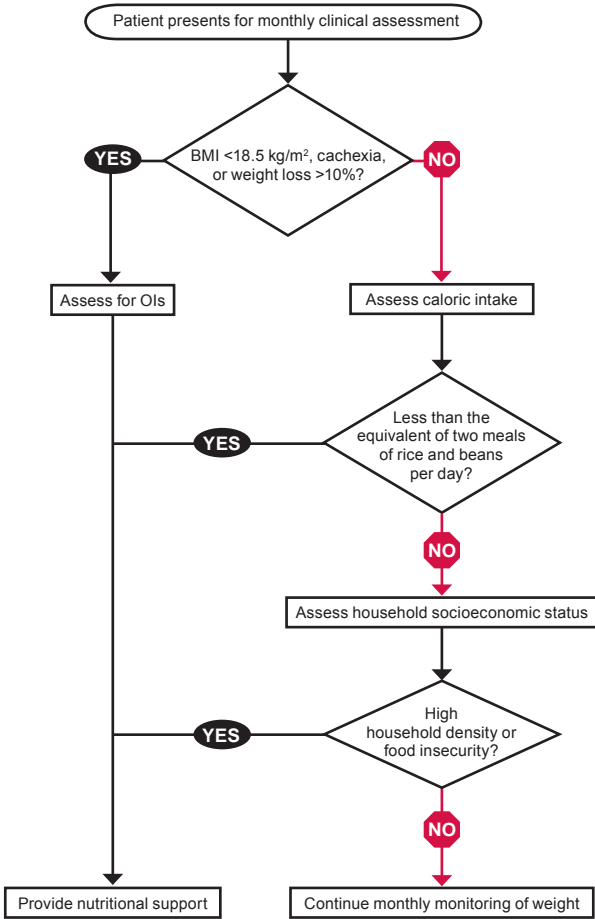
Protocol 3.25 Management of HIV-Positive Patients with Suspected Chronic Meningitis



Protocol 3.26 Management of Immune Reconstitution Syndrome



Protocol 3.27 Nutritional Assessment and Intervention



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Chapter 4: Monitoring and Evaluation: Data Collection, Record Management, and Electronic Telecommunications

In any setting, monitoring and evaluation (M&E) are key components of a successful HIV treatment program. M&E allow for accurate medical and programmatic management and also provides the means for carrying out the clinical and operational research and reporting vital to expanding global HIV treatment efforts. To enable both intranational and international comparisons and standard-setting, indicators of programmatic success must be measured at both the local and national levels. The degree to which clinics and countries have the capacity for M&E will vary widely, depending on staffing and resources.

This chapter addresses data collection and record management, presents the data management techniques and tools that have been developed by PIH, and outlines key M&E principles for implementing and managing an HIV treatment program. We believe that our systems can serve as a model for other resource-poor areas that are starting and scaling up treatment for HIV. In addition, the experiences presented below can inform data management and M&E for other projects addressing infectious or chronic diseases.

4.1 Patient Data Collection and Recordkeeping in Resource-Poor Settings

HIV care and programmatic M&E require effective information management. Projects should aim to collect individual patient data and not just aggregate data. Because HIV patients are expected to remain in treatment for many years, their clinical status, laboratory results, medication regimens, and adverse events need to be tracked continuously over time. For small numbers of patients at one or two sites, this can be accomplished by maintaining detailed paper records. Paper records become increasingly difficult to manage, however,

once the patient caseload expands or the number of project sites increases. Laboratory data—particularly blood counts, clinical chemistries, and CD4 counts—need to be assessed regularly and often must be communicated over long distances. Furthermore, paper records do not facilitate the extraction and analysis of data for programmatic monitoring, operational research, or reporting to funders.

Most HIV treatment programs will likely start with simple data collection and management tools, such as databases or spreadsheets. While useful for basic analyses, spreadsheets are particularly unreliable for data collection and storage beyond several dozen records.

In Haiti, reliable, long-term recordkeeping has been facilitated by the implementation of a secure, web-based electronic medical record (EMR) system. Creating a central database of core information has allowed clinical and administrative staff to track individual patients as well as monitor the care of the patient population as a whole. The advantages of managing individual patient data using such an electronic clinical information system include:

- the ability to accurately track patient outcomes;
- the enablement of more effective patient follow-up (by allowing health workers access to patient data on clinic attendance, medication pickups, etc.);
- the ability to track patient identities and detect duplicate records;
- the ability to store and analyze laboratory results;
- the provision of decision support to assist clinical staff in prescribing medications and administering patient care;
- improved drug supply management; and
- the ability to generate reports for project management and for funding agencies.

4.2 System Requirements

Deciding on an electronic information management strategy and system requires balancing the need for convenient and accurate data management with the associated costs. These costs include both capital costs (for example, equipment, Internet service) and human resources (data entry personnel and the provision of technical support and IT training). The strategies for information management will vary depending on the nature of the particular treatment program, the number of sites where patients are seen, and the availability of both technical infrastructure (such as electricity and computers) and human resources.

Not all AIDS treatment programs in resource-poor settings will have the capacity to implement the technologies described in this chapter. PIH is now involved in an international effort to standardize data collection so that a minimum data set can be easily collected by all programs. We believe that EMR systems can be maintained locally, without sophisticated on-site computer system expertise. Community members in almost any setting can be trained to perform data entry and basic maintenance tasks. While implementing electronic recordkeeping may be a labor-intensive process, it brings important skills to the community and allows for another area of capacity-building. All of the electronic tools that are used at PIH sites have been developed with open source software so that other projects can benefit from them and undertake evaluations with common metrics and tools.¹

The traditional approach to electronic data management in remote locations is to place individual, stand-alone servers at each site.^{2,3} In some systems, the data are periodically transmitted to a central server. Such stand-alone databases have the advantage of being easier and usually cheaper to develop and maintain, but they typically lack the ability to coordinate data between sites and may be problematic due to unstable electrical power, humidity, dust, and lack of

security. In contrast, ZL's secure, web-based EMR in Haiti has allowed data collection and review to occur from many remote sites while the information is kept on a shared server that is maintained in a secure environment with stable power and regular data backup. Moreover, with a shared server, the most up-to-date data, such as laboratory results, are always available to all users.

4.2.1 Internet access and electronic telecommunications

Different settings will have different options for Internet access. It is important to research the most cost-effective and reliable local systems, be they satellite, broadband cable, or dial-up. An increasingly popular strategy is wide area wireless networking. Signals can be sent tens of kilometers in the line of sight for a few thousand dollars in set-up costs, which often include towers to hold the aerials. Sites linked this way have much faster and more reliable interconnections and minimal ongoing costs.

Many of the ZL sites in rural Haiti are not connected to the national power grid, so it was necessary to first install generators (or to set up solar power, as at PIH sites in Rwanda). High speed Internet access that links the clinics to each other and to other PIH sites around the world is provided via satellite. While the initial investment is both monetarily and technically significant, the short- and long-term benefits are numerous. The initial capital costs for the satellite dish, server, and related equipment (modem, block upconverter, router) totaled approximately US\$8,000 per site in Haiti. Internet access costs approximately US\$5,800 per site per year. Computers, peripherals, and data staff comprise the rest of the cost of operating the program. Running the information systems and EMR program in Haiti represents less than 1.5 percent of the overall program budget.

Staff working at remote sites often lack access to up-to-date medical information and the support of more experienced colleagues. This situation is changing in many parts of the

world, as Internet access—in particular, the expanded use of e-mail for communication and consultation—increases.^{4–6} The ZL clinical staff and management, dispersed at remote, mostly rural clinics across central Haiti, have fully adopted e-mail to coordinate care between sites. Uses of e-mail include scheduling and obtaining the results of specialist investigations in the capital city or in the United States; ordering medications and equipment; and arranging patient transfers between sites. E-mail consultation with other doctors is used daily, especially by junior staff who frequently require advice regarding treatment options. These consultations may include the transmission of digital images—a technique termed “store-and-forward telemedicine.”^{7,8}

4.3 The HIV Electronic Medical Record: Data Collection and Management in Haiti

As increased funding becomes available, many interested parties are developing data collection forms with a view to using them in clinical consultation and for transfer to a database for M&E and for research. Thus, HIV treatment programs in resource-poor settings should make themselves aware of the many available data collection forms and ensure, if they do choose to use an EMR, that it fits well with local clinical practices and with the objectives of the program. Appendix H presents several EMR systems that are currently being developed by groups working in resource-poor settings.⁹

With the opportunity to expand ART access tenfold as a result of Global Fund monies, in 2003 ZL began to enter patient data into a computerized electronic medical record system, the HIV-EMR.¹⁰ The HIV-EMR, based on technology PIH used to develop a web-based EMR in Peru,¹¹ has both French and English interfaces. It was developed in close consultation with local users and is hosted on a central server (currently in PIH's U.S. office, due to security and access issues). Based on existing paper forms (see Appendix I for an example of ZL's

intake forms for ART patients), the following patient data are collected and entered into the EMR:

- patient demographics;
- history of presenting complaints;
- previous treatments and adverse events;
- symptoms;
- physical exam findings;
- laboratory and radiographic investigations;
- socioeconomic indicators (housing, occupation, economic status);
- contact data (number of persons in the home, number who are ill); and
- medications and treatment plan, including socioeconomic support services.

A checklist of patient management items is divided into categories of investigations, medications, and social items. Checking any of these items stores the appropriate medication orders in the database. (See Appendix J for screenshots of representative sections of the EMR that mirror corresponding sections on the paper forms.) Once the data are submitted to the web server, the subsequent page displays any drugs that have been selected. The physician can review the drugs and their dosing and administration. Finally, when the form is submitted, the system saves it in the database; the user can then print out an order for the pharmacy.

The EMR system also includes a library of web-based analysis and reporting tools that allow users to conduct searches for groups of patients based on characteristics such as age, treatment status, medication regimen, and laboratory results. The reporting tools allow local staff to generate reports for donor and governmental agencies. Data can also be downloaded to statistical analysis packages and database programs.

4.3.1 Data entry and quality checks

Once a medical record system is established, the chief task is to enter high-quality data. This is a challenge in any project, but is particularly difficult in resource-poor settings. Staff often lack not only familiarity with computers but also literacy, numeracy, and experience with data collection, management, and analysis. Overcoming these challenges necessitates several strategies:

- comprehensive and ongoing training and supervision;
- well-designed paper forms (where applicable);
- well-designed interfaces, with rules to restrict data types and ranges of permitted values;
- formal protocols to regularly check entered data against original records; and
- double-entry for critical data such as laboratory test results.

ZL and PIH staff perform regular comparisons of laboratory and medication data against original documents. At some sites, data may be available directly in electronic form from other sources (such as laboratory systems). While reducing the risk of introducing data entry errors, the electronic transfer of data usually requires additional computer programming; such transfers work best with EMR systems designed to meet specific data transfer standards (such as Health Level Seven (HL7)). Additional strategies, some employed at various PIH sites, include the use of handheld devices such as Palm Pilots® to allow point-of-care data entry,¹² scanning specially designed forms directly into a database,¹³ and touchscreen data entry.¹⁴

One of the most important and effective strategies to improve data quality is to give feedback to users in the form of reports and summaries and, where possible, to give users access to the EMR system and encourage regular use. In general, increasing users' reliance on high-quality data lessens the probability that errors will go unnoticed.

4.3.2 Obtaining consistent patient information

In resource-poor settings even something as seemingly straightforward as recording a date of birth or an address can be fraught with uncertainty. Strategies for dealing with problems such as these include:

- recording detailed, descriptive addresses;
- developing computer algorithms to match similar names and addresses;
- using a national ID (where available);
- providing all patients with an ID or clinic card to bring to consultations; and
- relying on community health workers to help track patients in treatment.

Initial reports on the use of clinical and ID cards in Haiti and in some African countries have shown that a high proportion of patients retain and carry their card. A large study in Malawi has also demonstrated the efficacy of adding a bar code to the card.¹⁵

4.3.3 Data security and confidentiality

Ensuring that all patient data are kept secure and confidential is vital both ethically and legally.¹⁶ In developing a web-based EMR, PIH built on extensive previous encryption and web security work in the fields of banking and medical records.^{17–19} Importantly, using a central database allows the entire computer and data system to be kept physically secure and backed up. In addition, the ability to look up patient information securely in a medical record system also eliminates or greatly reduces the need to send confidential data by nonsecure e-mail.

Regulations for clinical data collection and use differ from those for research data. Stripping out all identifying information from patient data allows them to be used for research and analysis; researchers should exercise caution, however, with “free text” data, which often contain identifying features such as family names or addresses.

Researchers and health workers at ZL follow strict rules for maintaining the confidentiality of medical data:

- users are required to have complex passwords and can only access the parts of the system they need;
- users must sign a form that details strict operating procedures and precautions;
- to ensure that no unauthorized access occurs, all log-ins and viewed pages are recorded and reviewed;
- the computer and any hard copies of data are physically secured; and
- data transfers are encrypted.

4.3.4 Dealing with unreliable or expensive Internet access: offline data entry

Network outages initially limited the use of the web-based EMR in Haiti, especially during the rainy season. We addressed this problem by developing an application for offline data entry that replicated the web-based EMR. Data are downloaded and stored in secure form in the application. Entered data can be stored locally for an unlimited length of time; however, upload delays increase the risk of data loss due to local computer problems. When the network is available, the offline EMR transmits data to the server using a secure web connection.

4.3.5 Data backup

Data integrity is fundamental to any data collection system. Maintaining uncorrupted data presents special challenges in resource-poor settings due to the difficulty of maintaining computers in remote areas. In such settings, data must be backed up every night, and copies for storage should be moved frequently. For stand-alone systems, a preferred backup medium is a CD-ROM, which is low-cost and high-capacity, and from which data cannot be deleted accidentally. Networked systems can also be automatically backed up to a server. Traditionally, servers have used tape backup systems, but these can be temperamental and expensive and require frequent replacement. The falling cost of data storage has

provided an alternative strategy: maintaining multiple copies of data on different machines, on a portable hard drive, or even a high-capacity memory stick. Backups must be checked regularly to ensure that the data are readable in the event of a system failure; however, off-site storage is still necessary. In addition, to prevent system crashes and data loss due to power outages, computers should have uninterruptible power supplies (UPS).

4.3.6 The OpenMRS

In 2005, PIH saw an important opportunity to build on our experiences developing, implementing, and using the HIV-EMR to create a new, open source EMR that is flexible, scalable, and easily adaptable by other programs. In collaboration with the Regenstrief Institute at the University of Indiana, we began developing the new system, OpenMRS.²⁰ To date OpenMRS has been launched at PIH sites in Rwanda and Peru and is being implemented in Lesotho and Malawi. It is also in use at other project sites in Haiti, Kenya, South Africa, Rwanda, Zimbabwe, Tanzania, and Uganda.

OpenMRS has a web-based interface similar to the HIV-EMR but with a much more general design, allowing it to be used for the management of a wide range of diseases. (See Appendix K for a representative screenshot of the OpenMRS's summary screen for a patient on ART.) OpenMRS offers several advantages over other existing systems, including the HIV-EMR. First, it is built with free, open source software, which enables the system to be widely accessible. Second, OpenMRS is based on open standards for data exchange (such as HL7), thus allowing for the exchange of patient records with other EMR systems. Third, OpenMRS has immense flexibility—it can run on a large server or on a laptop computer operating on Linux, Windows, or Apple platforms.

A fourth key advantage is that OpenMRS does not require expert programming to add new forms or to tailor the

system to new sites, languages, and diseases. All data stored in OpenMRS is coded using a “concept dictionary” that represents all the possible data items that can be collected. The concept dictionary greatly simplifies the process of linking OpenMRS to existing medical coding systems such as the WHO's International Classification of Diseases (ICD10) or Logical Observation Identifiers Names and Codes (LOINC®) and comparing data between projects or sites. (This feature has resulted in OpenMRS being adopted by the projects affiliated with the U.S. National Institutes of Health (NIH)-funded International Epidemiologic Databases to Evaluate AIDS (IeDEA) that are comparing HIV outcomes across multiple African countries.) It also allows new data items to be added to the system by non-programmers, greatly reducing the need for technical assistance. The OpenMRS also includes tools for data analysis, drug supply management, and reporting within a single, integrated system.

Finally, the OpenMRS system has a robust offline component. A local copy of the system runs at each PIH clinic in Rwanda that has stable electrical power. Users access the system over the local network and work without internet access. The server has a system for automatically synchronizing the data to an offsite central server using slow or intermittent internet connectivity. Data can also be manually transported on a memory stick.

While the basic use of the OpenMRS system does not require programming, an experienced IT professional needs to install the system and ensure that it is correctly configured and the data regularly backed up. Staff will need to be trained in data entry, and a data manager must be in place to ensure data quality and assist with the creation and use of reports. More information about the OpenMRS is available at www.openmrs.org.

4.4 Medication Management: Decision Support and Inventory Management

Medication management is a critical and complex programmatic function that is greatly assisted by EMR systems. The Brazilian HIV program, for example, uses custom drug management tools (SICLOM) to assist in the provision of care to more than 100,000 patients.^{21,22}

The HIV-EMR in Haiti has been helpful in medication management in two ways. First, as a real-time decision-support tool as described below, the HIV-EMR alerts the prescribing physician to possible problems. Second, at the level of the central pharmacy, the HIV-EMR allows drug utilization to be tracked and linked with inventory management; this feature is discussed in Section 4.5.

4.4.1 Decision support

Drug-prescription decision support for physicians has been shown to reduce medical errors, especially among less-experienced physicians.²³ Similarly, well-designed order entry systems for nurses in developing countries can substantially reduce data errors.²⁴ When physicians prescribe drugs through the HIV-EMR, the prescriptions are cross-checked for several types of potential problems, including allergies, inaccurate doses, incompatible combinations, or drugs that require a negative pregnancy test or the concomitant use of birth control. Warnings are generated about any problems detected; most can be overwritten but some—such as prescribing AZT with d4T—cannot. (See Appendix L for an example of an automatically generated alert.) Moreover, specific instructions can be generated for patients who are not prescribed standard regimens or who require investigations such as a CD4 count or sputum smear. These types of warnings work best if they are used sparingly, adapted for each project, and carefully tested.

Decision support also applies to laboratory results. Each night, after lab results have been entered, a program checks the lab data for low CD4 counts; the program then checks whether patients found to have low CD4 counts are being prescribed appropriate treatment. A notification e-mail sent to all clinicians flags patients who require additional attention.

4.4.2 Inventory management

Predicting, procuring, and maintaining an adequate stock of drugs is a critical component of any AIDS treatment program. The HIV-EMR supports two methods of providing up-to-date analysis of drug stocks and needs.^{25,26} First, it can aggregate drug regimen data to create custom reports of overall expected medication usage for a specified time period (and can also predict drug costs if unit price information is programmed into the system). The HIV-EMR can also provide electronic copies of stock cards to keep track of drug movement into and out of the warehouse, display current warehouse inventories, and generate warnings if inventories drop below pre-specified values. (Note that although a number of database systems have been developed to automate the process of calculating drug quantities from actual WHO stock cards, these systems generally require servers at each site.²⁷) Using facsimiles of warehouse stock cards has simplified staff training and data error checking. The HIV-EMR also has functions to record and track stock movement within and between all pharmacies and warehouses at the ZL clinical sites.²⁸

Recording regimen and usage data in a single EMR system allows automatic crosschecks of estimates from the two methods outlined here. Additionally, members of the international team of health workers, program administrators, and procurement managers have the same view of medication stock levels at all times.

4.5 Conclusion

Many questions regarding the most effective strategies for implementing comprehensive HIV care in resource-constrained settings have just begun to be addressed.²⁹ For some, clinical trials are necessary to obtain definitive answers. Many operational and strategic issues, however, can be immediately addressed with careful collection of data for evaluation at the local level. Although the following list is by no means exhaustive, some of the ongoing clinical and operational questions include:^{30,31}

- What are the barriers to HIV testing and care at the local level when treatment programs are available?
- What are the barriers to continued engagement in comprehensive HIV care?
- In the absence of laboratory facilities, what clinical criteria provide the most effective guidance regarding decisions of when to initiate and/or change therapy?
- What is the minimum laboratory monitoring level required to ensure the safety and efficacy of therapy?
- What are the main barriers to achieving patient adherence to therapy?
- How does scale-up of HIV treatment impact public-health infrastructure and engage additional individuals in general medical care?
- What is the impact of ART programs on local HIV resistance patterns? How can this information be used to choose effective first-line therapies?

Appendix M lists the minimum indicators that should be collected by all programs and suggests additional questions to be answered by programs having the capacity to perform more sophisticated data collection and operational research. These indicators can be generated at the local level and are important for programmatic evaluation; they may also be reported to national data collection efforts. In most cases, the indicators are consistent with the WHO's M&E strategy, which emphasizes evaluation at the national level.³²

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Epilogue

Many arguments have been raised over the past decade to justify not moving rapidly forward with ART programs in settings with limited resources. The standard litany of objections has included the price of therapy, the complexity of the intervention, the inadequacy of health infrastructure, and the staggering lack of trained health care providers. For years such arguments were supported by cost-effectiveness analyses and the false dichotomy of prevention versus treatment. The cumulative effect of these arguments was to allow the death of tens of millions of poor people in developing countries who were living with and becoming ill as a result of HIV infection. The statistics were unambiguous: more than 90 percent of HIV infections occurred in the developing world, 75 percent in sub-Saharan Africa alone; tuberculosis epidemics were fanned by HIV; fragile health infrastructures were overwhelmed.¹ By 2002, perhaps 1 percent of all sub-Saharan Africans needing ART were receiving it, and many ostensibly on therapy were unable to acquire their medications regularly.² In Africa alone, an estimated 14 million children had lost one or both parents to AIDS.³ Prevention efforts were hampered by stigma: who wanted to be tested for a disease for which treatment was in effect unavailable? Meanwhile, in countries rich in resources, the efficacy of antiretroviral therapy has been well-confirmed: in the United States, ART has prolonged life by an estimated 13 years⁴—a success rate that would compare favorably with that of almost any treatment for cancer or complications of coronary artery disease.

The inequity between rich and poor countries in terms of access to HIV treatment has at last reached the public consciousness and rightly given rise to widespread moral indignation. A few outstanding leaders have been consistent and courageous in their personal and public stances. The national AIDS treatment program in Brazil, for example, has long demonstrated what can be achieved when there is unswerving political commitment

and public health leadership. As documented in this manual, Partners In Health has worked with the Haitian and Rwandan Ministries of Health to launch and scale-up comprehensive AIDS treatment programs in those countries, ensuring that provision of primary care is part of the disease treatment model. Other innovative projects pioneered by NGOs in diverse settings have clearly established that a very simple approach to ART, underpinned by intensive community engagement and support, can achieve remarkable results.

In 2003, fueled by the momentum of these diverse efforts, the World Health Organization, together with the Joint United Nations Program on HIV/AIDS (UNAIDS), launched the “3 by 5” initiative, setting the ambitious goal of putting three million people in the developing world on antiretroviral therapy by 2005.⁵ There was no prior experience to draw upon because there had never been an attempt to provide, across national borders and in some of the poorest places in the world, lifelong suppressive therapy for a chronic infection. Although the 3 by 5 initiative did not achieve its ambitious overall target, under its aegis ART coverage in developing countries has more than doubled, and scale-up appears to be accelerating. Treatment algorithms have been standardized, and intensive training packages for health and community workers have been developed and implemented in many countries. Overall, most African countries report that demand for treatment is outstripping their capacity to supply it, underlining the urgent need for increased resources and technical support in order to maintain this momentum. And at the G8 meetings in Scotland in 2005, the final communiqué pledged a commitment to providing universal access to HIV treatment by 2010.

In the wake of these recent developments, a very different picture—and different expectations—has emerged. Billions of dollars of funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria and the U.S. President’s Emergency

Plan for AIDS Relief have helped to launch hundreds of treatment projects. For example, the Bill & Melinda Gates Foundation and Merck & Co., working with officials in Botswana, have begun to offer universal access to ART in one of the world’s most severely HIV-affected countries. The policy and action implications of the lessons learned from these efforts, five of which are detailed below, need to be front and center. Based on my experience in setting global AIDS policy, on the one hand, and implementing integrated projects in settings of extreme poverty, on the other, I believe that ambitious policy goals, adequate funding, and knowledge about implementation can move us toward the elusive goal of shared hope.

The first lesson is that selling AIDS prevention and care will pose insurmountable problems for those living in poverty, as there will always be those unable to pay even modest fees for services or medications, whether generic or branded. AIDS care should be seen, as is the case for airborne tuberculosis, as a public good for public health.⁶ Policy makers and public health officials, especially in heavily burdened regions, should adopt universal-access plans and waive fees for HIV care. The advent of generic medications, thanks to efforts by groups such as Médecins Sans Frontières and the Clinton Foundation,⁷ means that ART can now cost less than 50 cents a day, and costs continue to decline to levels that developing-country public health officials can hope to pay for their citizens. Furthermore, all first-, second-, and even third-line antiretroviral medications must be made available at these now-affordable prices. Generic manufacturers in China, India, and other developing countries stand ready to provide the full range of drugs. Whether through negotiated agreements or use of the full flexibilities of the TRIPS agreement, full access to all available antiretroviral drugs must quickly become the standard in all countries.

Second, effective scale-up of pilot projects will require strengthening and even rebuilding health systems. In previous years, a lack of health infrastructure has been labeled a barrier

to ART; we must now marshal AIDS resources, which are at last considerable, to rebuild public health systems in sub-Saharan Africa and other HIV-burdened regions. These efforts will not weaken attempts to address other ranking problems—malaria, maternal mortality, vaccination undercoverage, other diseases of poverty—if they are planned deliberately, with the public sector in mind. Only the public sector, not NGOs, can offer health care as a right.

Third, AIDS funding offers us a chance to stop and even reverse the “brain drain,” long cited as a reason that we cannot treat AIDS in the poor world. In addition to recruiting physicians and nurses to underserved regions and providing them with the tools of their trade, we must also train community health workers to supervise care, for AIDS and many other pathologies, in their home villages and neighborhoods. This should be done even if there is an abundance of physicians, since community-based, closely supervised care is simply the highest standard of care for chronic disease. This is as true in the first world as it is in the third. Also, community health workers must be compensated for their labor if these programs are to be sustainable over time.

Fourth, extreme poverty makes it difficult for many patients to comply with ART. Indeed, poverty is far and away the greatest barrier to scale-up of treatment projects. In many rural regions of Africa, hunger is the major “co-morbid disease” seen with both AIDS and tuberculosis, and these consumptive diseases cannot be treated effectively without food supplementation. Coordination between initiatives such as PEPFAR, the Global Fund, and the United Nation’s World Food Program can help in the short term; fair trade agreements and support of African farmers will help in the long run.

Fifth, investments in global AIDS and tuberculosis are much more generous than they were only five years ago, but these investments must be increased and sustained if we are to slow

these ever more complex epidemics. One of the most ominous recent developments is the advent of highly drug-resistant strains of both diseases. “Extensively drug-resistant tuberculosis,” or XDR TB, has been reported in the United States, eastern Europe, Asia, South Africa, and elsewhere; in each of these settings, HIV has amplified local epidemics of these almost untreatable strains.⁸ These tuberculosis strains cannot be wished away, and XDR HIV will surely follow. Only massive efforts to diagnose and treat these diseases ethically and effectively will stem these epidemics. We have already learned a great deal about how best to expand access to second-line antituberculous drugs while at the same time increasing control over their use;⁹ these lessons, too, must be applied in the struggle against AIDS and other infectious pathogens.¹⁰

Finally, there is a need for a renewed commitment of basic science to vaccine development, more reliable diagnostics—those widely used to diagnose tuberculosis are neither specific nor sensitive, which is unsurprising since they were developed a century ago—and novel classes of therapeutics. The research-based pharmaceutical industry has a critical role to play in drug development, even if the overall goal is a segmented market with higher prices in developed countries and generic production with affordable prices for developing countries. There has also been a heartening increase in basic science investments for tuberculosis and malaria; National Institutes of Health (NIH) funding for HIV research remains robust. Yet the fruits of such research will not arrive in time for those now living with, and dying from, AIDS and tuberculosis.

The past two years have shown us that we can make these services available to millions, even in the poorest reaches of the world. The unglamorous and difficult process of increasing access, to prevention *and* care, needs to be our primary focus if we are to move towards the lofty goal of equitably distributed medical services in a world riven by inequality. The model of

care beautifully presented in this volume offers great promise in moving us toward that goal.

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Appendix A: Selected Significant Drug Interactions with Rifamycins

Type of drug	Comments
Anticonvulsants	Therapeutic drug monitoring recommended; may require anticonvulsant dose increase. Phenytoin: monitor serum phenytoin concentrations and seizure activity; increase dosage if needed.
Antipsychotics	Monitor clinical response; may need to increase haloperidol dose.
Antiretrovirals	APV, IDV, LPV/r, and NFV should not be used with R. EFV requires a dose increase to 800 mg/day when used with R.
Atovaquone	R reduces atovaquone levels by 50%; RFB probably has a similar effect. Consider alternative treatments for PCP.
Azole antifungal agents	Itraconazole, ketoconazole, and voriconazole concentrations may be subtherapeutic with any of the rifamycins and should be avoided if possible. Fluconazole has less reduction in serum concentrations vs. other azoles; monitor clinical response and increase fluconazole dose as needed.
Benzodiazepines	Monitor clinical response; may need to increase diazepam dose.
β-Adrenergic blocking agents	Monitor clinical response; increased propranolol hydrochloride or metoprolol dose may be needed.
Chloramphenicol	Monitor serum chloramphenicol concentrations; increased chloramphenicol dose may be needed; consider an alternative antibiotic.
Clarithromycin	RFB level increases by 56% and clarithromycin level decreases by 50%. Avoid R. Monitor signs and symptoms of infection; more study needed.
Corticosteroids	Monitor clinical response; may require two- to three-fold increase in corticosteroid dose.
Dapsone	Monitor clinical response, including potential hematologic toxic effects; increased dapsone dose may be necessary; additional study needed when used for PCP prophylaxis.
Digitoxin	Monitor arrhythmia control, signs and symptoms of heart failure, and serum digitoxin concentrations.
Digoxin (oral)	Monitor arrhythmia control, signs and symptoms of heart failure, and digoxin serum concentrations.

Type of drug	Comments
Doxycycline	Monitor clinical response; increase doxycycline dose if needed; consider an alternative antibiotic.
Hypoglycemics	Monitor blood glucose; may require hypoglycemic drug dose increase or change to an alternative hypoglycemic drug.
Hypolipidemics	For simvastatin and fluvastatin, monitor hypolipidemic effect; may require use of an alternative hypolipidemic drug. Concurrent use of atorvastatin or pravastatin with rifamycins appears safe.
Levothyroxine sodium	Monitor thyrotropin level; increased dose of levothyroxine sodium likely needed.
Mefloquine	Consider an alternative malaria prophylaxis/treatment.
Methadone hydrochloride	Increase methadone dose with concomitant R therapy; monitor and control withdrawal symptoms.
Metronidazole	Monitor for decreased clinical response; increase metronidazole dose if needed; use another agent if possible.
Oral anticoagulants	Monitor international normalized ratio; increased anticoagulant dose will likely be needed.
Oral contraceptives	Use alternative form(s) of birth control, as rifamycins decrease levels of oral contraceptives.
Theophylline	Monitor serum theophylline concentrations; increase theophylline dose if needed.
TMP/SMX	R significantly reduces each TMP/SMX component. Increased TMP/SMX dose may be needed.
Tricyclic antidepressants	Therapeutic drug monitoring recommended; may require dose increase or change to alternative agent.

Sources: American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med* 2003;167:603–62. Bartlett JG, Gallant JE. *Medical management of HIV infection*. Baltimore, MD: Johns Hopkins University, 2005. Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin and rifabutin drug interactions. *Am J Med Sci* 2008;335:126–36. Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA. *The Sanford guide to antimicrobial therapy* 2006. 36th ed. Sperryville, VA: Antimicrobial Therapy, Inc., 2006.

This is a partial list of significant drug interactions and the reader is advised to check the drug insert information before prescribing any medications in conjunction with rifamycins.

Appendix B: WHO Clinical Staging of HIV Disease in Adults and Adolescents (2006 Revision)

Adult Clinical Stage I: 1. Asymptomatic 2. Persistent generalized lymphadenopathy
Adult Clinical Stage II: 1. Unexplained moderate weight loss (under 10% of presumed or measured body weight) ^a 2. Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) 3. Herpes zoster 4. Angular cheilitis 5. Recurrent oral ulceration 6. Papular pruritic eruptions 7. Seborrheic dermatitis 8. Fungal nail infection
Adult Clinical Stage III: 1. Unexplained severe weight loss (>10% of presumed or measured body weight) ^a 2. Unexplained chronic diarrhea of more than one month's duration 3. Unexplained persistent fever (intermittent or constant of more than one month's duration) 4. Persistent oral candidiasis 5. Oral hairy leukoplakia 6. Pulmonary tuberculosis (current) 7. Severe bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia, severe pelvic inflammatory disease) 8. Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis 9. Unexplained anemia (below 8 g/dl), neutropenia (below 0.5 × 10 ⁹ /L), and/or chronic thrombocytopenia (below 50 × 10 ⁹ /L)

Adult Clinical Stage IV:

1. HIV wasting syndrome
2. *Pneumocystis pneumonia*
3. Recurrent bacterial pneumonia
4. Chronic herpes simplex infection (orolabial, genital, or anorectal of more than one month's duration, or visceral at any site)
5. Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
6. Extrapulmonary tuberculosis
7. Kaposi's sarcoma
8. Cytomegalovirus infection (retinitis or infection of other organs)
9. Central nervous system toxoplasmosis
10. HIV encephalopathy
11. Extrapulmonary cryptococcosis, including meningitis
12. Disseminated non-tuberculous mycobacteria infection
13. Progressive multifocal leukoencephalopathy
14. Chronic cryptosporidiosis
15. Chronic isosporiasis
16. Disseminated mycosis (coccidioidomycosis or histoplasmosis)
17. Recurrent septicemia (including non-typhoidal *Salmonella*)
18. Lymphoma (cerebral or B cell non-Hodgkin's)
19. Invasive cervical carcinoma
20. Atypical disseminated leishmaniasis
21. Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Note: Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas and penicilliosis in Asia.

Adapted from: World Health Organization. Annex 1: WHO clinical staging of HIV disease in adults and adolescents. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*. 2006 revision. Geneva: World Health Organization, 2006: 78. (Accessed February 27, 2008 at: <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>.)

^a Assessment of body weight among pregnant woman needs to take into account the expected weight gain of pregnancy.

Appendix C: WHO Clinical Staging of HIV Disease in Infants and Children (2006 Revision)

Pediatric Clinical Stage I:

1. Asymptomatic
2. Persistent generalized lymphadenopathy

Pediatric Clinical Stage II:

1. Unexplained persistent hepatosplenomegaly
2. Papular pruritic eruptions
3. Fungal nail infections
4. Angular cheilitis
5. Lineal gingival erythema
6. Extensive wart virus infection
7. Extensive molluscum contagiosum
8. Recurrent oral ulcerations
9. Unexplained persistent parotid enlargement
10. Herpes zoster
11. Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

Pediatric Clinical Stage III:

1. Unexplained moderate malnutrition not adequately responding to standard therapy
2. Unexplained persistent diarrhea (14 days or more)
3. Unexplained persistent fever (above 37.5 °C, intermittent or constant, for longer than one month)
4. Persistent oral candidiasis (after first six weeks of life)
5. Oral hairy leukoplakia
6. Acute necrotizing ulcerative gingivitis/periodontitis
7. Lymph node tuberculosis
8. Pulmonary tuberculosis
9. Severe recurrent bacterial pneumonia
10. Symptomatic lymphoid interstitial pneumonitis
11. Chronic HIV-associated lung disease, including bronchiectasis
12. Unexplained anemia (<8.0 g/dl), neutropenia (<0.5 × 10⁹/L), or chronic thrombocytopenia (<50 × 10⁹/L)

Pediatric Clinical Stage IV:

1. Unexplained severe wasting, stunting, or severe malnutrition not responding to standard therapy
2. *Pneumocystis pneumonia*
3. Recurrent severe bacterial infections (e.g., empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
4. Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration, or visceral at any site)
5. Extrapulmonary tuberculosis
6. Kaposi's sarcoma
7. Esophageal candidiasis (or candida of trachea, bronchi, or lungs)
8. Central nervous system toxoplasmosis (after the neonatal period)
9. HIV encephalopathy
10. Cytomegalovirus infection; retinitis or CMV infection affecting another organ, with onset at age over one month
11. Extrapulmonary cryptococcosis (including meningitis)
12. Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)
13. Chronic cryptosporidiosis (with diarrhea)
14. Chronic isosporiasis
15. Disseminated non-tuberculous mycobacteria infection
16. Cerebral or B cell non-Hodgkin's lymphoma
17. Progressive multifocal leukoencephalopathy
18. HIV-associated cardiomyopathy or nephropathy

Note: Some additional specific conditions can be included in regional classifications (e.g., penicilliosis in Asia, HIV-associated rectovaginal fistula in Africa, and reactivation of American trypanosomiasis).

Adapted from: World Health Organization. Annex B, Part A: WHO clinical staging of HIV for infants and children with established HIV infection. *Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach*. 2006. Geneva: World Health Organization, 2006:85-6. (Accessed February 27, 2008 at: <http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf>.)

Appendix D: Adult Dosing Guidelines for Selected Antiretroviral Drugs

Drug	Adult dosing	Important side effects; comments
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Abacavir (ABC)	300 mg 2x/day	<ul style="list-style-type: none"> • Hypersensitivity in 2-5% of patients • Alcohol increases ABC levels by 40%
Didanosine (ddI)	<p><60 kg: 125 mg 2x/day or 250 mg/day; 100 mg 2x/day if combined with TDF</p> <p>≥60 kg: 200 mg 2x/day; 125 mg 2x/day if combined with TDF</p>	<ul style="list-style-type: none"> • Chills or fever, headache, nausea, vomiting, peripheral neuropathy, pancreatitis, lipodystrophy, weakness, abdominal pain, diarrhea, retinal changes, optic neuritis, fat redistribution/accumulation, rash, lactic acidosis, severe hepatomegaly with steatosis • Take on empty stomach • Increased toxicity with d4T • Avoid during pregnancy • Alcohol increases risk of pancreatitis • Adjust dose with renal failure
Emtricitabine (FTC)	200 mg/day	<ul style="list-style-type: none"> • Generally well-tolerated • Headache, decreased appetite, nausea, vomiting, rash, lactic acidosis, hepatomegaly, skin hyperpigmentation • Related chemically to 3TC, but more potent
Lamivudine (3TC)	150 mg 2x/day or 300 mg/day	<ul style="list-style-type: none"> • Generally well-tolerated • Headache, decreased appetite, nausea, diarrhea, vomiting, lactic acidosis, hepatomegaly, pancreatitis (especially in children)

Drug	Adult dosing	Important side effects; comments
Nucleoside reverse transcriptase inhibitors (NRTIs), continued		
Stavudine (d4T)	30 mg 2x/day	<ul style="list-style-type: none"> • Peripheral neuropathy, lipodystrophy, lactic acidosis, hepatomegaly with steatosis, pancreatitis, hyperlipidemia • Fatal pancreatitis has been reported when used with ddI • Avoid during pregnancy • Do not use with AZT
Zidovudine (AZT)	300 mg 2x/day Perinatal HIV transmission prevention (for the mother): <ul style="list-style-type: none"> • 100 mg 5x/day or 200 mg 3x/day or 300 mg 2x/day starting at the 14th week of gestation until labor, then 2 mg/kg IV over 1 hour followed by 1 mg/kg/hour IV until umbilical cord clamping • Alternative: 2 mg/kg IV over 1 hour followed by 1 mg/kg/hour until delivery + single-dose NVP 200 mg orally at onset of labor 	<ul style="list-style-type: none"> • Anemia, headache, insomnia, malaise, anorexia, constipation, nausea, vomiting, lactic acidosis, hepatomegaly with steatosis, leukopenia, myopathy, neuropathy • Do not use with d4T • See Appendix E and Protocols 2.3 and 2.4 for appropriate PMTCT management
Nucleotide reverse transcriptase inhibitor (NRTI)		
Tenofovir (TDF)	300 mg/day	<ul style="list-style-type: none"> • Nephrotoxicity, including Fanconi syndrome • Take with food

Drug	Adult dosing	Important side effects; comments
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz (EFV)	600 mg/day If used concurrently with R, 800 mg/day	<ul style="list-style-type: none"> • Dizziness, agitation, vivid dreams, hepatitis, lipodystrophy, depression, hallucinations, impaired concentration, insomnia, somnolence, rash (very common, especially in children), hyperglycemia, hyperlipidemia and fat redistribution (less common) • Administer at bedtime without food (at least 2 hours after a meal) • Avoid during pregnancy • Decreases effectiveness of oral contraceptives
Nevirapine (NVP)	200 mg/day for 14 days, then 200 mg 2x/day Perinatal HIV transmission prevention for women with no prior ART: single-dose NVP 200 mg orally at onset of labor (plus two weeks AZT and 3TC postpartum)	<ul style="list-style-type: none"> • Rash (most common), headache, fatigue, diarrhea, nausea, fat redistribution (less common), hepatitis (generally within 12 weeks of initiation), hepatic failure (severe, life-threatening hepatotoxicity, some fatal cases), severe skin reactions (Stevens-Johnson syndrome) • Women with CD4 >250 cells/mm³, including pregnant women, are especially vulnerable for fatal hepatotoxicity • See Appendix E and Protocols 2.3 and 2.4 for appropriate PMTCT management

Drug	Adult dosing	Important side effects; comments
Protease inhibitors (PIs)		
Amprenavir (APV)	1200 mg 2x/day If with RTV (APV/r): 600 mg APV 2x/day + 100 mg RTV 2x/day	<ul style="list-style-type: none"> • Nausea, vomiting, diarrhea, rash, Stevens-Johnson syndrome, lipodystrophy • Avoid taking with high-fat meal • Decrease dose in liver failure to 300 mg • Decreases effectiveness of oral contraceptives • Avoid during pregnancy
Atazanavir (ATV)	400 mg/day If with RTV (ATV/r): 300 mg/day ATV + 100 mg/day RTV Boost if used with TDF, EFV, or NVP.	<ul style="list-style-type: none"> • Asymptomatic hyperbilirubinemia, GI intolerance, rash, prolongation of PR interval (first-degree atrioventricular block) • Take with food
Indinavir (IDV)	800 mg 3x/day If with RTV (IDV/r): 800 mg IDV 2x/day + 100 mg RTV 2x/day	<ul style="list-style-type: none"> • Abdominal pain, nausea, vomiting, asymptomatic hyperbilirubinemia, back pain, acute hemolytic anemia, hyperglycemia (including cases of new onset diabetes mellitus), hepatitis (rare), nephrolithiasis, lipodystrophy • Take with plenty of water to avoid nephrolithiasis • Take on empty stomach
Lopinavir/Ritonavir (LPV/r)	400 mg LPV 2x/day + 100 mg RTV 2x/day If with EFV, APV, NFV, or NVP: 533 mg LPV 2x/day + 133 mg RTV 2x/day	<ul style="list-style-type: none"> • Diarrhea, lipodystrophy, nausea • Refrigeration required • Take with food
Nelfinavir (NFV)	1250 mg 2x/day	<ul style="list-style-type: none"> • Secretory diarrhea, nausea, vomiting, lipodystrophy • Take with food

Drug	Adult dosing	Important side effects; comments
Ritonavir (RTV)	Start at 300 mg 2x/day and escalate to 600 mg 2x/day over 2 weeks	<ul style="list-style-type: none"> • Hepatitis, lipodystrophy • Refrigeration required • Poorly tolerated when used alone at 600 mg 2x/day; best used to boost levels of other PIs

Adapted from: Bartlett JG, Gallant JE. *Medical management of HIV infection*. Baltimore, MD: Johns Hopkins University, 2005.

Appendix E: Pediatric Dosing Guidelines for Selected Antiretroviral Drugs

Drug	Pediatric dose Maximum dose	Commonly available formulations
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Abacavir (ABC)	8 mg/kg 2x/day Max 300 mg 2x/day	Syrup: 20 mg/ml Tablet: 300 mg
Lamivudine (3TC)	4 mg/kg 2x/day Max 150 mg 2x/day	Syrup: 10 mg/ml Tablet: 150 mg
Stavudine (d4T)	1 mg/kg 2x/day Max 30 mg 2x/day	Syrup: 1 mg/ml Capsule: 30 mg, 40 mg
Zidovudine (AZT)	8-15 mg/kg (180-300 mg/m ²) 2x/day Postpartum prophylaxis: 4 mg/kg 2x/day for 1-6 weeks ^a Max 300 mg 2x/day	Syrup: 10 mg/ml Capsule: 100 mg Tablet: 300 mg
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz (EFV)	~15 (10-20) mg/kg/day Max 600 mg/day	Capsule: 200 mg Tablet: 600 mg
Nevirapine (NVP)	Induction dose (14 days): 4 mg/kg/day (200 mg/m ²) Maintenance dose, <8 years: 7 mg/kg 2x/day Maintenance dose, ≥8 years: 4 mg/kg 2x/day Max 200 mg 2x/day Postpartum prophylaxis: 2 mg/kg (6 mg if weight unknown) within 72 hours of birth ^b	Syrup: 10 mg/ml Tablet: 200 mg
Protease inhibitors (PIs)		
Lopinavir/ Ritonavir (LPV/r)	<15 kg: 12 mg/kg LPV 2x/day + 3 mg/kg RTV 2x/day ≥15 kg: 10 mg/kg LPV + 2.5 mg/kg RTV 2x/day Max 400/100 mg 2x/day	Capsule: 133.33 mg LPV + 33.33 mg RTV Tablet: 200 mg LPV + 50 mg RTV
Nelfinavir (NFV)	55 mg/kg 2x/day Max 1250 mg 2x/day	Tablet: 250 mg

Fixed-Dose Combinations

Formulations	Pediatric dose Maximum dose
3TC 150 mg + AZT 300 mg	2x/day Max 1 tablet 2x/day
3TC 150 mg + d4T 30 mg	
3TC 150 mg + d4T 40 mg	
3TC 150 mg + d4T 30 mg + NVP 200 mg	

^a AZT can be used alone or in combination with NVP for HIV-exposed infants postpartum, depending on what treatment the mother has received (see Protocol 2.4).

^b NVP is used postpartum in combination with AZT for HIV-exposed infants (see Protocol 2.4).

See Appendix D for drug side effects and recommendations for ingestion with food or drink.

Appendix F: HIV-Related Complications of the Skin, Lymph Nodes, and Mucous Membranes

Disease	Etiology and presentation	Treatment
Enlarged lymph nodes, nodules, or masses		
Generalized lymphadenopathy	May be HIV-related or the result of OIs such as TB, atypical mycobacteria, histoplasmosis, coccidioidomycosis, lymphoma, Kaposi's sarcoma, Epstein-Barr virus, toxoplasma, tularemia, CMV, or Castleman's disease; also seen in immune reconstitution syndrome (see Section 3.9.7 and Protocol 3.26); less often lymphoma.	Treatment should be directed at the specific OI. If no OI can be identified, consider initiating ART.
Kaposi's sarcoma	Firm, subcutaneous brown-black or purple nodules at any cutaneous site, especially face, chest, genitals, and extremities.	May resolve with ART. Surgical excision, intralesion or systemic chemotherapy, radiation, cryotherapy, or laser therapy in specialist centers may be successful if the sarcoma is extensive and widespread.
Lymphoma	Increased risk in patients with HIV. Often in body cavities or CNS. Hard, painless lymph nodes are typical. May be associated with fever.	If specialized care centers are available, consider biopsy and treatment based on definitive diagnosis.
Salivary gland enlargement	Enlargement of submandibular, parotid, and other glands; may be mistaken for lymphadenopathy. Rule out abscess and lymphoma. If parotid swelling, consider mumps in differential diagnosis.	Usually resolves or improves with ART. If evidence of pus or infection present, consider drainage and treatment with dicloxacillin 250-500 mg orally 4x/day for 10-14 days or clindamycin 150-300 mg orally 4x/day for 10-14 days. Promote good oral hygiene.
Sexually transmitted infections	May present with inguinal mass or adenopathy.	See Section 2.6.

Disease	Etiology and presentation	Treatment
Tuberculosis	Typically a single swollen lymph node, most commonly in the cervical chain; may be generalized. Lymph nodes initially firm and small; can become large and fluctuant. Suppuration with drainage and chronic fistulization may occur. Diagnosis can be confirmed on biopsy or aspirate.	See Section 2.4.
Infected skin lesions (lesions that are red, tender, warm, pustular, or crusty)		
Abscess or folliculitis	Most commonly caused by <i>Staphylococcus aureus</i> .	Incise and drain fluctuant abscesses with sterile technique. Start dicloxacillin 250-500 mg orally 4x/day or cephalixin 500 mg orally 4x/day or clindamycin 150-400 mg orally 4x/day. Treat for 7-14 days or until resolved. Follow-up in 1-2 days to confirm improvement.
Cellulitis	Skin is red and warm; patient may be systemically unwell with fever. May progress to more severe soft tissue infection.	Start dicloxacillin or cephalixin 500 mg orally 4x/day for 7-14 days or until resolved.
Impetigo	Red, tender, warm papules, often with a honey-colored crust. Frequently on the face (around the mouth), trunk, and groin of adults. Contagious. May appear as ulcerating lesions.	Dicloxacillin 250-500 mg orally 4x/day or cloxacillin 250-500 mg orally 4x/day or erythromycin 250-500 mg orally 4x/day or clindamycin 150-400 mg orally 4x/day, each for 5-10 days.
Other lesions	Eczema, psoriasis, contact dermatitis, prurigo nodularis, and other lesions can mimic infection.	See sections on eczema, psoriasis, contact dermatitis, and prurigo nodularis in this table. Generally do not require antibiotics unless superinfection is present.

Disease	Etiology and presentation	Treatment
Severe soft tissue infection	Rapidly progressing skin infection, may involve subcutaneous fascia, pyomyositis, systemic toxicity. May be life- or limb-threatening.	Start benzathine penicillin 4 MU IV 6x/day. Add clindamycin 600 mg IV 3x/day if IV not available, start dicloxacillin and clindamycin orally. May need hospitalization and possibly specialist care or surgery.
Skin conditions that present as blisters or vesicles		
Adverse drug reactions	Some drug reactions can cause generalized blistering or small bumps. A peeling rash involving the eyes or mouth can represent a very serious drug reaction leading to Stevens-Johnson syndrome.	Stop all medications. Administer oral antihistamines. If Stevens-Johnson syndrome is suspected, hospitalize for supportive care. If reaction is severe, give prednisone 1-2 mg/kg orally, tapering 5-10 mg every 1-3 days. If patient was on ABC, do not reintroduce (may be fatal). See Protocol 3.7.
Contact dermatitis	Typically limited to the area in contact with the causative agent.	Hydrocortisone 1% cream or ointment 3x/day. If severe, with blisters or edema, consider prednisone 1 mg/kg/day orally, tapering 5-10 mg/day over 7-10 days.
Herpes simplex	Vesicles with an erythematous base. Usually oral, genital, or peri-rectal. Generally in clusters. May have a history of recurrence.	If first episode or recurrence, administer acyclovir 400 mg orally 3x/day for 7-10 days. See Protocol 3.21.
Herpes zoster	Vesicles with an erythematous base in a dermatomal distribution. Lesions in more than one dermatome or lesions in the eye are considered to be disseminated (or complicated) disease.	All patients with HIV should receive antiviral therapy regardless of timing of lesion onset. Administer acyclovir 10 mg/kg IV over 1 hour 3x/day for 7 days. Administer analgesia as required. See Protocol 3.21.

Disease	Etiology and presentation	Treatment
Skin conditions that present as generalized or itching rashes		
Adverse drug reactions	Generalized widespread red rash with small papules, usually on the trunk. Blistering or a peeling rash involving the eyes or mouth can represent a very serious drug reaction leading to Stevens-Johnson syndrome.	Stop all medications. Administer oral antihistamines. If Stevens-Johnson syndrome is suspected, hospitalize for supportive care. If reaction is severe, give prednisone 1-2 mg/kg orally, tapering 5-10 mg every 1-3 days. If patient was on ABC, do not reintroduce (may be fatal). See Protocol 3.7.
Early secondary syphilis	Macular rash on trunk, palms, and soles.	Single-dose benzathine penicillin 2.4 MU IM.
Eosinophilic folliculitis	Itchy papules and pustules most commonly on the head, trunk, and upper part of extremities. Difficult to differentiate from infective folliculitis; a biopsy will reveal eosinophilic infiltrate in the follicular epithelium. May occur with immune reconstitution.	Usually resolves once ART is initiated. Permethrin cream and topical steroid creams can help; antihistamines for pruritus.
Norwegian scabies (Scabies crustosa)	Usually in advanced immunosuppression (CD4 <100 cells/mm ³). Can mimic psoriasis. Itching may be absent. Extensive crusting.	Permethrin cream 5% leave on for 24 hours; 6% sulfur on days 2-7. Repeat for several weeks. Single-dose ivermectin 200 mcg/kg reported to be effective.
Prurigo nodularis	Hyperpigmented, hyperkeratotic, often excoriated papules and nodules up to 1 cm. May be due to insect bites. Scratching results in worsening pruritus.	Give oral antihistamines. Insecticides and bed-netting may be effective in preventing new lesions. Topical corticosteroid cream may help; can use high-potency steroid creams under an occlusive dressing. Aim to break the itch-scratch cycle, which may take several weeks or months. Condition may also improve with ART.

Disease	Etiology and presentation	Treatment
Scabies (also head and body lice)	Rash and excoriations on the torso. Burrows can often be seen in the web space between the fingers and on the wrist. The face is usually not affected. Itching can persist for two weeks after treatment.	Trim fingernails, wash clothes and bedding. Permethrin cream 5% (preferred): apply from chin to toes. Wash hair if involved. Leave on for 8-10 hours, then wash. Repeat in one week. Safe for children >2 months of age. Alternative: lindane 1%, same usage as permethrin. Seizures can occur from coverage of broad areas. Do not use in children or pregnant women.
Skin lesions caused by fungal infections		
Candidiasis (skin)	In children: causes a diaper-rash-type rash involving the trunk and extremities. In adults: causes flat or slightly raised red lesions; also common in the mouth (see section on lesions of the mucous membranes elsewhere in this table).	Topical ketoconazole, miconazole, clotrimazole, econazole, or nystatin, all 2x/day, or single-dose fluconazole 150 mg/week orally, each for 2-4 weeks. Or single-dose fluconazole 150 mg orally. Ringworm: topical ketoconazole 2x/day may be sufficient if lesions are few or small. If extensive, consider fluconazole 150 mg/week orally for 2-4 weeks or griseofulvin 500 mg/day orally for 4-6 weeks. In children: griseofulvin 10-20 mg/kg/day until hair regrows, usually 6-8 weeks.
Dermatophytic fungi	Red, often itchy lesions; may cause changes in skin pigment. Lesions can occur in the groin (<i>T. cruris</i>), on the feet (<i>T. pedis</i>), or on the body (<i>T. corporis</i>). <i>T. capitis</i> (ringworm) causes pale round scaling patches on scalp or round patches with thick, reddish edges on the body or web of the feet; it is harder to treat than the aforementioned fungal infections.	

Disease	Etiology and presentation	Treatment
Seborrhea	Very common in HIV-infected individuals. Can present as mild dandruff or scaly patches with indistinct borders. Common in the scalp, hair-line, central face; also seen in body folds and chest. Usual etiology is <i>Malassezia</i> species.	Ketoconazole (1% or 2%) shampoo or lotion. If severe, consider corticosteroid cream and ketoconazole. Often resolves or improves with ART.
Tinea versicolor	Typically causes areas of hypopigmentation. May be confused with vitiligo, which is not an infectious disease and will not respond to antifungal agents.	Usually resistant to topical agents. Administer ketoconazole 200 mg or 400 mg orally for 7 days, or single-dose fluconazole 400 mg orally.
Other skin lesions		
Dry skin (xerosis)	Often very itchy; antihistamines do not provide much relief.	Apply humectants or moisturizing creams.
Eczema	Red rash; often, itchy, flaking lesions that may have whitish patches or scaling; may become superinfected. Often on the groin and face (especially in children), under the arms, on the elbows, and elsewhere. Can be confused with contact dermatitis or psoriasis.	Apply topical corticosteroid creams. Treat itching with antihistamines. Dry the skin gently and avoid harsh or perfumed soaps.
Insect bites	Fleas: lower legs. Mosquitoes and other biting insects: arms and legs.	Fleas: wash clothes and bedding; do not allow pets and other animals in the house. Mosquitoes and other biting insects: use bed nets with insecticide; use topical insect repellent as needed; give antihistamines for itching. Monitor for signs of superinfection.

Disease	Etiology and presentation	Treatment
Leprosy	Skin patches with no sensation to soft touch, heat, or pain; not itchy. Can occur in any location of the body. Hypopigmented, pale or reddish; flat, raised, or nodular. Chronic (>6 months).	If never treated in the past, treat with multidrug therapy per WHO guidelines.
Longitudinal pigmented nail beds	Seen in almost 50% of persons on AZT; more common in dark-skinned patients. Occurs 4-8 weeks after initiation of treatment.	No treatment necessary.
Molluscum contagiosum	Pearly white or flesh-colored papules with central umbilication; most common on the face and genitals. Diagnosis is usually made by clinical appearance.	Usually no treatment needed. Lesions will disappear in patients responding to ART.
Psoriasis	Thick, red, scaling patches with distinct margins. Often on elbows, knees, scalp, hairline, and lower back. May be itchy.	Coal tar ointment 5% in salicylic acid 2%.
Warts (human papillomavirus)	Flesh-colored papules or raised areas of skin; common in genital or perianal area.	Topical treatment with cryotherapy or topical podofilox 0.5%.
Lesions of the mucous membranes		
Angular cheilitis	Sores at the corners of the mouth. Most often caused by candidiasis but can also be present with malnutrition and vitamin B deficiency.	Consider empiric fluconazole 100 mg/day orally for 10-14 days; provide nutritional supplementation.

Disease	Etiology and presentation	Treatment
Aphthous ulcer	Cause is unknown; however, HIV, HSV, CMV, and drug reactions can also cause ulcers of the mouth.	Topical lidocaine or triamcinolone hexacetonide in orabase; if severe and refractory, consider prednisone 40 mg/day orally for 1-2 weeks.
Candidiasis	Oropharyngeal: white plaques on an inflamed base on tongue, palate, buccal mucosa, or oropharynx (thrush). Vaginal: whitish vaginal discharge.	Oropharyngeal: fluconazole 200 mg/day orally for 7-14 days or nystatin rinse 500,000 units 5x/day for 14 days. Esophageal: fluconazole 400 mg/day orally for 14-21 days. Vaginal: miconazole cream vaginally at bedtime for 7 days or single-dose fluconazole 200 mg orally. See Section 2.6.3, Section 3.9.4, Protocol 2.7, and Protocol 3.22.
Gingivitis/periodontitis	Redness or dead tissue around teeth and gum line; receding gum line; painful chewing. Can become necrotizing and cause loss of teeth.	Metronidazole 500 mg orally 2x/day for 7-10 days. Promote good oral hygiene. If necrotizing, may need dental consultation for debridement and tooth extraction.
Oral hairy leukopenia	Whitish or grayish, feathery, irregular-appearing lesions, usually at base of tongue or gums.	Usually improves or resolves with ART.

Sources: Bartlett JG. *The Johns Hopkins Hospital 2005-6 guide to medical care of patients with HIV infection*. Baltimore, MD: Johns Hopkins University, 2005; Sande MA, Gilbert DN, Moellering RC. *The Sanford Guide to HIV/AIDS Therapy*. Hyde Park, VT: Antimicrobial Therapy, 2005.

Appendix G: Treatment and Prophylaxis for Common Infections in HIV-Positive Patients

Disease Likely CD4 count at occurrence	Preferred treatment regimen(s)	Preferred prophylactic regimen(s)
Candidiasis, esophageal CD4 <200 cells/mm ³	Fluconazole 400 mg/day orally for 14-21 days	No prophylaxis
Candidiasis, oropharyngeal CD4 <200 cells/mm ³	Fluconazole 200 mg/day orally for 7-14 days or nystatin rinse 500,000 units 5x/day for 14 days	No prophylaxis
Candidiasis, vaginal	Miconazole cream vaginally at bedtime for 7 days or single-dose fluconazole 200 mg orally	No prophylaxis
Herpes simplex, genital (first episode)	Acyclovir 400 mg orally 3x/day for 7-10 days	Acyclovir 400 mg orally 2x/day (reduces frequency of outbreaks)
Herpes, uncomplicated varicella-zoster	Acyclovir 800 mg orally 5x/day for 10 days	No prophylaxis
Herpes, disseminated (or complicated) varicella-zoster	Acyclovir 10 mg/kg IV over 1 hour 3x/day for 7 days; max dose 20 mg/kg 3x/day	No prophylaxis
Malaria, chloroquine-sensitive	Chloroquine 1 g (600 mg base) followed by 500 mg in 6 hours, then 500 mg/day for 2 days Alternative: quinine 640 mg 3x/day orally or IV + doxycycline 100 mg 2x/day orally for 7 days	In endemic areas, consider prophylaxis for pregnant women based on local resistance patterns
Malaria, chloroquine-resistant	Quinine 650 mg 3x/day orally or IV + doxycycline 100 mg 2x/day orally for 7 days	In endemic areas, consider prophylaxis for pregnant women based on local resistance patterns

Disease Likely CD4 count at occurrence	Preferred treatment regimen(s)	Preferred prophylactic regimen(s)
Meningitis, cryptococcal CD4 <100 cells/mm ³	Amphotericin B 1 mg/kg/day IV + flucytosine 25 mg/kg orally if available for 14 days, followed by fluconazole 400 mg/day orally or IV for 8-10 weeks	Secondary prophylaxis after treatment: fluconazole 200 mg/day orally
Mycobacterium avium complex CD4 <50 cells/mm ³	Clarithromycin 500 mg orally 2x/day + E 15 mg/kg/day + RFB 300 mg/day Alternative: azithromycin 600 mg/day orally + E 15 mg/kg/day + RFB 300 mg/day	Primary prophylaxis if CD4 <50 cells/mm ³ : azithromycin 1200 mg/week orally Alternative: clarithromycin 500 mg 2x/day orally
Pneumocystis jiroveci pneumonia CD4 <200 cells/mm ³	TMP/SMX 2 DS tablets 3x/day for 21 days Alternatives: atovaquone 750 mg 2x/day orally for 21 days or clindamycin 300-450 mg 4x/day orally + primaquine 30 mg/day orally for 21 days	Primary and secondary lifelong prophylaxis: TMP/SMX 1 DS tablet/day or 3x/week Alternatives: dapsone 100 mg/day orally or atovaquone 750 mg/day orally
Syphilis, early or less than one year	Single-dose benzathine penicillin 2.4 MU IM Alternative: doxycycline 100 mg orally 2x/day for 14 days	No prophylaxis
Syphilis, latent or more than one year	Benzathine penicillin 2.4 MU/week IM for 3 weeks Alternative: doxycycline 100 mg orally 2x/day for 28 days	No prophylaxis
Syphilis, neurosyphilis	Benzathine penicillin 3-4 MU IV 6x/day for 10-14 days Alternative: procaine penicillin G 2.4 MU/day IM + probenecid 0.5 g orally 4x/day for 10 days	No prophylaxis

Disease Likely CD4 count at occurrence	Preferred treatment regimen(s)	Preferred prophylactic regimen(s)
Toxoplasmosis CD4 <100 cells/mm ³	Preferred: pyrimethamine 100 mg orally first day, then 50-100 mg/day + sulfadiazine 0.5-2 g 4x/day + folinic acid 10 mg/day for at least six weeks, then life-long prophylaxis Alternatives: TMP 10 mg/kg/day divided 2x/day (not first-line therapy) for at least 6 weeks, followed by suppression regimen; or pyrimethamine 200 mg loading dose orally followed by 75 mg/day + sulfadiazine 6-8 g/day orally in 4 divided doses	Primary prophylaxis if CD4 <200 cells/mm ³ : TMP/SMX 1 DS tablet/day Secondary prophylaxis: pyrimethamine 25-50 mg/day + sulfadiazine 0.5-1 g 4x/day + folinic acid 10 mg/day
Tuberculosis	See Tables 2.1 and 2.2	Primary prophylaxis if PPD >5 mm: H 300 mg/day + pyridoxine 50 mg/day for 9 months
Typhoid fever, less severe cases	Ciprofloxacin 500 mg orally 2x/day for 10 days Alternatives: TMP/SMX 1 DS tablet 2x/day for 10 days or cefixime 10-15 mg/kg orally 2x/day for 10 days	No prophylaxis
Typhoid fever, severe cases	Ceftriaxone 50 mg/kg/day IV for 14 days (max dose 2 g/day)	No prophylaxis

Appendix H: Examples of Information Systems to Support HIV Treatment and Program Scale-Up in Resource-Poor Settings

Stand-alone databases
<p>Mosoriot medical record, Kenya^a Microsoft Access®. Used for general medical care in one hospital for more than two years and was extended to support HIV treatment at Moi University. Now being superseded by a system built on the OpenMRS architecture.^b</p>
<p>Children's Hospital, Lilongwe, Malawi^c Microsoft SQL Server® and Visual Basic® now converted to open-source software (Linux and MySQL) and extended to collect information on HIV patients. Physicians, nurses, and other staff perform all data entry, including medication orders. Has made heavy use of a touch-screen medical record system.</p>
<p>Ministry of Health database, Cuba Includes extensive clinical data on the approximately 1,200 patients in the country who require ART.</p>
<p>Department of Health and Human Services, United States Careware system (using Microsoft Access®) provides comprehensive tools for tracking HIV patients and their treatment. Currently used in more than 300 health centers and hospitals in the U.S. Deployed in Uganda in October 2003. An Internet-accessible version has now been deployed in the US and several African countries. Careware is closed-source but available free of charge at http://hab.hrsa.gov/careware.</p>
<p>FUCHIA (Follow-Up of Clinical HIV Infection and AIDS Guide for Users) Microsoft Access® and the Delphi programming language. Developed by Epicentre, the epidemiology group of Médecins Sans Frontières. It supports clinical care and long-term follow-up of patients, including scheduling of visits; contains data on medications and certain investigations and generates some reports. Available free of charge at http://www.epicentre.msf.org/tools.</p>
Internet-based medical record systems
<p>PIH-EMR, Peru^d Linux operating system, Apache web server, Tomcat Java Servlet engine, and an Oracle® database. Supports clinical care, logistics such as assessment of drug requirements, and research studies on drug-resistant tuberculosis. In heavy use for over six years. Most data are entered from paper forms, with nurse order entry of medications now implemented. Extensions link TB laboratories to clinics and allow data collection with personal digital assistants.</p>

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- ^a Rotich JK, Hannan TJ, Smith FE, et al. Installing and implementing a computer-based patient record system in sub-Saharan Africa: the Mosoriot Medical Record System. *J Am Med Inform Assoc* 2003;10:295-303.
- ^b Mamlin B, Biondich, PG , Wolfe B, et al. Cooking up an open source EMR for developing countries: OpenMRS - a recipe for successful collaboration. *Proc AMIA Symp* 2006:529-33.
- ^c Douglas G. The Lilongwe Central Hospital patient management information system: a success in computer-based order entry where one might least expect. *Proc AMIA Symp* 2003:833.
- ^d Fraser H, Jazayeri D, Mitnick C, et al. Informatics tools to monitor progress and outcomes of patients with drug resistant tuberculosis in Peru. *Proc AMIA Symp* 2003:270-4.
- ^e Geissbuhler A, Ly O, Lovis C, L'Haire J. Telemedicine in western Africa: lessons learned from a pilot project in Mali, perspectives and recommendations. *Proc AMIA Symp* 2003:249-53.
- ^f Oberholzer M, Christen H, Haroske G, et al. Modern telepathology: a distributed system with open standards. *Curr Probl Dermatol* 2003;32:102-14.
- ^g Fraser HS, Jazayeri D, Bannach L, et al. TeleMedMail: free software to facilitate telemedicine in developing countries. *Proc MedInfo* 2001;10:815-9.

[illegible]

This is the first page of PIH's comprehensive HIV intake form that is currently being finalized. Subsequent sections of this form collect information on the results of clinical, laboratory, and radiographic investigations; previous diagnoses; previous treatment with antiretroviral or anti-TB drugs; previous adverse effects; known allergies; and social history and socioeconomic status, including living conditions, employment, education, mode and ease of transportation to the clinic, and activities of daily living. A different (shorter) form is used for follow-up visits and collects information on treatment status, adherence issues, adverse events from medications, and any changes to the treatment regimen.

Appendix J: Screenshots of Treatment Plan and ART Initiation Sections of EMR Intake Form

Conduite à tenir

41. ☐ Prophylaxie: ☐ INH
☐ fluconazole 200 mg pour muguet non-invasif
☐ TMP/SMX

☐ Autre prophylaxie pour infections opportunistes (spécifier):

☐ Traitement antirétroviral
☐ Traitement antituberculeux: (si autres, spécifier:)

☐ Autres traitements pour infections opportunistes
☐ fluconazole 400 mg pour œsophagite (spécifier dose):
☐ amphotéricine B pour méningite cryptococcose (3-5 mg/kg/jour):
☐ TMP/SMX pour PCP ou toxoplasmose (15 mg/kg/jour q6h):
☐ chloroquine (spécifier dose):
☐ autres (spécifier):

☐ Planification familiale:

Résumé antirétroviral

42. (a) Ce patient nécessite-t-il le traitement antirétroviral? ☐ oui ☐ non ☐ traitement en cours
 Si le patient doit commencer les ARVs aujourd'hui ou reçoit déjà les ARVs, compléter alors le tableau ci-dessous.
 Indiquez les ARVs. Vous allez spécifier la dose complète dans une page suivante.

(b) Médicament et préparation Date du début du traitement (jour/mois/année)
 NRTI NRTI NNRTI/PI 7 j juil m, 2006 a

43. Est-ce que le patient débute les ARVs pour PTME? ☐ non ☐ oui

44. Est-ce que le patient débute les ARVs pour prophylaxie? ☐ non ☐ oui
 Si oui,

Appendix K: Screenshot of OpenMRS Patient Summary

Back

IMB ID:
 Gender: **Male**
 Age: **39 yrs** (~Jun 1, 1968)
 Last Visit: **6 months ago** (May 23, 2007)
 Unknown UWAYEZU, Mulindi

HIVEMR-V1:

Alerts
NO X-RAY, CHEST
NO CD4 COUNT IN THE LAST 6 MONTHS
NO CD4%

Comments
 No adverse effects
 No symptoms
 No previous diagnoses

Drug Order	Dose	Frequency	Start Date	Stop Date	Comments
Trismune-40	1.0 tab(s)	2/day x 7 days/week	Jul 27, 2005		

Lab Test	Result	Date	Comments
CD4 COUNT	245.0	Jan 9, 2007	
CD4 COUNT	183.0	Jul 12, 2005	
CD4 COUNT	255.0	Feb 28, 2006	

PULSE
 No Data Available

WEIGHT (KG)

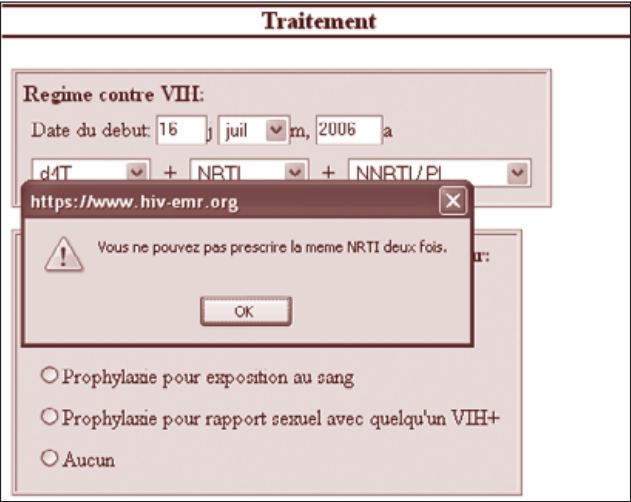
Date	Weight (KG)
Jul-05	64
Jan-06	64
Jul-06	64
Jan-07	64

CD4 COUNT

Date	CD4 COUNT
Jan-06	180
Jul-06	245
Jan-07	245

This concise patient summary in OpenMRS presents lab results, drug orders, and alerts for missing lab tests and lapsed clinic visits. It also includes graphs to allow clinicians to visually track a patient's progress.

Appendix L: Example of EMR Decision Support: Automatic Warnings



Appendix M: Suggested Indicators for Program Monitoring and Evaluation

Minimum data set

1. Percentage of people with advanced HIV infection receiving ART
 - Numerator: Number of people receiving ART according to UNAIDS/WHO standards at the start of the year + number of people who started treatment in the last 12 months – number of people for whom treatment was stopped (including those who died)
 - Denominator: Number of people with advanced HIV disease (often estimated to be 15 percent of total number with HIV infection)
2. Number of drug regimens distributed each month
3. 12-month program retention rate
 - Numerator: Number of individuals who are still on treatment 12 months after beginning therapy
 - Denominator: All patients who are started on therapy over a given period of time
4. Percentage of adults on treatment who gain weight
 - Numerator: Percentage of adults who gain at least 10 percent body weight at month six after initiation of ART
 - Denominator: All adults who were started on ART after presenting with weight loss or cachexia
 - Note: This number uses weight gain as a rough indicator for therapeutic success. As treatment is made available earlier in the course of disease, this parameter may become less helpful. It also has less utility in centers where CD4 cell counts are available.

5. Survival rate
 - Numerator: Number of people still alive at 6 months, 12 months, and 24 months after initiation of ART
 - Denominator: Total number of individuals in treatment
6. Prevention of mother-to-child transmission
 - Numerator: Number of HIV-positive pregnant women who received ART for PMTCT
 - Denominator: Number of HIV-positive pregnant women who are offered ART

Additional useful programmatic data

1. Number of patients who are offered VCT
2. Percentage of patients who accept HIV testing
3. Proportion of HIV tests that are positive
4. Mean increase in CD4 cell count in patients on therapy
5. Percentage of HIV-infected patients who are screened for STIs and TB, and number who complete treatment
6. Percentage of patients receiving social support (e.g., educational and nutritional assistance)
7. Number of HIV-positive patients receiving prophylaxis for opportunistic infections
8. Toxicities of ART
9. Number of patients switched from first-line therapy and reasons for change
10. Percentage of patients who have significant increase in CD4 cell count six months after initiation of therapy
11. Percentage of children who have a definitive diagnosis of HIV infection among all children whose mothers received ART

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