HIV Infection in Women

Quantum Units Education
Affordable. Dependable. Accredited.

www.quantumunitsed.com

Chapter 1:

Epidemiology and Natural History of HIV Infection in Women

Ruth M. Greenblatt, MD
Professor of Clinical Pharmacy, Medicine, Epidemiology and Biostatistics
University of California, San Francisco

The author declares no conflict of interest

Chapter 1: Epidemiology and Natural History of HIV Infection in Women

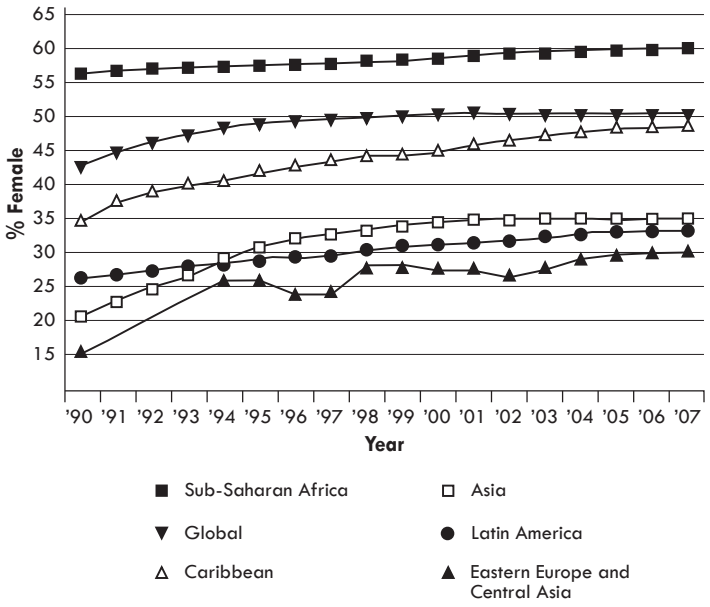
Chapter 1 at a Glance

The Global Epidemic of HIV Among Women

In 2008, the Joint United Nations Programme on HIV/AIDS estimated that 15.7 million women worldwide were living with HIV infection and that about half of all people living with HIV infection are women (Figure 1-1). Although HIV remains a major global health threat, the epidemic is highly regionalized in terms of overall prevalence, demographics, access to therapy, and modes of transmission. What follows is an overview of the epidemic, focusing on major trends, particularly trends among women.

Major Trends

Figure 1-1
Percentage of Women Aged ≥15 Years Living With HIV by Geographic Region, 1990–2007



Source: UNAIDS/World Health Organization (WHO). *AIDS Epidemic Update*. 2009. Reprinted with permission.

Beyond the overall feminization of the HIV epidemic and the epidemic's continued impact on years of life lost among women, several other trends are now obvious as well.

Prevalence

The prevalence of HIV infection among women has increased in several regions, most notably sub-Saharan Africa, where almost 60% of cases occur in women and girls. However, at least seven African countries are meeting epidemic-control goals for the first time, with the prevalence of HIV infection among pregnant women aged 15–24 years now below 25%.

The worldwide HIV epidemic continues to afflict young women; at the same time, the number of women who acquired HIV infection at birth is slowly rising. In the United States, the largest number of new cases of HIV infection was in women and girls aged 13–29 years, but the highest prevalence of HIV infection was among women aged 30–39 years (*Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas*, 2009. U.S. Centers for Disease Control and Prevention [CDC]; http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/. Accessed 7/31/2012).

HIV infection in children peaked between 2000 and 2002 and has slowly decreased since 2003, most dramatically in areas where screening and treatment of pregnant women are common (*Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas*, 2009. CDC).

Focused or "concentrated" epidemics: In several regions, focused epidemics among injection drug users are expanding to include heterosexual women, a pattern of evolution that introduces HIV into a huge population pool in which individual behaviors may not be overtly high risk. In Eastern Europe and Russia, a rapidly growing HIV epidemic is linked to injection drug use (IDU) and is currently extending into heterosexual young women who often lack the skills needed to assess risk and advocate for themselves (*J Urban Health* 2009;86 Suppl 1:121; *Eur J Public Health* 2011;21(5):613).

Declines in transmission: Recent declines in transmission to women have been clearly documented in three countries: the Dominican Republic, Tanzania, and Zambia (*AIDS Epidemic Update*. UNAIDS/World Health Organization (WHO). 2009). However, the prevalence of risk behaviors such as sex with a person who was not a spouse or a coresident has increased in some locations; thus, sustained control of the HIV epidemic among women in high-prevalence regions is far from assured.

Aging

Numbers increasing: The number and proportion of HIV cases in people aged ≥50 years has increased steadily since the introduction of potent antiretroviral therapy (ART) in high-resource areas. In the United States, before 2000, fewer than 10% of people living with HIV were aged ≥50 years; in 2007, however, 24% of those living with HIV infection were ≥50 and 16% of all HIV/AIDS diagnoses were made in that age group (calculations done on data in *Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas*, 2009).

The distribution of cases by race and location among older women is similar to that among women as a whole, although in the United States the prevalence of a history of IDU is lower among younger women living with HIV compared with older women. This pattern occurs in Europe as well; however, data documenting aging among HIV cases in resource-limited settings are sparse.

True incidence unknown: Although the number of infections identified in the ≥50 age group has increased, as has the total number of persons with HIV who are living to ages ≥50, the true *incidence* of HIV infections among people aged ≥50 years is not known. When compared with younger people, however, those aged ≥50 years are more likely to have clinical AIDS at the time of HIV diagnosis and they tend to have a shorter survival after diagnosis.

Current U.S. screening guidelines recommend routine opt-out screening of people aged 13–64 years. This is important because risk-based screening will miss many asymptomatic older women with HIV, who often do not have recognized risk factors.

Menopause: The emergence of HIV cases among women who are progressing through menopause raises new issues for clinicians, researchers, and patients. Conditions related to aging that may be promoted by HIV, such as cardiovascular disease, must be managed, as must metabolic perturbations (e.g., diabetes, bone demineralization) and neurocognitive deficits. In women, the effects on immune function of hormonal changes or hormonal replacement therapy must also be monitored and managed.

Sexual activity: Compared with younger women, older women are less sexually active and are less likely to use condoms and other risk-reduction strategies (*J Acquir Immune Defic Syndr* 2003;33 Suppl 2:S122; *Health Care Women Int* 1997;18(4):343). With the availability of drugs that support sexual function in men, however, rates of sexual activity among older women may increase. Thus, although older sexually active women are at risk for HIV infection, the precise extent of that risk is not known.

Demographics

Greater diversity among women: In resource-rich countries, the demographic characteristics of HIV and AIDS cases have been heavily influenced by the large proportion of infections among men who have sex with men, many of whom are educated and economically stable. However, patterns of cases among women demonstrate a much greater representation of ethnic minorities and people who are poor, less educated, mentally ill, and/or drug dependent, all of which are factors that may limit personal autonomy when it comes to making key decisions, including decisions related to sexual behavior. Among new HIV diagnoses in US women in 2011 63% were black/African-Americans, 17% Hispanic/Latino and 17% white; in the US population as a whole, 66% of women are white, 15% are Hispanic/Latino and 12% are black/African American (http://www.cdc.gov/hiv/library/slideSets/index.html) (accessed 05/14/2013).

In resource-limited countries, HIV cases among women can be linked with commercial sex work (often in an effort to support a family), social disruption, violent conflict, governmental policies, and/or local culture that tends to limit women's economic or sexual autonomy. For example, in some locations, married women do not have the right to refuse sex. In other areas, social and economic sanctions associated with widowhood, divorce, or HIV infection can promote denial of infection or avoidance of testing. Lack of autonomy over key personal decisions is a common theme among populations of women affected by HIV.

Key Trends in HIV Epidemiology Among Women

- The proportion of HIV cases among women is increasing globally, led by increases in sub-Saharan Africa and the Caribbean region.
- Some countries have demonstrated decreases in the incidence of new HIV cases among young women and children, which indicates that intensive public health interventions can be effective.
- In areas in which IDU has been the major means of HIV transmission, new trends show extension of the epidemic to young, heterosexually active women.
- The largest number of new cases and the highest HIV prevalence rates are among young women in their childbearing years.
- Increased survival related to potent ART has resulted in a substantial increase in cases among women aged ≥50 years; the incidence of new infections among women in this age group is largely undefined.

HIV Transmission to Women

Patterns of Transmission

Although sexual intercourse is a common occurrence in the general population, the estimated average HIV transmission rate per intercourse event is low. Tracking studies indicate that the likelihood of transmission is highly variable among individuals and that high rates of transmission occur in specific situations. Table 1-1 summarizes the risk of HIV transmission to women through heterosexual intercourse in various situations. Epidemiologic patterns of HIV transmission are summarized in Table 1-2.

Table 1-1

Risk of HIV Transmission to Women Per Sexual Contact Event

Exposure	Transmission Probability Per Act
Any male to female vaginal intercourse	0.124 (0.078-0.199)
No commercial sex, male to female intercourse	0.143 (0.088-0.233)
Commercial sex, male to female intercourse	0.051 (0.020-0.131)
High-income countries, male to female intercourse	0.081 (0.060-0.109)
Low-income countries, male to female intercourse	0.193 (0.086 – 0.433)

Source: *Lancet Infect Dis* 2009; 9:118

Table 1-2

Epidemiologic Patterns of HIV Transmission

Pattern	Unique Characteristics	Related Factors	Regions
Epidemic* heterosexual	Risk often not recognized; often related to high-risk male partner	Poverty, lack of women's sexual and economic autonomy, sex work	Worldwide
Endemic† heterosexual	Seen in high-prevalence areas; affects general population of women	Poverty, lack of women's sexual and economic autonomy, sex work	High-prevalence epidemics in sub-Saharan Africa, Caribbean, Asia
Drug use predominant	IDU is major factor; often coincides with high rates of viral hepatitis; often overlaps with sexual risk	Poverty and sex work; bridging to non-IDU, especially among young women	Worldwide, notably in Eastern Europe and Russia; current rapid expansion of epidemic
Perinatal	Most common cause of HIV infection in children; some perinatally infected infants are now adults	Preventable with use of ART drugs; greatly diminished in high-resource countries and some lower-resource countries; failure to screen pregnant women is major risk factor for ongoing transmission	Worldwide; large epidemic in sub-Saharan Africa
Occupational	Usually preventable; PrEP is available	Rare; implementation of universal body fluid precautions can prevent most exposures	Worldwide

Table 1-2 *continued*

Epidemiologic Patterns of HIV Transmission

Pattern	Unique Characteristics	Related Factors	Regions
Iatrogenic	Related to poor medical practices (e.g., inadequate blood screening, unsafe injection practices)	Failure of adequate blood product handling, sterilization procedures; re-use of needles/ syringes for injections; children often affected	Often seen in local epidemics, primarily in Eastern Europe and sub-Saharan Africa; cannot sustain epidemic as single mode of transmission

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* Epidemic: Cases exceed the expected pattern in a population over a defined time period

† Endemic: The habitual presence of a disease within a geographic area

(*Epidemiology: An Introductory Text*. Philadelphia: W.B. Saunders Company; 1974)

Factors Influencing HIV Transmission in Women

Partner infectivity: Infectivity is increased when male partners have a higher plasma viral load (VL), which has been linked to higher rates of HIV shedding in semen. Infectivity is highest during acute or recent HIV infection, when VL and viral shedding are maximal and host immune response is incomplete (*AIDS* 2007;21:1723). Exposure during early infection is estimated to account for half of all transmission events in North America (*J Infect Dis* 2007;195(7):951). Use of ART decreases the risk of HIV transmission between heterosexual partners; however, limited study size and infrequent events make precise assessment of the extent of protection difficult (*AIDS* 2009;23:1397). Results from HPTN 052, a randomized clinical trial designed to evaluate the efficacy of ART for the prevention of sexual transmission among serodiscordant couples, found that earlier initiation of ART, at CD4+ cell counts of 350–550 cells/mm^3, reduced HIV transmission to the uninfected partner (*N Engl J Med* 2011;365(6):493).

Number of partners and commercial sex: It has been demonstrated in multiple settings that being paid for sex is associated with higher rates of HIV infection. In a systematic review of data from multiple sub-Saharan African countries, the odds ratio for HIV infection for women who reported being paid for sex was 2.29 compared with women who had never been paid for sex (*PloS One* 2007;2(10):e1001).

For women, having a larger number of male sexual partners is also consistently associated with an increased risk for HIV infection, with the effect size dependent on the number of partners, the region, and the population prevalence of HIV. Female sexual partners of women appear to present minimal risk of HIV transmission (*AIDS* 1998;12:450).

Genital tract infections: Many genital tract infections have been reported to increase both infectivity and susceptibility to HIV, including gonorrhea, *Chlamydia trachomatis*, bacterial vaginosis, trichomonal vaginitis, and human papillomaviruses (*J Reprod Immunol* 2008;77:32; *PLoS One* 2010;5(4):e10094). The most consistent and significant association is seen with genital ulcer diseases such as syphilis, chancroid, and genital herpes. Because genital herpes simplex is the most prevalent cause of genital ulcers and is a chronic infection, it likely has the strongest and longest duration of influence on an individual's susceptibility to acquisition of HIV infection. Chen and colleagues, in a systematic review of published reports, found that having herpes simplex type 2 infection (usually genital) increased the odds of HIV infection 3.69-fold as compared with not having genital herpes (95% confidence interval, 2.78–4.89); the increase in the likelihood of infection was similar for both men and women (*PloS One* 2007; 2(10):e1001).

Region: Although significant regional differences exist in the predominant means and risk factors for HIV infection, all regions demonstrate multiple transmission modalities, which over time tend to extend into populations of young sexually active persons and often disproportionately afflict the poor.

Use of hormonal contraceptives or spermicides: Studies of the effects of hormonal contraceptives on susceptibility to sexually transmitted HIV infection have yielded mixed results (*AIDS* 2007;21:85; AIDS 2007;21:1771). A consensus is emerging, however, that oral estrogen-progestin contraceptives do increase susceptibility to HIV (*Endocr Rev* 2010;31(1):79). The evidence is even more consistent that depot medroxyprogesterone acetate (DMPA), an injectable progestin-only contraceptive, increases the risk of HIV acquisition. Studies of other progestin-only contraceptives and other delivery mechanisms are currently underway. Although further study is clearly warranted, hormonal contraception remains safe and highly effective for the prevention of unintended pregnancy and the promotion of reproductive autonomy, and the benefits are believed to strongly outweigh the risks. Use of the topical spermicide nonoxynol-9, which was evaluated as a candidate HIV microbicide, demonstrated a paradoxical increase in HIV susceptibility that was likely the result of increased genital tract inflammation (*J Acquir Immune Defic Syndr* 2005;40(1):1).

Pregnancy: Although the overwhelming volume of research and publications on pregnancy and HIV is focused on perinatal transmission, several studies indicate that pregnancy may be associated with increased rates of sexual HIV transmission to women (*Lancet* 2005;366:1182; *J Clin Virol* 2010; 48:180; *AIDS* 2009;23:1255), even when the analyses are controlled for sexual risk behaviors (*Lancet* 2005;366:1182). It is hypothesized that this heightened risk may be attributable to hormonal changes affecting the genital tract mucosa or immune responses. Condom use may also be less common during pregnancy, as many couples continue to view condoms primarily as a means of contraception. Healthcare providers must address appropriate preventive practices with at-risk pregnant women and be alert to signs and symptoms consistent with acute HIV infection during pregnancy. Surveillance for incident infections associated with pregnancy should extend to the postpartum period (*BMC Public Health* 2010;10:668) because women who are infected in late pregnancy may still be HIV seronegative at delivery.

Because of the possibility of increased susceptibility to HIV infection during pregnancy, and with the recent encouraging results with antiretroviral-based preexposure prophylaxis, it is important that pregnant women in HIV-discordant relationships be included in further testing of these interventions (see Chapter 7, ***Preconception Care and Contraception***).

HIV Mortality in Women

Leading Cause of Death

Although the prevalence of HIV infection among women varies significantly by world region, AIDS remains a leading cause of death among women in many regions, including high-resource countries. Depending on age group, AIDS is among the top 10 causes of death for African-American and Hispanic women; among African-American women 25–54 years, HIV is the 4th leading cause of death (*Natl Vital Stat* Rep 2012;61(7):1).

AIDS deaths are a conservative indicator of the impact of HIV on women's survival because they are derived from statistics on deaths directly due to AIDS-defining conditions and do not include excess deaths due to non-AIDS conditions that are associated with HIV, such as cardiovascular disease, metabolic diseases, and malignancies. In addition, HIV is a prominent cause of years of life lost for women in the years of prime economic and childrearing activity.

Antiretroviral Therapy and Mortality

The prominence of AIDS as a cause of death among women has emerged during an era in which ART is generally available, which tends to refute the notion that the existence of effective treatment has diminished the major threat to women's health posed by HIV. Receipt of potent ART has been the strongest predictor of survival among women with HIV since those drugs were introduced in the 1990s. Even in populations with easy access to ART, however, excess deaths due to AIDS and non-AIDS conditions still occur among HIV infected patients, including women.

WIHS cohort: Sustained ART is associated with reduced AIDS and non-AIDS mortality. After the introduction of ART in the United States, the AIDS mortality rate within the WIHS, a large U.S. multisite observational cohort study of HIV in women, declined by almost 50%; however, HIV infection continued to be associated with AIDS deaths and with excess deaths due to heart disease and cancer (*J Acquir Immune Defic Syndr* 2009;51(4):399). Trauma/accidents/suicide and liver disease remain prominent causes of death among HIV infected and high-risk HIV uninfected WIHS participants. During the pre-ART era, HIV infected women demonstrated a lower incidence of breast cancer than did uninfected women; in the era of potent ART, however, breast cancer rates are equal in the two groups, perhaps owing to increased survival or other

factors (*Clin Infect Dis* 2010; 51(8):957; *J Natl Cancer Inst* 2011;103(9):753; *Breast J* 2011;17(1):87). Use of alcohol and/or recreational drugs was also a predictor of mortality in WIHS participants (*Clin Infect Dis* 2007;44(2):287; *Addiction* 2005;100:990; *AIDS* 2008;22:1355).

Predictors of mortality: In the WIHS, CD4+ cell count below 200 cells/mm^3, VL of ≥1000 copies/mL, hepatitis B surface antigenemia, body mass index (BMI) <18.5, and a high depressive symptom score were each independently associated with mortality (*J Acquir Immune Defic Syndr* 2009;51(4):399). Hepatitis C infection was a predictor of mortality after the use of potent ART became commonplace, which is consistent with other observations that liver disease has become a prevalent cause of mortality among U.S. women whose survival with HIV infection is extended by ART. In resource-limited areas, low BMI and anemia are leading predictors of mortality after ART (*AIDS* 2006;20:2355; *S Afr Med J* 2007;97:587). In these settings, HIV infection continues to be associated with AIDS and non-AIDS mortality, with tuberculosis and CNS infections being the leading causes of death (*AIDS* 2006;20:1181).

Sex differences: In both the pre-ART and potent ART eras, there have been indications that HIV infected women have higher mortality rates than do their male counterparts. These findings, which result from studies conducted in both resource-rich and resource-poor countries, are sometimes attributed to sex differences in access to treatment, although in some studies the results were independent of treatment utilization (*J Infect Dis* 2009;199(7):991; *AIDS* 2005;19:357). Several reports have identified a difference in age at death between males and females, with peak deaths in females occurring 5–10 years earlier than in men (*S Afr Med J* 2007;97:587; *Lancet* 2008;371:1603); however, no clear independent sex difference in age at death has been seen in the setting of ART availability. Thus, although countered to some extent by studies that show no independent sex difference in survival among HIV infected adults in the ART era (*Clin Infect Dis* 2007;44(2):287; *AIDS* 2001;15:1115; *AIDS Patient Care STDS* 2007;21:321), the range of findings indicating higher mortality among women is cause for concern and warrants additional study.

Natural History of HIV Infection in Women

Staging of HIV Infection in Women

Case definitions for HIV infection—the criteria for diagnosis of HIV infection—are now based largely on serologic screening tests. The CDC issued its last case definition for AIDS in 1994. That definition incorporated the opportunistic infections, cancers, and wasting conditions that are closely linked with HIV infection and disease progression as evidenced by CD4+ lymphocyte cell depletion. The case definition also included invasive cervical cancer, a female-specific condition, as an AIDS-defining condition (in the presence of HIV infection) and chronic vaginal candidiasis and pelvic inflammatory disease as HIV-associated, but not AIDS-defining, conditions.

The CDC has recently revised the staging system and surveillance case definitions into a single case defintion sytem for HIV because of diagnostic and treatment improvements and to make the system simpler and easier to use (*MMWR* 2008;57(RR10):1–8). Clinical categories A and B have been eliminated, since many of the clinical conditions listed under these categories were not discrete diseases, were not necessarily indicators of immunosuppression, poorly matched current treatment guidelines and were not integrated into routine surveillance practices; furthermore, the role of CD4+ cell counts/percentages are central in the new system, as objective measures of immunosuppression and are routinely used in care. As with the older system, HIV disease progression is classified from less to more severe, and once cases are classified into a surveillance severity stage, they cannot be reclassified into a less severe stage. This system is intended for public health surveillance and not as guide for clinical diagnosis or care.

The CDC HIV/AIDS disease staging system (Table 1-3) assesses disease severity by CD4+ cell counts and by the presence of specific HIV-related conditions. By contrast, the WHO clinical staging and disease classification system (Table 1.4) is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS. This staging system is particularly useful in resource-limited settings in which CD4+ testing or other laboratory-testing methods are not readily available and is used in many countries to assess eligibility for antiretroviral therapy.

Table 1-3

CDC Classification System for HIV-Infected Adults and Adolescents (2008)

Must meet laboratory criteria for HIV infection

Stage 1: no AIDS-defining condition and CD4+ cell count >/= 500 cells/microliter ot CD4+ % of total lymphocyte >/= 29%

Stage 2: no AIDS-defining condition and CD4+ cell count 200–499 cells/microliter or CD4+ % of total lymphocyte 14-28%

Stage 3 (AIDS): CD4+ cell count <200 cells/microliter or CD4+ % of total lymphocyte <14% or documentation of an AIDS-defining condition. Documentation of an AIDS-defining condition supersedes CD4+ cell count/%.

Stage Unknown: documented HIV infection but no information available on CD4+ counts/% or AIDS-defining conditions.

Table 1-3 *continued*

CDC Classification System for HIV-Infected Adults and Adolescents (2008)

†Category C AIDS-Indicator Conditions

- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 mo in duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision) (may be diagnosed presumptively)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 mo in duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 mo in duration)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, pulmonary or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* (formerly *carinii*) pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent (non-typhoid)
- Toxoplasmosis of brain
- Wasting syndrome caused by HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥2 loose stools per day for ≥1 mo) or chronic weakness and documented fever for ≥1 mo

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR* 2008;57(RR10):1–8.

Table 1-4

World Health Organization HIV/AIDS Clinical Staging and Disease Classification System

Primary HIV Infection

- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1

- Asymptomatic
- PGL

Table 1-4 *continued*

World Health Organization HIV/AIDS Clinical Staging and Disease Classification System

Clinical Stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrheic dermatitis
- Fungal nail infections

Clinical Stage 3

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for >1 mo
- Unexplained persistent fever for >1 mo (>37.6°C, intermittent or constant)
- Persistent oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anemia (hemoglobin <8 g/dL)
- Neutropenia (neutrophils <500 cells/mcgL)
- Chronic thrombocytopenia (platelets <50,000 cells/mcgL)

Clinical Stage 4

- HIV wasting syndrome, as defined by CDC (see Table 1-3)
- *Pneumocystis* pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 mo or visceral herpes at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- CNS toxoplasmosis
- HIV encephalopathy
- Cryptococcosis, extrapulmonary (including meningitis)
- Disseminated nontuberculosis mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of the trachea, bronchi, or lungs
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
- Recurrent nontyphoidal *Salmonella* bacteremia
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: AIDS Education & Training Centers National Resource Center. *HIV Classification: CDC and WHO Staging Systems.* 2012

Natural History of HIV Infection in the Absence of Antiretroviral Therapy

Sex differences: Sex differences exist in CD4+ lymphocyte counts among HIV infected and uninfected individuals; when corrections can be made for differences in the extent of disease progression, females have CD4+ cell counts that are approximately 100 cells/mm^3 higher than those of males early in HIV infection (*Clin Infect Dis* 2002;35(3):313). Assessing sex differences in rates of viral replication and plasma HIV RNA levels (VL) is more complex. Early in the course of HIV infection, females have lower HIV VLs than do males (*AIDS* 2007;21:835; *Clin Infect Dis* 2002;35(3):313). Because VL is a predictor of disease progression, a lower VL in females should be followed by slower progression as indicated by declines in CD4+ cell counts and clinical progression; however, no significant differences in rates of progression by sex have been identified (*Am J Epidemiol* 2008;168(5):532; *AIDS* 2003;17:353; *J Infect Dis* 1999;180:1018; *Lancet* 1998;352:1510). It appears, therefore, that females have better control of HIV replication than do males early in HIV infection, but lose this control later and progress more rapidly, thus catching up to their male counterparts. One clue to this loss of immunologic advantage was provided by Altfeld and colleagues, who reported that women have significantly more vigorous dendritic cell responses to HIV, which leads to greater CD8+ cell activation. CD8+ cell activation may result in the early control of HIV replication, but over time it could produce a chronic inflammatory state and increased lymphocyte loss (*Nat Med* 2009;15:955).

Host immune response: Variations in the pattern of HIV disease progression in the absence of ART are the focus of many studies that seek to characterize host immune responses to HIV. Much interest has been directed at *HIV controllers or elite controllers*, i.e., people whose CD4+ cells remain normal and stable and who have very low or undetectable VLs after HIV infection in the absence of ART. Because women tend to have higher CD4+ cell counts and lower HIV RNA levels than men, at least in the early stages after initial infection, one might expect sex differences in HIV control to exist. Such differences, however, have not been identified (*J Virol* 2009;83:329; *Immunity* 2007;27:406; *AIDS Res Ther* 2007;4:11), perhaps because natural HIV controllers are few in number and therefore studies of natural HIV control are small. Anecdotal reports indicate that sex differences exist in the prevalence of natural controllers, with a somewhat higher occurrence among women, but further study is needed.

Disease Progression in the Era of Antiretroviral Therapy

Sex differences in CD4+ cell counts persist after the initiation of ART; if these parameters form the basis for assessing ART outcome, women tend to fare better (*AIDS* 2007;21:835; *J Antimicrob Chemother* 2007;60(4):724; *AIDS Res Hum Retroviruses* 2010;;26:133). Most ART clinical trials, however, are not adequately powered to assess sex differences. The CASCADE Collaborative, which assessed sex differences in the survival of adult seroconverters in Europe, Canada, and Australia, concluded that ART increased the survival advantage of women, though sex differences existed in ART use and the results were not

adjusted for adherence (*Am J Epidemiol* 2008;168(5):532). In Europe, as in the United States, HIV risk factors and access to care appear to contribute to sex differences in HIV mortality during the ART era (*Int J Epidemio1* 2010;39:135; *J Epidemiol Community Health* 2004;58(11):944). In general, ART viral suppression does not differ by sex, and many reported sex differences in outcome disappear when the analysis is adjusted for treatment (*Clin Infect Dis* 2009;49:1570; *Lancet* 2003;362:1267; *J Womens Health (Larchmt)* 2007;16(7):1052). For both women and men, the use of ART is the strongest predictor of survival in HIV infection.

Influence of Pregnancy, Exogenous Steroids, and Aging

In both HIV infected and uninfected women, the absolute number of CD4+ lymphocytes temporarily declines during the third trimester of pregnancy as a result of hemodilution, but the CD4+ percentage remains relatively stable. No differences in overall HIV disease progression have been found to be related to pregnancy (*AIDS* 2005;19:357). Whether the use of hormonal contraception influences HIV disease acquisition or course is a controversial topic on which data conflict (see Chapter 7, ***Preconception Care and Contraception***). Because sex steroids are important immune mediators, it is plausible that the changing hormone levels associated with menopause or hormone replacement therapy may influence the course of HIV infection. Data that might shed light on this issue are not currently available. Aging is associated with more rapid progression of untreated HIV disease, and sex differences in this phenomenon have not been reported (*Am J Med* 2008;121:1032; *J Am Geriatr Soc* 2009;57:2129).

Case Detection in Women

Unrecognized Risk

In resource-rich countries, most men with HIV report risk factors for infection such as sex with other men or parenteral drug use. For a woman, however, risk for HIV may be determined by the (often unknown) behavior of a male sexual partner or partners. In 2009, women accounted for 24% of new HIV infections in the United States, a figure that is likely to be artificially low because providers and patients underestimate the risk of HIV infection and may not test for it. For 2009, the CDC reported that heterosexual contact was the risk factor for 85% of women with HIV infection, IDU was associated with 15% of cases, and less than 1% of cases had no clear risk factor (*Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas*, 2009. CDC; http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/. Accessed 7/19/12).

The process of risk assignment in this report differed significantly from past years in that cases reported with no known risk factor were assigned a likely risk factor, which for most women is heterosexual contact. The revised data, however, should not be seen as indicating that HIV infected women are now more likely to be aware that they are at risk for heterosexually acquired HIV infection. Prior to the adoption of the imputation approach, 30%–40% of HIV infected women had no recognized HIV risk factor.

It is likely that women frequently are unaware of their risk for HIV infection because that risk is related to the drug use or sexual behaviors of a male sexual partner or partners. Without awareness of their risk for HIV infection, women often do not express concerns about HIV or seek out screening. Routine HIV screening, in which HIV testing is included as part of routine healthcare, is an important means of increasing case recognition and access to early HIV treatment among women. In the absence of routine screening, HIV cases in women tend to be detected at the time of pregnancy or presentation of an AIDS-defining condition. Both scenarios represent lost opportunities for early treatment and prevention of transmission to others, because women may be less likely than men to delay entry into care once HIV infection has been detected (*AIDS Patient Care STDS* 2009;23:765).

Key Points on Natural History of HIV in Women

- Among HIV infected adults, women have higher CD4+ cell counts than men.
- During early infection, women have lower VLs than men, but this difference disappears as infection continues. Differences in CD8+ cell activation may explain some of the sex differences in VL.
- Overall, the rate of progression of HIV disease appears to be similar in women and men.
- Receipt of ART is the strongest predictor of survival with HIV among both women and men.
- Women and men respond to ART similarly; differences in outcomes are often related to drug use and access to treatment.

Summary

A Global Women's Health Problem

Even in resource-rich regions, HIV is a leading cause of death for women. Moreover, the number of HIV-related deaths among women is much higher when HIV-associated but non–AIDS-defining conditions are also considered. HIV kills women who are at the peak of their social and economic productivity. HIV, therefore, must be considered a major health concern for women.

Autonomy is Key

Reducing the incidence of HIV infection in women and improving access to treatment requires increased autonomy among vulnerable women. Autonomy can be viewed broadly as control over one's life and decision making, including decisions about sexuality and health, and depends on cultural factors, access to educational resources, and enlightened public policy. Women's autonomy, especially in matters of sexuality and health, also requires the availability of resources such as drug and mental health treatment that can assist women in avoiding drug use, violence, and coercive sex. Autonomy is also related to the acquisition of personal skills that support young women's ability to adhere to safe-sex practices and assess the risk of specific situations. Biological factors such as sexually transmitted infections and male-partner VL are important, but Dworkin and others have persuasively argued that the paradigm of risk for HIV infection in women should be extended to include social vulnerability (*Am J Public Health* 2010;100:435).

Routine HIV Screening Is Essential

Most women acquire HIV infection from a male sexual partner, and this trend is increasing. Furthermore, because many women are not aware that a male partner is HIV infected or at risk, risk-based screening is likely to miss cases of HIV among women. Making HIV screening a routine part of medical and reproductive healthcare for adolescents and adults is an important way to improve the ability to identify and provide care and treatment to women early in the course of HIV infection. Achievement of this goal is crucial for control of the HIV epidemic in women.

Chapter 2:
Approach to the Patient

Jean R. Anderson, MD
Director, The Johns Hopkins HIV Women's Health Program
Professor, Gynecology and Obstetrics
The Johns Hopkins Medical Institutions

The author declares no conflict of interest

Chapter 2: Approach to the Patient

Chapter 2 at a Glance

The Woman With HIV Infection

She could be any woman: The woman with HIV infection is not distinguishable from most women seen in primary care today. She may be any age or color, live anywhere, have any cultural background, and have any level of education and income. She has all the health and lifestyle concerns that any other woman has. She is often asymptomatic, and she may not know she is infected. Often, she is a mother and a caretaker for other family members.

HIV is just one part of her life: The issues most important to the woman with HIV will be shaped by her personal circumstances. HIV is just one aspect of an infected woman's life; the perception of its role in her life will vary from woman to woman and from time to time. The healthcare provider–patient relationship begins with the particular circumstances and needs of each individual woman. To be most effective, that relationship must become a partnership based on mutual trust and respect.

This chapter reviews general guidelines for healthcare provider interactions with all patients, highlighting points that are particularly relevant to women with HIV infection. It also provides an overview of the initial and ongoing medical and psychosocial evaluation of women with HIV and discusses the changes in models of care as HIV has evolved into a chronic disease.

General Guidelines

Communication

Clear and nonjudgmental: The initial interaction of patient and provider should begin with introductions, and ensuing communications should be clear and nonjudgmental. The care provider's language and terminology should be sensitive, inoffensive, and easily understood by the patient. A patient's ability to understand what is being said to her will vary according to her age, cultural background, and level of education. Translation (of written materials) and/or interpretation (of speech) will be needed for women who are not able to understand or express themselves adequately in the language of the medical provider.

Whenever possible, questions should be asked in an open-ended manner, including questions about behavior and treatment adherence, and the patient should be given permission to be honest and to acknowledge failure with regard to relapse or nonadherence. She should be given adequate time and opportunity to ask questions and express concerns.

Written instructions: Patients should be given written instructions that detail how to make appointments and how to reach the care provider when there is a problem or when the patient has questions. Whenever possible, patients should be provided with written information about HIV and its treatment as well as with information about other health issues to supplement face-to-face discussions.

Communication for the gynecologic exam: Women undergoing gynecologic exams may feel especially anxious, vulnerable, or embarrassed, or they may fear discomfort or the discovery of pathology. This anxiety and vulnerability may be particularly pronounced in women with a history of sexual abuse, rates of which are greater in some populations of women living with HIV. If a woman needs additional time to develop trust and overcome anxiety, then the gynecologic exam may have to be postponed until a subsequent visit.

Adequate preparation for the exam is important. The care provider should explain what will be done and why, and he or she should explain the amount of discomfort the woman may experience. The process may be demystified by showing the patient charts, models, or equipment (such as specula). During the exam, before doing anything, the care provider should tell the patient what is going to happen next, and then describe what s/he sees or feels during the exam. The patient should be reassured when findings are normal.

Nonverbal communication: The importance of nonverbal communication should not be underestimated. Facial expression and body posture often convey far more than words. The most effective care providers are sensitive to these cues and use their own body language with care. Maintaining frequent eye contact encourages the patient's candor, builds rapport and trust, helps allay embarrassment and fear, and conveys a care provider's interest and attention.

Respect

Every patient deserves respect: Care providers should never be condescending, patronizing, or judgmental toward patients. Under no circumstances should a patient be treated as a sexual object. Although different circumstances may dictate different levels of formality, addressing a patient by her first name (without her express consent) or, especially, by terms of endearment (e.g., "honey" or "dear") is usually inappropriate and offensive.

Respect for the patient includes respect for her beliefs and values. The use of complementary therapies among HIV infected patients is common and should be respected, not ridiculed. This respect should be maintained even if a care provider must discourage potentially harmful remedies and emphasize the proven effectiveness of currently recommended regimens.

Sensitivity

Essential to effective care: Sensitivity is essential to a care provider's ability to gather and impart important information, foster trust, and ensure ongoing follow-up. It requires attention to how words are used, how questions are asked, and what body language and other unspoken aspects of communication convey. Responding to a patient's fear, anxiety, denial, or anger is an inevitable part of the health provider's role, and it requires consideration of the whole person and the entire context of her life, not just of her disease process. Any chronic and life-threatening disease carries with it an enormous burden of vulnerability and loss of control. Anything a care provider can do to give back some control to the woman will help ease that burden. The

importance of adherence to antiretroviral therapy (ART) regimens for optimal effectiveness and for reduced potential for drug resistance has been well established. Taking into account a patient's values and lifestyle (e.g., work schedule, child care obligations) when choosing a treatment regimen may enhance adherence. In addition, understanding a woman's cultural background will enhance a care provider's sensitivity. For example, among Hispanic women, it is often important and reassuring when a patient's spouse or mother is involved during visits.

Confidentiality

Confidentiality is a cornerstone of the therapeutic relationship. It carries special meaning for HIV infected individuals, who may have experienced discrimination in the workplace and other settings, stigmatization, or even abandonment by friends or family. HIV infected women may be particularly vulnerable to the effects of stigma because of lower economic status, cultural traditions, general societal beliefs about the role of women, minority status, and child care or other caretaking responsibilities. Information about a patient's HIV status or details about her medical condition should be kept strictly confidential by providers and shared only with the express permission of the patient. At the same time, the patient should be encouraged and assisted in disclosing her status to others who need to know, such as sexual partners and healthcare providers.

Reporting: All States require reporting of AIDS cases, and in all 50 States, the District of Columbia, and six dependent areas, HIV cases are reported confidentially by name. The need to report and the safeguards of confidentiality that are in place should be discussed with each woman. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 furthermore provides a federal mandate and standards for the protection of certain health information, addressing the use and disclosure of individuals' health information and standards for individuals' privacy rights to understand and control how their health information is used (See: http://www.hhs.gov/ocr/privacy/hipaa/understanding/summary/index.html).

Evaluation of the HIV Infected Woman

Team Approach

A complex disease: Because HIV disease is medically and socially complex, a team approach is essential to the care of women with HIV, and care should be coordinated and integrated with all members of the team. Moreover, as the time that primary care providers have available to spend with individual patients grows ever more limited, the role of other team members in educating and supporting women with HIV is becoming more important.

Multispecialty care: The expertise needed to provide care for women with HIV includes specialists in HIV medicine (including management of ART), gynecology, nursing, pharmacy, counseling, and social service assistance and case management. Primary medical management of HIV may be provided by physicians and, increasingly, by nurse practitioners or physician assistants with appropriate training and supervision. Throughout the course of HIV infection, multidisciplinary medical collaborations should be available for evaluation and management of the varied medical problems associated with HIV. As HIV has become a chronic disease, the inclusion of the patient and her family or other personal supporters as part of the team is ever more important. The involvement of peer counselors may be especially useful for helping women deal with the complexities of negotiating safer sexual practices, contraception and other reproductive concerns, medication adherence, and other issues where similar cultural background and personal experience with HIV may facilitate candid discussion and education.

HIV Experience

HIV expertise improves outcomes: Patients have better outcomes when their care, including ART, is managed by healthcare providers with expertise in treating HIV. Care provider experience is one of the few factors (specific to either providers or healthcare systems) that has been shown over time to increase the likelihood that a patient will receive effective ART and to prolong the life of people with HIV infection (*N Engl J Med* 1996; 334:701; *AIDS* 1998;12:417; *Arch Intern Med* 2005;165:1133). Care provider experience is increasing in importance as antiretroviral (ARV) management becomes steadily more complicated. Awareness of drug interactions and the ability to prevent and manage ARV-related adverse effects and drug resistance have significant effects on the short- and long-term health of HIV infected patients.

Role of primary care providers: As women with HIV infection live longer, the role of their primary care provider in treating other medical conditions is critical. When a woman must be referred to an HIV expert, it is important that her primary care provider assure the patient that she is not being abandoned. Primary care providers who have little or no experience treating patients with HIV, including providers in communities or geographic areas where there is a shortage of HIV expertise, should make referrals to and consult with HIV experts to ensure optimal patient care. Part C & D of the Ryan White HIV/AIDS Program funds clinics that can serve as resources for identifying experienced HIV providers and healthcare sites. The list of Ryan White–funded programs, including Part C & D programs, can be found at the website http://hab.hrsa.gov/.

HIV specialist care: Current U.S. Public Health Service (USPHS) treatment guidelines can be accessed at www.aidsinfo.nih.gov; many of these guidelines are living documents that are updated regularly online. The Health Resources and Services Administration also supports the AIDS Education and Training Centers warmline (800-933-3413), which is a resource for clinicians who need expert consultation. The HIV Medicine Association of the Infectious Diseases Society of America has outlined several qualifications that HIV physicians should meet to demonstrate appropriate experience, including direct care of at least

25 HIV infected patients over 36 months and completion of at least 10 hours of Category 1 continuing medical education credits per year. The American Academy of HIV Medicine offers HIV specialist certification to MDs, DOs, nurse practitioners, and physician assistants who have at least 20 HIV patients, have acquired at least 30 HIV-related educational credits over the previous 24 months, and pass an examination every 2 years (www.aahivm.org).

Cultural Sensitivity

Cultural sensitivity is essential to a clinician's ability to provide optimal patient care and is addressed in more detail in Chapter 9, ***Psychosocial Issues, Mental Health, and Substance Abuse***. It is important that the provider recognize and understand the factors, including culture, that influence and guide a patient's behavior and decisions. A woman's traditions and beliefs affect her understanding of health and disease as well her acceptance of conventional medical treatment and reliance on alternative or complementary therapies. Her background shapes her view of herself as a woman, her role and responsibilities in society, and her beliefs and practices with regard to childbearing and contraception. Other factors may create barriers to care, as when a patient who has difficulty speaking, understanding, or reading English and receives care from a provider who can communicate only in English. Immigration status, as well as culturally based fears and mistrust of the U.S. healthcare system, also may impede care.

Special Circumstances

Many life circumstances may necessitate special approaches to care and unique sensitivity on the part of the care provider, as may be the case in treating women who are incarcerated, are victims of domestic or other violence, are addicted to alcohol or drugs, or have a psychiatric illness. Lesbians and transgender women also may require special sensitivity for treatment to be effective.

Some patient circumstances may arouse strong emotions in a care provider because of the provider's background or beliefs. It is essential that providers be willing and able to separate themselves from any personal connotations or associations they may assign to a patient's lifestyle or circumstances. They must provide care that is unbiased, sensitive, kind, and empathetic. If doing so is not possible, then the provider should refer the patient to a provider who can remain unbiased.

Spirituality

The spiritual dimension of a woman's life encompasses her beliefs and values and may give her life meaning and a sense of wholeness (*J Palliative Care* 2000;3:129). Spirituality is important throughout life, during periods of health and of illness, and a patient's beliefs and values can have a profound effect

on the way she views illness and its treatment. For instance, some women may view HIV as a punishment, and this belief may lessen their acceptance of treatment or put them at risk of nonadherence.

Major spiritual questions that often arise during illness may include the following:

- What gives my life meaning?
- Why is this happening to me?
- How will I survive this loss?
- What will happen to me when life ends?

It is important that the healthcare provider consider spirituality an essential component of a woman's physical, emotional, and mental health and that the provider learn about a patient's beliefs and what is important to her. A spiritual history should include specific questions about the patient's faith or beliefs, their importance and influence in her life, her involvement in a spiritual or religious community and its importance to her, and ways in which the healthcare provider may be able to help the patient integrate her beliefs and spiritual concerns into her care.

An ongoing concern: Spirituality may affect patient health outcomes directly or indirectly. Recent studies involving primary care and oncology patients found that spiritual well-being was positively associated with several outcomes relating to healthcare utilization and life satisfaction (*Ann Fam Med* 2008;6:412) and to quality of life (*Psychooncology* 2008;17:1121).

Spirituality should be addressed throughout a patient's care. Referrals to ministers, priests, rabbis, other spiritual guides, and community resources can be an important component of care. A care provider's personal spiritual beliefs may be a source of strength and may enhance the patient–provider relationship, but they should not be imposed on patients; the patient's beliefs should be recognized and respected.

Identifying Support Systems and Disclosure

During the initial evaluation, the HIV infected woman's social and emotional support system should be identified and reinforced; this information should be updated at each visit. The care provider also should ask about disclosure—to whom has the patient disclosed her HIV status, and what response(s) has she experienced? Many HIV infected women experience feelings of guilt and shame or fear violence or abandonment, and they are reluctant to trust anyone with knowledge of their infection or to share their feelings about it. Many communities still attach enormous stigma to HIV. A woman's fears about ostracism and abandonment should be addressed openly; a sense of isolation may harm a patient's physical and emotional well-being and lead to avoidance of clinic visits and nonadherence to drug therapy. Peer advocates and support groups may help many women with HIV cope with these fears and other issues on an ongoing basis.

Disclosure to sexual partners, children, and other healthcare providers may require careful attention and assistance. A woman should be encouraged to disclose her status to partners and others who may be or have been at risk of HIV transmission; barriers to disclosure, such as fear of violence, should be identified and addressed. The care provider should offer assistance with disclosure when appropriate. A mother's decision to disclose or not disclose her HIV status to children, who may or may not be infected themselves, should be honored. The timing of a mother's disclosure to her perinatally infected child can be especially difficult and may reinforce a mother's feelings of guilt. The care provider should discuss the variety of considerations inherent in these decisions and offer the patient assistance if she needs it.

Education and Counseling

Despite dramatic advances in therapy, significant decreases in mortality and hospitalizations, and overall improvement in quality of life, HIV remains a life-threatening and often life-ending disease, and no cure is on the horizon. For women, life with HIV infection often is enveloped by poverty; isolation; personal, partner, or community drug use; and the competing priorities of children and family. Mental illness, substance abuse, or domestic violence may complicate a woman's clinical picture. Personal management of HIV disease now requires that a patient have a basic understanding of HIV infection and intense involvement in her own care.

Early and often: When encountering a woman newly diagnosed with HIV, care providers should be certain to educate the patient about the infection—natural history; clinical, immunologic, and virologic monitoring; and treatment—and about her medical condition in particular, including CD4+ cell count, clinical stage, and her need for treatment. The critical importance of adherence to care and to ART should be explained early and often. Barriers to care and to ART adherence, such as medication side effects and disclosure issues, should be assessed and addressed proactively.

Lifelong learning: Unlike patients with most other chronic medical conditions, those with HIV remain infectious for the rest of their lives and must learn about and become empowered to change behaviors that put themselves or others at risk (i.e., "prevention for positives"). Doing so successfully entails ongoing, lifelong learning and requires continual reinforcement. Perhaps the most important intervention for reducing sexual transmission to others is the use of effective ART. Observational studies and a meta-analysis have demonstrated decreased rates of HIV transmission among heterosexual serodiscordant couples on ART (particularly with fully suppressed HIV-RNA levels) as compared to those not on therapy (*AIDS* 2009;23:1397). Recent data from HPTN 052, a randomized clinical trial designed to evaluate ART as prevention of sexual transmission among serodiscordant couples, found that earlier initiation of ART (at CD4+ cell counts 350–550/mm^3) reduced HIV transmission to the uninfected partner by 96%. (*N Engl J Med* 2011; 365:493-505). Pre-exposure prophylaxis (PrEP) (see Chapter 3) is an additional option that can be considered to help protect HIV-uninfected partners.

Providers' ongoing patient education efforts should aim to correct misconceptions and uncover myths. Relapses in unsafe sexual or drug-using behaviors and at least episodic problems with adherence should be recognized as the norm rather than the exception. Patients also should be counseled about health-promoting practices in general (e.g., smoking cessation, exercise, nutrition) and about other personally relevant issues when appropriate (e.g., substance abuse, domestic violence). Education and counseling must be provided throughout the course of a patient's care, as knowledge and disease management change and the patient's life circumstances evolve. Peer advocates (HIV-affected women from similar cultural backgrounds) can be effective members of the clinical team to help educate patients, advocate for them, and provide counseling as needed.

Medical Evaluation

Several closely spaced visits: The initial medical evaluation of an HIV infected woman should include a comprehensive medical and psychosocial history and physical examination. It should also include gynecologic history—menstrual history, sexual practices (including genital, oral, and anal sex), contraception and condom use history, previous sexually transmitted and other genital tract infections, prior abnormal Pap smears, and other gynecologic illnesses or symptoms—as well as pelvic examination and recommended laboratory testing. This initial assessment should take place over several closely spaced visits. This approach will allow the woman and her clinical care team to become familiar with one another and to develop the trust and partnership that will form the foundation of the woman's ongoing care. It is particularly important for a woman newly diagnosed with HIV, who may be struggling with the shock, fear, denial, and despair that accompany the discovery of a life-threatening illness, to be given the opportunity to assimilate information about HIV and her own clinical status in small bites.

The intervals at which follow-up visits are scheduled should be based on the patient's HIV clinical, immunologic, and virologic status as well as other medical or comorbid conditions (e.g., substance abuse, mental illness) and her counseling or psychosocial support needs. At each visit, the patient should be questioned about new symptoms and side effects, her adherence with medications, and psychosocial issues and concerns. Her last menstrual period, current sexual activity, and use and consistency of use of condoms and contraception should be documented. Risk behaviors should be reassessed at regular intervals because sexual and drug-use patterns may change over time. Safe practices should be reinforced through positive prevention counseling (*MMWR* 2003;52 RR12:1). Pelvic examination should be repeated at least annually and should take place more frequently if gynecologic signs or symptoms develop or if the patient has a history of abnormal Pap smears, or current or recent unsafe sexual practices, or exposure to sexually transmitted infections. Medical and gynecologic evaluation of HIV infected women is described in more detail in Chapter 4, ***Primary Medical Care**, and* Chapter 6, ***Gynecologic Problems***.

Family-Centered Care

HIV is a disease of families. An infected woman's husband or partner and her children also may be living with HIV. Even when other family members are not infected, a woman is likely to be deeply affected by the presence of chronic and life-threatening illness within the family; she may be fearful of HIV transmission, and she may fear or face stigma. An HIV infected woman may neglect her own care while providing care to sick family members or to her children. The provider should encourage all HIV infected family members to receive appropriate care and should enlist family support for the infected woman by providing the family with information and education about HIV along with updates on the woman's condition (with her permission). The care provider also may help by identifying support systems for the entire family.

Access to Care

Two studies conducted at several multistate primary and specialty HIV care sites in different geographic regions highlighted persistent gender disparities in care by demonstrating that women were less likely to receive effective ART (*J Acquir Immune Defic Syndr* 2005;38:96) and had higher hospitalization rates (*Med Care* 2005;43 suppl 9:40). If women with HIV are to benefit equally from the advances in understanding and management of this disease, then attention must be paid at the individual, community, and societal levels to the many factors that continue to hinder equal access to care. Such factors include lack of empowerment; difficulty accessing child care, transportation, and insurance coverage; stigma and isolation; violence against women; and the competing concerns that many women face when they are responsible for providing food, housing, and care for other family members while caring for themselves. It is important to create appropriate linkages to services not available at the primary site of care, including substance abuse treatment, food and housing assistance, and additional medical expertise.

Limited-Resource Settings

(see also Chapter 16, ***International Perspectives***)

In limited-resource settings, great progress has been made in scaling up access to HIV testing and counseling, ART, interventions to prevent mother-to-child transmission, and treatment of TB and other HIV-related infections, largely because of resources committed to the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the U.S. President's Emergency Plan for AIDS Relief (PEPFAR); and other international organizations. Increasingly, HIV education and training is being integrated into medical, nursing, and midwifery school curricula to prepare new generations of healthcare providers for the ongoing pandemic. Moreover, task-shifting strategies have been implemented in many countries to expand the human resource pool rapidly and to use scarce human resources more efficiently. (*Task shifting* entails assigning specific tasks to less specialized healthcare workers, such as shifting responsibility for HIV testing and counseling to community workers or assigning nurses to prescribe and dispense ART.)

In settings with few resources, issues of cost, accessibility, stigma, and laboratory and healthcare infrastructure limit the use of ARVs; moreover, as new infections continue to occur, they threaten to overwhelm any fragile progress that has been made. Increasingly, attention is turning to the need for robust prevention programs and the use of biomedical prevention tools, such as male circumcision, in addition to—and integrated with—treatment resources. A new focus on integration and coordination of HIV prevention, care, and treatment with broader global health efforts, including linkage to women and children's health programs, has developed. Community involvement, laboratory infrastructure, and patient and provider education are interrelated and essential to all levels of HIV care. These components of the healthcare system must exist and must be strengthened if prevention, care, and treatment services are to succeed and ART is to reach those most in need.

The Chronic Care Model for HIV

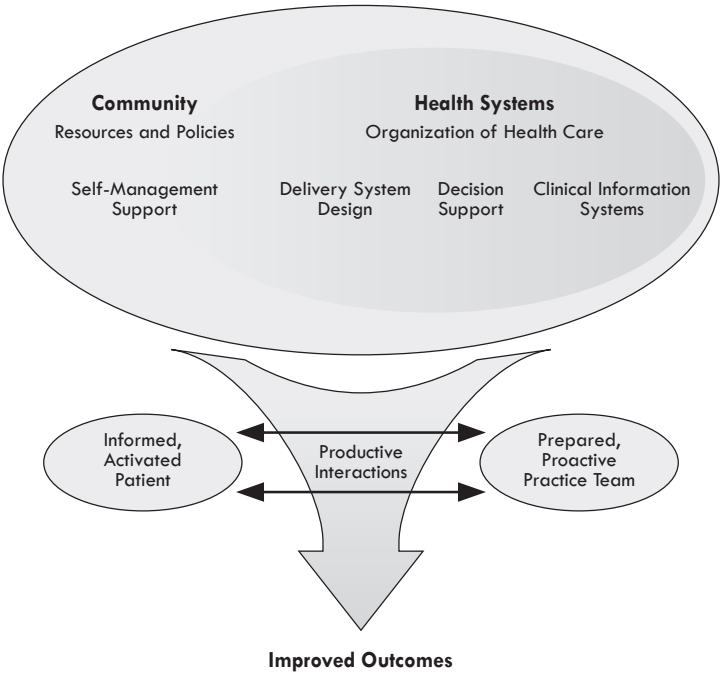
With the advent of effective ART, life expectancy for HIV infected persons has been significantly extended and symptoms and disability related to HIV have decreased. This shift has required replacement of the acute and terminal illness model of care with a chronic care model. Analysis of a multinational cohort found that the average life expectancy for a 20-year-old with HIV who started ART between 2003 and 2005 is now extended to 49 years (*Lancet* 2008;372:293). However, a recent analysis based on HIV surveillance data from 25 States found that life expectancy improved less for women after a diagnosis of HIV from 1996 to 2005 than it did for men (*J Acquir Immune Defic Syndr* 2010;53:124). As people with HIV live longer, they are also subject to the same chronic illnesses as the general population. In some cases, they may be at increased risk for certain chronic diseases, such as cardiovascular and metabolic syndromes (see Chapter 4, ***Primary Medical Care***).

Chronic disease criteria: HIV meets several chronic disease criteria. It has an uncertain course and a prescribed treatment regimen; it requires self-care and carries some degree of stigma; it brings about changes in identity, roles, and relationships; and it may cause psychological distress (*AIDS* 2002;16 suppl 4:s69). As more HIV infected persons around the world have access to ART and are living longer, chronic disease management programs have become a global priority (UNAIDS 2008).

Objectives of chronic disease care: The objectives of chronic disease care include management of physical symptoms, maintenance or improvement of independence, and increased quality of life (*Psychology and Psychiatry: Integrating Medical Practice*. Chichester, UK: John Wiley & Sons; 2001; *Public Health* 2002;119:1130). The Chronic Care Model (www.improvingchroniccare.org) illustrated in Figure 2-1 was developed and refined by experts in chronic illness management to encourage high-quality integrated chronic disease care. It can be applied to a number of chronic illnesses, including HIV/AIDS. The

model identifies key elements in a system of care that can help patients to be healthier, providers to be more satisfied, and cost reductions to be realized throughout the system.

Figure 2-1
The Chronic Care Model



Source: *Eff Clin Pract* 1998;1:2. Copyright © 1998 by the American College of Physicians. Reprinted with permission.

Community Resources and Policies

Community programs can support and extend care for patients with HIV/AIDS. They can provide resources, fill gaps in needed services, promote better self-care, and play a broad role in advocating for patients and promoting health policies that can better sustain the lives of people living with HIV/AIDS.

Organization of the HIV Healthcare System

In delivering care for patients with HIV/AIDS, the healthcare system should be organized to promote safe and high-quality care. It should be flexible and nimble (i.e., able to change), offer appropriate resources

and support for providers and patients, and emphasize prevention and health maintenance rather than crisis-oriented care. The system also should encourage open and methodical handling of errors and quality problems and should promote effective improvement strategies aimed at comprehensive system change. Coordination of care within and across health system components, including coordination with primary and specialist clinical care, as needed, should be facilitated.

Decision Support

Because of the rapid advancements in knowledge about HIV and changes in clinical practice, HIV care providers need ongoing education and training to remain current. Treatment decisions should be founded on evidence-based guidelines. Primary care providers also should be kept informed and involved when patients are referred for specialist care. The USPHS has supported the development of evidence-based guidelines for HIV prevention and care (available at www.aidsinfo.gov).These and other high-quality online and consultative resources (e.g., warmlines, hotlines) are available to assist HIV providers in ensuring that care is based on the most current information and recommendations (see Chapter 15, ***Resources***).

Healthcare Delivery System Design

The healthcare delivery system should be proactive and focused on keeping patients as healthy as possible. This approach requires determining what care is needed, delineating roles clearly among care team members, ensuring that team members have current information about patient status, and facilitating follow-up as a part of standard care. When necessary, care should be coordinated and integrated across different clinical settings, and access to community resources should be facilitated. Attention should be given to patient understanding of care, and care should be sensitive to a patient's cultural background and belief system. *Case management services*—defined as intensive, individually tailored, goal-oriented care—that are planned, coordinated, and managed by a single individual (case manager) or members of a team also should be provided.

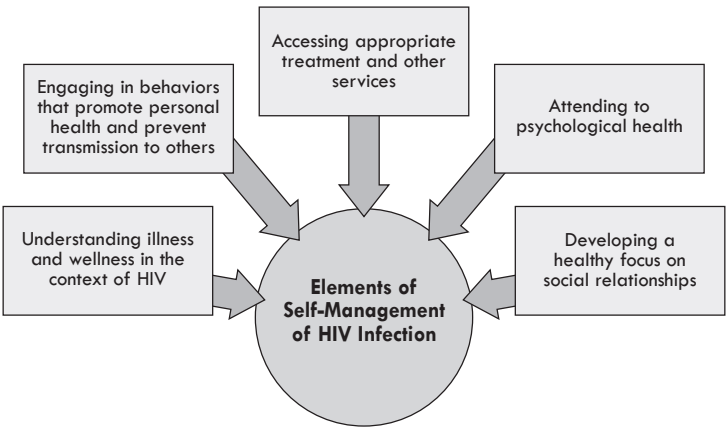
Patient Self-Management Support

Successful HIV care depends on a well-informed and motivated patient. Although care providers are responsible for prescribing ARVs appropriately and can facilitate adherence, a woman with HIV is ultimately responsible for taking her medications properly and returning for regular care and follow-up. It is essential that patients be given tools to help them care for themselves, including information about how to take medications, recognize adverse effects, and minimize or prevent side effects. Patients often need help with developing problem solving, coping, and assertiveness skills. Finally, a woman should have a central role in making decisions about her care and in problem solving, both of which will help foster personal responsibility and a collaborative and trusting relationship with her care provider.

A patient's ability to engage in self-management of her HIV infection depends on specific knowledge and behaviors (*AIDS Care* 2009;21:1321), listed below and illustrated in Figure 2-2:

- **Understanding illness and wellness in the context of HIV,** including understanding the need for ART to strengthen the immune system and the importance of adherence to reduce risk of resistance
- **Engaging in behaviors that promote personal health and prevent transmission to others,** such as safer sexual and drug injection practices and substance abuse treatment
- **Accessing appropriate treatment and other services,** such as regular HIV care and other needed clinical care
- **Attending to psychological health,** which may include developing an improved sense of control over one's life and actions, working to accept HIV as a part of life, and managing stress
- **Developing a healthy focus on social relationships,** which may include coping with stigma and decision making about disclosure, developing collaborative relationships with healthcare professionals, and seeking out supportive and affirming social networks.

Figure 2-2
Elements of Self-Management of HIV Infection



Source: *AIDS Care* 2009;21:1321

Clinical Information Systems

Information systems, such as electronic health records, are essential for tracking individuals and populations of patients with HIV/AIDS and can be used for both clinical and quality management purposes. They can facilitate efficient, coordinated, and effective care by supporting the sharing of patient information among care providers. Increasingly, telemedicine capabilities are being used to complement and extend standard care delivery by enabling greater exchange

of information among providers and with patients, virtual consultations, and telepharmacy for sending e-scripts, among other innovations (*Int J Med Inform* 2006;75:638). Clinical information technology can help prevent serious errors in care, such as medication errors (*JAMA* 1998;280:1311), and can provide timely reminders for providers and patients.

Quality Management

As the care of individuals with HIV has become increasingly complex and multifaceted, the importance of care monitoring to ensure quality and comprehensiveness has been highlighted. For instance, the American Medical Association recently led a collaborative initiative to explore opportunities to improve the quality of outpatient chronic care (*Jt Comm J Qual Patient Saf* 2009;35:248). That effort focused on incorporating validated and nationally endorsed performance measures and tools into clinical care. Performance measures specific to the care of patients with HIV have been developed as well (see Chapter 14, ***Quality Management***) and can be used as both clinical aids by providers and quality measures in auditing comprehensiveness and effectiveness of care.

Effectiveness of the Chronic Care Model

To date, no studies have assessed the effects of implementing the chronic care model specifically in HIV care. However, a recent review of the model's use in the care of patients with other chronic illnesses found that multidisciplinary care, care coordination, patient self-management, and provider education had the greatest and most consistent effects on both clinical outcomes and process-of-care measures, such as increased provider adherence to treatment guidelines (*Intern Med J* 2008;38:427). In addition, patient self-management has been shown to reduce emergency and other outpatient visits, decrease health distress, and improve self-efficacy (*JAMA* 2002;288:2469). Some studies also indicate that decision support and feedback for healthcare providers, as well as case management and telemonitoring or telephone support for patients, confer clinical benefit (*Intern Med J* 2008;38:427).

From Research to Practice

Community-based participatory research is an emerging model that involves community members and patients to enhance ongoing clinical research. *A practice-based research network* is a group of care practices committed to patient care and to investigation of questions related to community-based practice and to improvement of outcomes and quality of care. These new research models are well positioned to examine such issues as healthcare disparities, prevention, chronic disease management, and mental health. The melding of the two research models has great potential for solving intractable problems, ensuring that studies match the needs of all stakeholders, and allowing rapid translation of results into clinical practice (*Exp Biol Med* 2010;235:290).

Chapter 3:
Prevention of HIV Infection

Jared M. Baeten, MD, PhD
Assistant Professor, Departments of Global Health and Medicine
Adjunct Assistant Professor, Department of Epidemiology
University of Washington

Connie Celum, MD, MPH
Professor, Departments of Global Health and Medicine
Adjunct Professor, Department of Epidemiology
University of Washington

The authors declare no conflicts of interest

Chapter 3: Prevention of HIV Infection

Chapter 3 at a Glance

Introduction: A Global Public Health Priority

Women account for half of the 33 million adults living with HIV worldwide and more than half of new infections in global settings with the highest rates of HIV. Prevention of HIV infection in women is a global public health priority for the health of women, their sexual partners, and their children.

This chapter discusses HIV prevention with a focus on risk assessment, what does and does not work in prevention, and strategies in the research pipeline that may hold promise.

Daunting Challenges

Nearly three decades into the HIV epidemic, scientists and clinicians working to prevent HIV continue to face daunting challenges. Measures that women can take to prevent HIV acquisition are well known—abstaining from intercourse, selecting low-risk partners, negotiating mutual monogamy, and using condoms. However, high rates of HIV among women in many parts of the world are a testament to the barriers that women may face in successfully implementing effective prevention strategies.

Multiple vulnerabilities: Women are often not aware of their partners' infection status or level of risk, and in many cases, they may not be able to negotiate sexual safety. Young women often face particularly high HIV risk because of emotional and physiological immaturity. In many areas of the world, risk is magnified by poverty and social vulnerability, leading to a greater likelihood of engaging in sexual relationships that lead to HIV exposure.

Risk magnified by disempowerment: Women in economically disadvantaged nations and in socially marginalized groups in the industrialized world may have less access to medical care for treatment of sexually transmitted infections (STIs) and contraception. They may not feel empowered to negotiate condom use, abstinence, or monogamy within their sexual relationships or to initiate HIV testing for themselves or their partners. An important issue is that fertility desires may overwhelm HIV prevention intentions, particularly condom use, even for women who perceive HIV risk.

Interventions for behavioral and biologic risk factors: Women who use injection drugs and some noninjection drugs (e.g., methamphetamine, cocaine) are at higher risk of HIV and need counseling that addresses both safe sexual practices and harm-reduction strategies related to drug use. Culturally sensitive interventions that target both behavioral and biologic risk factors for HIV are necessary to reduce transmission to women and girls. There remains, as well, a critical need to address the complex forces that fuel the HIV epidemic in women, including poverty, migration of populations, social and cultural disruption, gender discrimination, and stigma about STIs and HIV.

HIV Risk Assessment and Risk Reduction Counseling

Given that many patients will not voluntarily discuss their sexual activity or potential risk of HIV or STIs, it is incumbent on health care providers to ask a few open-ended questions in a comfortable, nonjudgmental manner. Otherwise, providers enable avoidance of discussion of sensitive sexual behavioral and HIV risks (e.g., "I won't ask; they won't tell"). Suggestions for risk assessment and patient-centered counseling are provided in the sections that follow.

Risk assessment for every patient: Just as most people would find celibacy an impractical means of reducing sexual risk, many individuals may find changing other specific sex behaviors difficult or unappealing. Although some sexual behaviors may be less mainstream than others, remember that participation in such behaviors reflects not a lack of morals or willpower but rather differing perceptions of what is enjoyable. Moreover, sexually active women may not realize that they are practicing behaviors that put them at risk for HIV infection. Guidelines for physicians and other healthcare providers recommend that HIV and STI risk assessment be conducted for every patient, ideally on a regular basis; however, most primary care physicians do not routinely incorporate questions about sexual behavior into routine patient care.

Managing provider discomfort: Clinician discomfort and fear of embarrassing or offending a patient when discussing sex may be impediments to effective risk assessment. In such circumstances, a clinician may find it more acceptable to frame the discussion by explaining the routine nature of such questions, thereby demonstrating that the patient is not being singled out because of mannerisms, appearance, or ethnicity. One effective approach may be to emphasize the importance of the discussion to the patient's care: "To be able to provide the best care for you today, we need to understand your risk for certain infections by talking about your sexual practices." Another may be to allude to the universality of many concerns: "Many women find it difficult to get their partners to wear condoms. Has this been a problem for you?" As with any type of medical history taking, open-ended questions probably serve as the most effective means of eliciting information when taking a sexual history. Language should be clear, easy to understand, and nonjudgmental.

Low threshold for recommending HIV testing: Some HIV risk factors for women can be derived from epidemiologic studies, such as history of gonorrhea or syphilis, crack cocaine use, and injection drug use (IDU). Increased risk with drug use is often mediated through both exposure to infected blood (especially with IDU) or through association with unsafe sexual practices. However, sometimes women are at risk through monogamous relationships with their HIV infected husbands. Factors that may increase risk in women, such as a history of unwanted pregnancy or an incarcerated sex partner, are not well recognized among healthcare providers. Therefore, identifying risk behaviors in women requires care and attention on the part of the provider. In many cases, a low threshold for recommending HIV testing is necessary. Important risk topic areas to cover are listed in Table 3-1 and can be ascertained through a written or computerized patient-administered questionnaire.

Table 3-1

Risk Assessment for STI/HIV for Women

Number of sex partners: ___ previous year ___ lifetime

Sex partners: ___ men ___ women ___ both

Sexual practices: ___ vaginal intercourse ___ anal intercourse
___ oral sex ___ sex toys ___ other (specify) _____

Consistent condom use: ___ yes ___ no

Use of: ___ injection drugs ___ crack cocaine ___ crystal methamphetamine

Patient perceives sex partner(s) to be at risk: ___ yes ___ no

Patient feels that sex partner(s) put her at risk: ___ yes ___ no

How does patient protect herself from HIV? _____
_____
_____

How does the patient protect herself from unplanned pregnancy? _____
_____
_____

History of abnormal PAP smear? ___ yes ___ no

History of STI? ___ yes ___ no

History of sex partner who was incarcerated? ___ yes ___ no

History of alcohol or drug abuse? ___ yes ___ no

History of: ___ injection drug use ___ sharing needles
___ crack cocaine use ___ crystal methamphetamine use

History of sexual, physical, or psychological abuse? ___ yes ___ no

Is there anything else that she feels she should mention to ensure good medical care? _____
_____
_____

Practical Approaches to Risk Reduction Counseling

Individualize to the patient: Risk reduction counseling may seem overwhelming to a healthcare provider who has no special training in behavioral theory. However, the underlying principle is one that can be applied by any practitioner in any setting: Counseling should be individualized to the person receiving the counseling, and any attempt to individualize is superior to simply providing a didactic message.

Practical aspects of counseling:

- **Focus** the counseling session on risk reduction topics.
- **Listen** and react to the patient.
- **Do not** stick to a practiced script.
- **Avoid** overambitious risk reduction plans; focus on realistic goals.
- **Give** the patient written documentation of the risk reduction plan.
- **Use** culturally sensitive and ethnicity-specific language and terminology, when available and appropriate.
- **Consider** issues specifically relevant to women.

Focus the session: The cornerstone of the counseling session is to focus the session on a patient's recent sexual activities, her perception of their risk, and her motivation to reduce her risk of HIV/STI exposure. The provider should redirect the patient to this topic whenever necessary. Clinicians and counselors may become distracted by providing excessive information about scientific data and principles in response to patient questioning. Such information is probably more effectively dispensed in pamphlet form or by referral to other patient information sources. In addition, women at risk for STIs, including HIV, often come to clinic with multiple complicating issues, including poverty, domestic violence, substance abuse, and child care problems. A counselor may begin to feel responsible for addressing all of these issues and discouraged by what seems to be a host of insurmountable problems. Moreover, because the patient may be uncomfortable discussing her own risk, she may be emotionally invested in distracting the counselor from that subject. For these reasons, the counselor should remember that, during a limited period of interaction with a woman, the primary goal is to directly address and, ideally, have an impact on risky sexual behavior.

Appropriate objectives of risk reduction counseling
(Adapted from Kamb ML, 1998):

- **Enhance the patient's self-perception of risk:** Identify risk behavior; assess level of concern; identify ambivalent feelings about risk.
- **Explore specifics of the patient's most recent risk:** Identify specific risk details; address ability to communicate with partner(s).
- **Assess the patient's patterns of risk behavior:** Identify situations that make the patient vulnerable to risk and triggers of high-risk behavior.
- **Review previous risk reduction experience:** Identify successful attempts at risk reduction and obstacles to risk reduction; summarize, reflect, and synthesize patient risk patterns.
- **Address risk in the context of the patient's life:** Convey concerns and urgency regarding risk; support and encourage the patient to action.

Other longstanding issues may not be easily solvable and may be more appropriately referred to a social worker, substance abuse counselor, or mental health counselor.

Listen and react: While trying to convey prevention messages it is important to listen and react to the patient. It is a human quality that we enjoy talking and thinking about ourselves. The counseling technique of summarizing a patient's descriptions and viewpoints about her risk is an extremely effective communication tool. In an effort to be nonjudgmental, counselors may find themselves nodding supportively to just about any statement that the patient may make. Instead, direct and clear feedback from the counselor about self-destructive behavior may communicate more effectively the importance of reducing risk. For example, if a patient is describing an evening during which she had sex with multiple men while using crack cocaine, it may be more appropriate for the counselor to respond with emphasis that such behavior is dangerous. It would also be important to explore the emotional or physical needs leading to such risky sexual behavior and to identify potential alternatives to fulfilling such needs.

Avoid overambitious risk reduction plans: The most common error made by counselors is developing an overambitious risk reduction goal, particularly during sessions in which good rapport has been established. In many cases, a counselor may be convinced that a woman has acknowledged her risk to such a degree that she is now ready to eliminate any subsequent episodes of unprotected sex. Such goals are likely unrealistic. Behavioral specialists favor extremely concrete goals, such as "On Friday night I am going to ask my partner to wear a condom." Even modest goals, such as stopping at a drugstore and purchasing condoms on the way home from the session, may be suggested. Other possible goals are listed in Table 3-2.

Table 3-2

Examples of Concrete Individualized Risk Reduction Plans

Type of Plan	Patient Actions
Patient will talk about HIV/STI concern/risk to partner/friends.	• Disclose or communicate with partner, peers, and others
Patient plans to get herself tested or have partner(s) tested for HIV/STIs before having sex.	• Get tested again to ensure she is not infected • Have partner(s) tested for HIV/STI • Use condoms until partner(s) tested for HIV/STI • Abstain from sex until partner(s) is tested for HIV/STI
Patient plans to reduce, change, or eliminate at-risk partner(s).	• Break up with high-risk partner(s) • Eliminate a particular type of high-risk partner (e.g., prostitutes, anonymous partners) • Have fewer partners
Patient will change the type of partners she has.	• Get to know partners better before having sex • Remain monogamous with one partner for 3 mo • Abstain from sex for 3 mo
Patient plans to change use of alcohol and drugs.	• Decrease or eliminate alcohol and drug use when having sex • Generally decrease or eliminate a specific drug or alcohol • Will not share needles (she will exchange or obtain new) • Use clean needles or only share needles with partners known to be HIV uninfected • Seek medication-assisted therapy if addicted to heroin or other opiates
Patient plans to increase condom use or increase situations in which she uses condoms.	• Talk to partner(s) about using condoms • Buy condoms or have them more available • Have sex with condom use more often • Use condoms with all partners (vaginal and anal sex) • Use with all non main partners (vaginal and anal sex) • Use condoms with main partner (vaginal and anal sex)
Patient plans to change the kind of sex she will have.	• Have oral sex instead of vaginal or anal sex • Engage in mutual masturbation or petting (no penetrative sex)
Patient plans to make changes in the situations that are associated with risky behavior.	• Eliminate going to particularly risky place (e.g., bar, clubs) • Reduce frequency of going to a particularly risky place • Substitute behavior—go to gym, movies, etc., instead

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Adapted from *JAMA* 1998;280(13):1161 and from Beth Dillon, Project RESPECT training materials

Prevention Messages for HIV Infected Women

Important for women already infected with HIV: Although this chapter focuses on factors that may increase a woman's risk of acquiring HIV, prevention messages are equally important for women who are already HIV infected. Studies have shown that women with HIV are concerned about factors that may increase their infectiousness to their sexual partners and children. In general, the central messages for preventing sexual HIV transmission apply to HIV infected women as well as to those who are not infected but are at risk through their or their partners' behaviors. Important messages include the importance of knowing one's HIV status and that of one's sexual partner(s), the effectiveness of behavioral change in preventing transmission, and the potential role of consistent condom use in significantly reducing risk of HIV transmission.

What Works in HIV Prevention

Knowledge of Serostatus

Essential to prevention: Knowledge of one's HIV serostatus is the starting point for HIV prevention. An HIV-seropositive woman must know her status to prevent transmission to her infant and her partner(s) and so she can seek medical care for herself. For a seronegative woman, HIV testing is an opportunity for risk reduction counseling and strategizing on ways to remain uninfected. Unfortunately, most women at risk for HIV infection remain unaware of their HIV status, in part because they are often unaware of their partners' risks.

Routine provision of HIV testing recommended: Selective HIV screening — i.e., targeting patients at highest risk, such as intravenous drug users, men who have sex with men (MSM), and STI clinic attendees—has long been central as a strategy for HIV testing. The advantage of selective screening is cost savings, particularly in low-prevalence settings. However, selective screening has the potential to miss many people with HIV infection, particularly women, who may not possess traditional risk factors for HIV or who may not recognize their own HIV risk, and experts have increasingly favored recommendations for universal HIV screening. Estimates are that 1 in 5 HIV infected persons in the United States is unaware of his or her HIV serostatus. Universal screening offers several important advantages, including increased detection rates and, potentially, increased test acceptance, as universal screening reduces the stigma of HIV testing by eliminating testing based on sexual orientation, socioeconomic status, or race.

In the United States, the Centers for Disease Control and Prevention (CDC) recommends an opt-out approach to HIV screening, in which testing will be performed unless a patient declines. To increase routine HIV testing as a part of routine medical practice, the target populations for opt-out testing are broad: all pregnant women, everyone aged 13–64 years seeking health care (e.g., in primary care or emergency room settings, unless the prevalence

of undiagnosed HIV in that community has been documented to be <0.1%), everyone initiating TB treatment, and everyone seeking treatment for STIs (*MMWR* 2006;55:1). Making HIV testing routine and universal is cost effective (*N Engl J Med* 2005;352:586). The evidence is insufficient to determine optimum time intervals for HIV screening. One reasonable approach would be one-time screening of adolescent and adult patients to identify persons who are already HIV-positive, with repeated screening of those who are known to be at risk for HIV infection, those who are actively engaged in risky behaviors, and those who live or receive medical care in a high-prevalence setting.

Minimizing operational barriers to testing: Separate written consent for HIV testing should not be required unless mandated by local jurisdiction. Instead, general consent for medical care should be considered sufficient to encompass HIV testing. Rapid tests should be used to increase the likelihood that patients will receive their results. Unfortunately, routine HIV testing, particularly for hospitalized patients and those presenting to emergency care settings, has not yet been adopted widely, despite CDC guidelines. Some of the barriers to implementation of routine HIV testing include healthcare provider misconceptions about the amount of time testing requires, stigma associated with HIV/AIDS, and lack of reimbursement by some healthcare insurers.

In higher prevalence countries outside the United States, multilayered national programs have been initiated to increase universal knowledge of HIV serostatus, including widespread voluntary testing and counseling; opt-out testing in antenatal clinics; and door-to-door, home-based HIV counseling and testing, which rapidly increases knowledge of serostatus within a community and among families. Opt-out testing significantly increases HIV testing rates among pregnant women and is a key strategy in increasing uptake of antiretroviral (ARV) medications for prevention of mother-to-child HIV transmission.

Recommendations for counseling: In recognition that written consent and extensive pre- and posttest counseling reduced health care provider willingness to recommend and offer HIV testing, the 2006 CDC guidelines indicated that prevention counseling should not be required as part of HIV screening programs in healthcare settings. Prevention counseling is strongly encouraged for people at high risk for HIV, such as those seen in STI clinics.

Brief information about HIV tests should be provided with routine HIV testing, including the need for confirmatory tests if a rapid HIV test is positive. Patients at ongoing risk of HIV exposure should be counseled about risk reduction, and a concrete plan for reducing risk should be established by the patient. The need for annual HIV testing also should be communicated.

Table 3-3 describes appropriate goals for posttest counseling. For people who learn that they are HIV infected, disclosure to partners and the importance of linkage to care and antiretroviral therapy (ART) should be emphasized. Given that a substantial proportion of newly identified HIV infected persons do not follow up with care, it is important to obtain a CD4+ cell count, provide active referrals, and follow up with newly identified HIV positive persons within 2–4 weeks to determine whether they have had clinical follow-up with an HIV care program.

Table 3-3

Goals of HIV Posttest Counseling

Test Result	Counseling Messages
HIV seronegative	• Readdress and reinforce risk reduction plan. • Discuss need for repeat testing for people with recent (<3 mo) exposure or ongoing sexual and/or drug using risk behavior. • Discuss disclosure of results to sexual and drug-using partners.
Indeterminate HIV-1 Western blot	• Discuss prevalence of and risk factors for indeterminate test results. • For patients with p24 bands and those with high-risk behavior, discuss possibility of acute HIV infection. • Arrange for repeat testing in 1 mo and perform HIV DNA or RNA PCR to confirm infection status.
HIV seropositive	• Differentiate between being HIV infected and having AIDS. • Emphasize importance of early clinical intervention and make medical referral. • Discuss ways to avoid transmitting HIV to others. • Discuss disclosure of results to sexual and drug-use partners and offer assistance with disclosure, if needed. • Assess need for psychological support and provide referral if appropriate. • Assess possibility of domestic violence and provide referral if necessary. • Ensure patient has follow-up care.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Rapid HIV testing: HIV testing is of value only if patients return for their test results; however, low return rates have been described in the United States and in many developing countries. Many U.S. testing programs use an ELISA with confirmation through Western blot. Rapid testing for HIV yields substantial cost savings and avoids high patient nonreturn rates for test results.

A number of rapid tests—defined as requiring less than 2 hours—are approved by the U.S. Food and Drug Administration (FDA) and available in the United States (Table 3-4). Some tests require as little as 5 minutes, use blood obtained from a fingerstick, and can be performed easily by clinical staff using only minimal laboratory facilities. Some have been approved by the FDA with a waiver from the Clinical Laboratory Improvements Amendments (CLIA) regulations; such waivers allow trained but nonprofessional staff to use the tests outside of traditional laboratory settings. Experience from CDC-led demonstration projects of rapid testing has been encouraging, and the assays have been found to have high sensitivity and specificity (*AIDS* 2006;20:1655). An increased rate of false positive results (<2%) with tests that use oral fluid rather than blood has been reported; positive results require confirmatory testing.

Patients who test negative can be given a definitive result without a return visit. Patients who test positive should be informed that their screening test was positive and that they should return to receive a confirmed test result.

In July 2012 the FDA approved the OraQuick In-Home HIV Test, a rapid home-use HIV test kit that provides a test result in 20–40 minutes and is approved for sale in stores and online to those 17 years and older. As with other rapid tests, positive tests must be confirmed by follow-up laboratory-based testing. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310542.htm)

Table 3-4

Rapid HIV Tests Approved by the FDA

Test	Manufacturer	Specimen Type	Sensitivity (%)	Specificity (%)	CLIA Waived
Clearview COMPLETE HIV 1/2	Inverness Medical Professional Diagnostics www.invernessmedicalpd.com	Whole blood*	99.7	99.9	Yes
		Serum/ plasma	99.7	99.9	No
Clearview HIV 1/2 STAT-PAK	Inverness Medical Professional Diagnostics www.invernessmedicalpd.com	Whole blood*	99.7	99.9	Yes
		Serum/ plasma	99.7	99.9	No
Multispot HIV-1/ HIV-2 Rapid Test	BioRad Laboratories www.biorad.com	Serum	100	99.9	No
		Plasma	100	99.9	No
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	OraSure Technologies, Inc. www.orasure.com	Oral fluid	99.3	99.8	Yes
		Whole blood*	99.6	100	Yes
		Plasma	99.6	99.9	No
Reveal G-3 Rapid HIV-1 Antibody Test	MedMira, Inc. www.medmira.com	Serum	99.8	99.1	No
		Plasma	99.8	98.6	No
Uni-Gold Recombigen HIV	Trinity Biotech www.unigoldhiv.com	Whole blood*	100	99.7	Yes
		Plasma/ serum	100	99.8	No
OraQuick In-Home HIV Test	Orasure Technologies, Inc., www.orasure.com	oral fluid	99.3	99.8	Yes

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

*e.g., fingerstick

Adapted from FDA-Approved Rapid HIV Antibody Screening Tests. February 4, 2008

Settings where rapid tests are valuable: Rapid testing is particularly valuable in areas of high prevalence where clinic return rates are low (e.g., STI clinics, emergency departments, nonmedical venues) or when an HIV diagnosis will influence immediate management decisions (e.g., postexposure prophylaxis, unknown HIV status in a pregnant woman presenting for labor and delivery). Rapid testing also has proven especially valuable in economically disadvantaged countries where HIV seroprevalence is high; laboratory resources are limited; and patient travel to and from clinic may be inconvenient, difficult, or too expensive.

Counseling remains the same: Some have expressed concern that rapid HIV testing may not offer patients sufficient time to digest counseling information and to decide whether they truly desire to know their HIV status. The principal components of HIV counseling remain the same for rapid testing as for traditional screening programs. Regardless of how HIV testing is performed, patients must be informed of the nature of the test and the risks and benefits of knowing their HIV status. They should consent voluntarily to the testing procedures, be informed that they can refuse testing, and have their confidentiality strictly preserved. Finally, they should be told that refusal of testing will not lead to denial of usual clinical services.

Does knowledge of HIV status change behavior? The literature in this area is difficult to synthesize, largely because of evolving counseling practices, varying lengths of follow-up, and few randomized trials with well-defined endpoints. A large study conducted in Kenya, Tanzania, and Trinidad randomly assigned individuals and couples to either voluntary HIV counseling and testing or basic health information (*Lancet* 2000;356:103). This trial found that counseling and testing resulted in a significant decline in unprotected intercourse with nonprimary partners by both male and female study participants. Newly identified HIV infected participants were more likely than HIV-uninfected participants to reduce episodes of unprotected intercourse. Among couples, unprotected intercourse was reduced more in those in which one or both members were diagnosed with HIV than in couples in which both members were HIV uninfected.

An ongoing randomized trial, Project Accept (HPTN 043), is evaluating whether community mobilization and mobile HIV testing reduce HIV incidence in South Africa, Tanzania, Thailand, and Zimbabwe. Studies have demonstrated the potential of HIV testing in couples with mutual disclosure of results. Among 963 HIV serodiscordant couples from Zambia, condom use increased from <3% to >80% after joint voluntary counseling and testing (*AIDS* 2003;17:733). Counseling and testing for couples should be a top HIV prevention priority, because it facilitates mutual disclosure of HIV serostatus between partners in the presence of a trained counselor.

Behavioral Interventions

Knowledge alone does not motivate change: Several well-designed randomized controlled trials have been conducted to assess the efficacy of various behavioral intervention strategies. Most of the studies conclude that such interventions result in decreased sexual risk taking (primarily unprotected

sex); some indicate decreased STI and HIV incidence. In contrast to didactic education sessions, behavioral interventions focus on recognizing risk and formulating effective risk reduction strategies. However, knowledge alone does not motivate change. To translate this concept into an issue many of us have experienced, consider the issue of weight reduction and diet modification. Despite widespread knowledge about the adverse health effects of eating fatty foods, adhering to a diet is notoriously difficult. Similarly, knowledge about STIs and HIV is not enough to implement change in sexual behavior, which involves changes in behavior for two people.

Brief counseling sessions may be effective: The 20-minute Project RESPECT counseling sessions may be most applicable to busy practitioners interested in conducting effective behavioral counseling (*JAMA* 1998; 280:1161). This study demonstrated that individual brief counseling, involving two sessions of 20 minutes each, was as effective in reducing STI incidence as four enhanced 60-minute sessions. Both intervention arms—the two 20-minute and four 60-minute counseling sessions—were superior to a didactic message.

The first of the two brief 20-minute sessions focused on recognizing HIV risk and barriers to risk reduction. After working with the client to agree on an achievable risk reduction plan, the counselors concluded the sessions by identifying a small risk reduction step that could be achieved before the second session. At the second session, counselors reviewed progress and barriers in achieving the behavioral goal and helped clients develop a long-term risk reduction plan.

Although the four 60-minute enhanced sessions also included recognizing risk and formulating risk reduction plans, more energy was focused on key theoretical behavioral elements, such as self-efficacy, attitudes, and social norms underlying risk behavior. The fact that the two brief 20-minute counseling sessions demonstrated efficacy equivalent to four 60-minute sessions is encouraging for healthcare providers who would like to integrate effective HIV counseling into busy clinical settings. Busy clinicians who cannot afford to offer even two 20-minute counseling sessions should determine whether referrals may be made to community-based organizations or to case managers who can provide brief client-centered counseling.

Use of Condoms

Effective for prevention: The National Institutes of Health (NIH) reviewed the scientific evidence and concluded that consistent use of latex condoms reduces a woman's risk of HIV by at least 85% (www.niaid.nih.gov/about/organization/dmid/documents/condomreport.pdf). Polyurethane condoms are thought to be as effective as latex condoms for preventing HIV. Natural skin condoms, however, are not effective in preventing transmission of HIV. Transmission of HIV that occurs with use of latex male condoms is likely due to technical failures or improper usage rather than to manufacturing defects. Studies reporting higher breakage rates tended to include populations from underdeveloped areas or those who participated in anal intercourse. Given the higher condom slippage and breakage rate with anal sex, use of water-based lubricants in conjunction with latex condoms is recommended for anal sex.

More control with female condoms: The female condom, made of polyurethane or nitrile, has been available for use in the United States since 1993; this device offers women more control over its use than does the male condom. The female condom is a sheath, closed at one end, with flexible rings at both ends. The FC2 device (shown in Figures 3-1 and 3-2) is inserted into the vagina by compressing the closed-end ring and pushing against the cervix; the outer ring covers the labia.

Results from a viral penetration study indicated that the physical-barrier properties of the FC2 Female Condom should provide adequate protection against viral particles *(FDA Summary of Safety and Effectiveness Data*. 2008; available at http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080002b.pdf. Accessed 9/25/2012). New female condom prototypes have been developed; the development process included substantial evaluation of women's preferences and acceptability. The new devices are designed to address user complaints about the noise, appearance, and lubricant of the initial commercially available female condoms. When counseled about condom use, women should be advised to avoid simultaneous use of a female and a male condom, because doing so could increase the risk of slippage or breakage. Counseling messages about correct storage and use of condoms are important as well (see Table 3-5).

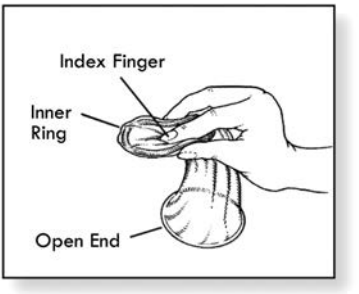
Figure 3-1
FC2 Female Condom

Source: © The Female Health Company. Chicago, IL. Reprinted with permission.

Figure 3-2
FC2 Female Condom Insertion and Positioning

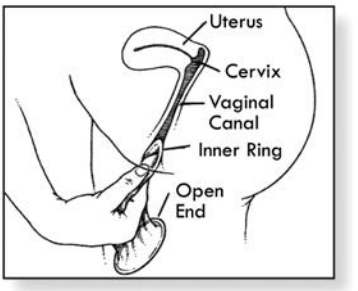
Step 1

Inner ring is squeezed for insertion.



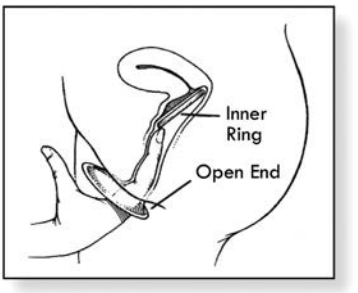
Step 2

Sheath is inserted, similarly to a tampon.



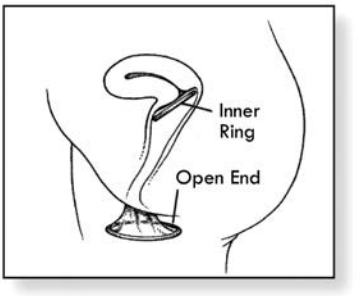
Step 3

Inner ring is pushed up as far as it can go with index finger, behind the pubic bone and over the cervix.



Step 4

Female condom is in place.



Source: © The Female Health Company. Chicago, IL. Adapted with permission.

Table 3-5

Proper Storage, Use, and Lubricants for Condoms

Condom Storage		• Store in cool, dry place, such as a bedroom drawer. • Avoid excessive humidity (e.g., don't store in a bathroom). • Avoid excessive heat (e.g., don't carry in wallet in trouser pocket). • Avoid exposure to direct sunlight.
Proper Use	**Lubricant**	• Use appropriate water-based lubricant that does not contain nonoxynol-9. • Avoid use of compounds that contain mineral oil, such as petroleum jelly, cooking oils, shortening, or lotions, because they can weaken latex.
	Male Condom	• Use at onset of male arousal, before penetration. • Hold tip of condom to create air-free reservoir for semen. • Make sure that condom is unrolled to extend completely to the penis base, leaving the reservoir. • Use enough lubrication to prevent excessive friction that might lead to breakage. • Hold condom at base during withdrawal to prevent slippage.
	Female Condom	• Inner ring must be placed completely onto cervix, or condom may twist. • Additional lubrication may be needed to prevent condom from twisting. • Care must be taken not to insert the penis between condom and vaginal wall. • The outer ring may need to be held in place to keep condom from slipping into vagina or anus. • Use of male and female condoms together is not recommended due to higher failure rate. • During anal intercourse, it may be advisable to remove inner ring to reduce likelihood of rectal bleeding.

Condom acceptability: Factors that influence condom use are complex and often differ between men and women. Surveys have shown that both men and women are influenced by perceived social norms and attitudes about condom use and by the recognition that condoms may prevent HIV and STIs. Ability to obtain condoms without excessive cost or embarrassment, ease of use, and preservation of pleasurable sexual sensation are clearly concerns for both men and women.

Acceptability of the male condom for both men and women is increased by normal appearance and feel, lack of odor, lack of slippage, the presence of a reservoir tip, and spermicidal lubrication. A man may be more likely to use the male condom if he feels that a woman may perceive him as being more sensitive and caring if he uses one. Conversely, women have complained that the interruption of foreplay has a negative effect on acceptability of both male and female condoms.

Both men and women have complained about the aesthetic appearance of the external ring of the female condom and the noise it creates during intercourse. Interestingly, in several surveys more women have said that they would be likely to use the female condom again than have said they liked using it, suggesting that women may be willing to sacrifice comfort and pleasure during sex for protection against HIV, STIs, and pregnancy. Many women have also expressed a strong preference for a female-controlled device to prevent STIs, even though the female condom cannot be used secretly.

Considerations for women who have sex with women: Discussion of recommended protective sexual practices should not be limited exclusively to heterosexual women. Sexual transmission of HIV between women has been described (*Clin Infect Dis* 2003; 36:e40). The use of barriers, such as cellophane or latex dental dams, should be recommended for oral–genital contact, particularly in HIV-discordant relationships. Sexual activity should be avoided during menstruation or when there are symptoms of genital tract infection. The sharing of sex toys contaminated with blood was implicated in at least one case of female-to-female sexual transmission of HIV.

Risk Reduction for Injection Drug Users

Drug abuse treatment is effective HIV prevention: Substance abuse treatment often removes HIV risk that accompanies sharing of contaminated syringes while reducing sexual transmission risks. For people who cannot or will not stop injecting drugs, provision of single-use sterile needles and syringes is a highly effective HIV prevention strategy. Syringes that have been cleaned with bleach or other disinfectants likely reduce HIV risk, but not nearly as well as sterile equipment. Other important strategies for reducing HIV risk in injection drug users include preventing initiation of drug injection, providing HIV prevention programs to drug users (including on the streets and in jails and prisons), and making risk reduction counseling and HIV testing available to drug users and their sex partners.

Male Circumcision

Benefits for men: In three landmark clinical trials, adult male circumcision was conclusively demonstrated to reduce men's susceptibility to HIV (*PLoS Med* 2005; 2:e298; *Lancet* 2007; 369:657; *Lancet* 2007; 369:643). Conducted in Kenya, South Africa, and Uganda, the studies together randomly assigned >11,000 uncircumcised HIV seronegative men to immediate versus delayed circumcision, then followed participants for HIV seroconversion for up to 2 years. Each study found a statistically clear 50%–60% reduction in HIV risk among men who were circumcised. In addition, the studies found direct benefits for the female partners of circumcised men in reduced rates of STIs, including genital ulcer disease, vaginitis, and HPV.

Adverse events associated with the circumcision procedure were rare. Sex should be deferred until complete healing of the glans is observed, because early resumption of sexual activity could increase risk of HIV acquisition if exposure occurs. Another significant finding is that concurrent research found no increase in risk-taking behaviors among men who underwent circumcision, suggesting that participants did not compensate for a perceived reduction in HIV risk by relaxing condom use and other behavioral prevention strategies.

More than 20 years of epidemiologic evidence, including more than a dozen prospective cohort studies, preceded the trial results. These epidemiologic studies generally compared HIV rates in men who were circumcised as infants or children with those who remained uncircumcised. Infant circumcision is technically easier than adult male circumcision and carries a lower risk of complications. Many countries are including infant circumcision promotion in their national rollout programs as part of an effort to decrease HIV transmission into the future. Biologic plausibility supports the association between a lack of circumcision and HIV risk—the foreskin contains large numbers of HIV target cells poorly protected by thin keratinized epithelium, and micro- and macroulceration of the foreskin may provide a portal of HIV entry.

Indirect benefits for women: Mathematical modeling studies suggest that widespread male circumcision will translate indirectly into substantial reductions in HIV among women in areas where male circumcision is uncommon. Acceptability surveys have found that a majority of women (69% across studies) favor circumcision of their male partners, and anecdotal reports suggest that women's positive opinions about circumcision have enhanced male uptake in areas in which rollout of the procedure has begun. In the United States, 79% of men are circumcised; prevalence of circumcision is lower in men of color.

Studies of circumcised HIV infected men have not shown conclusive evidence of protection from HIV transmission for women, and sex during wound healing after circumcision may increase the risk of a transmission from a man to his female partner. Nonetheless, circumcision substantially reduces HIV acquisition among men, thereby potentially decreasing the likelihood that a woman will encounter an HIV infected male partner. To the extent that this is true, make circumcision could translate into reduced risk for women, but it does not lead to a direct reduction in male-to-female HIV transmission. Finally, remember that circumcision is only partially protective against HIV for men; behavioral change, and particularly consistent condom use, should be emphasized for circumcised men to further reduce HIV risk for themselves and their partners.

What Has Not Worked in HIV Prevention

Nonspecific Vaginal Microbicides

Disappointing trial results: The concept of a topical microbicide—a vaginal or rectal gel, foam, or ring containing an active agent that protects against HIV infection—has been a topic of considerable interest. Microbicides hold great appeal because they can be female controlled, may be used without male partner knowledge, and would be active directly at the site of HIV exposure. To date, clinical trials have been completed for microbicide products that are designed to interfere with HIV through nonspecific mechanisms, such as by acting as a surfactant and disrupting the viral structure. Unfortunately, no product has shown encouraging protective results despite demonstrated high antiviral activity in laboratory studies and good safety profiles in early clinical studies (Table 3-6). Current attention in the microbicide field is being directed to ARV-containing products, which have the potential to target the virus specifically (discussed below). An important challenge in conducting microbicide research has been achieving high adherence to daily or coitally dependent products; future studies will explore novel ways to promote and accurately measure adherence. Community engagement has been particularly central to efforts to develop vaginal microbicides against HIV.

ARV-based microbicides: In July 2010, encouraging results from the first ARV-based topical microbicide, 1% tenofovir gel, were reported from the CAPRISA 004 trial (*Science* 2010; 329:1168). The risk of HIV acquisition was reduced by 39% among women randomized to use 1% tenofovir gel twice within 24 hours of having sex compared with women who used a placebo gel. Notably, there was higher efficacy among women who reported >80% adherence in use of the gel. In addition, a significant reduction in incidence of herpes simplex virus type 2 (HSV-2), the etiologic agent of genital herpes, occurred among women who used the tenofovir gel. The CAPRISA 004 results have invigorated the microbicide field, and multiple ARV-based compounds and delivery systems (e.g., vaginal rings) are in clinical development and undergoing evaluation. Disappointingly, in the VOICE study, a multi-country, multi-arm Phase IIb study of vaginal and oral PrEP in women at high risk of acquiring HIV, 1% TDF gel used daily was no better than placebo at reducing HIV transmission. (see Table 3-9).

Table 3-6

Completed Clinical Trials of Nonspecific Vaginal Microbicides

Product	Sponsor; Trial Location(s)	Outcome
Nonoxynol-9 sponge	University of Washington; Kenya	Trend for increased risk of HIV acquisition among women randomized to nonoxynol-9 compared with placebo (RR 1.7)
Nonoxynol-9 film	FHI; Cameroon	No effect on HIV acquisition
Nonoxynol-9 gel	UNAIDS; Benin, Côte d'Ivoire, South Africa, Thailand	Increased HIV incidence among nonoxynol-9 users compared with placebo users (HR 1.5); greater among women who used the product more than the mean of 3.5 times per day
Savvy (1% C31G) gel	FHI; Ghana, Nigeria	Two Phase III trials discontinued prematurely for futility because of lower than anticipated HIV incidence in the trial population. No evidence for protection against HIV or for harm
Carraguard gel	Population Council; South Africa	No statistically significant reduction in HIV incidence among women randomized to active product vs. placebo
Cellulose sulfate gel	CONRAD; Benin, India, Uganda, South Africa FHI; Nigeria	Two Phase III trials stopped when independent data and safety monitoring board of one study detected a trend toward increased HIV risk among women randomized to cellulose sulfate compared with placebo; no increased risk was observed at the time in the other study
PRO 2000 gel	NIH; Malawi, South Africa, United States, Zambia, Zimbabwe MDP; South Africa, Tanzania, Uganda, Zambia	Smaller Phase IIb study (NIH) suggested potentially 30% reduced HIV risk as a result of 1% PRO 2000 gel, but larger Phase III trial (MDP) subsequently found no reduction in risk
Buffergel	NIH; Malawi, South Africa, United States, Zambia, Zimbabwe	No statistically significant reduction in HIV incidence among women randomized to active product vs. placebo

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

HIV Vaccines

No efficacy yet: The search for a vaccine that protects against HIV acquisition has been challenging and has yielded surprising and sometimes perplexing results. Initial strategies focused on candidate vaccines that would elicit neutralizing antibodies, such as recombinant gp120, to envelope glycoproteins, a strategy that was tested through two parallel trials for subtype B and E infections in North America and Thailand, respectively (Table 3-7). No efficacy in reducing HIV acquisition was seen in either trial.

Table 3-7

Completed Efficacy Trials of Candidate HIV Vaccines (Through 2009)

Trial	Candidate Vaccine	Population	Outcome	Comments
AIDSVAX 003 and 004	Recombinant gp120 (subtypes B and E)	MSM in North America and IDUs in Thailand	No reduction in HIV-1 acquisition	
STEP	Adenovirus serotype 5 vector with HIV-1 gag/pol/nef inserts	3,000 high-risk MSM and women in North and South America and Caribbean	1.2-fold increased risk of HIV acquisition in vaccine recipients Trial stopped at first interim analysis Increased risk of HIV associated with lack of circumcision; no significant association with adeno-5 seropositivity among MSM	75% of vaccine recipients developed a CTL response, as determined on the basis of gamma interferon response by ELISpot. Ongoing studies to assess mucosal immune response in uncircumcised men
RV144	Canarypox vector (vCP1251) with recombinant AIDSVAX subtype B/E gp120 boost	Low-risk population in southern Thailand	Vaccine efficacy 31% (95% CI 1–51%) in modified intent-to-treat analysis (nonsignificant trend of 26% efficacy in per protocol analyses)	First potential efficacy "signal" in HIV vaccine trial, although low efficacy No difference in viral set-point in breakthrough infections No humoral or cellular correlate in initial immune correlate assays; additional studies underway

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

The vaccine field moved to candidate immunogens that would stimulate a cellular and humoral immune response, including an HIV-specific CD8 T-cell response that might lower viral load in early HIV infection and thus reduce HIV infectiousness and disease progression in people who became infected in spite of the vaccine. Merck developed a trivalent HIV candidate vaccine by inserting three HIV gene constructs (gag/pol/nef) from subtype B into an adenoviral serotype 5 vector (MRK Ad5). The vaccine was tested through the NIH's HIV Vaccine Trial Network (HVTN), in the STEP trial. The STEP trial was stopped after the first interim analysis, when a modest increased risk of HIV acquisition was observed in the vaccine arm in modified intent-to-treat analyses. This result was surprising and disappointing, given promising nonhuman primate studies and high immunogenicity in the human trials, in which 75% of vaccine recipients had a cytotoxic T-cell response to HIV immunogens (*Lancet* 2008;372:1881&1894). Among MSM vaccine recipients, uncircumcised men had a 2.5-fold increased risk, but this risk was not seen in placebo recipients.

Another study, called Phambili, of the trivalent MRK Ad5 vaccine in a heterosexual population in South Africa was stopped soon after the surprising STEP results. A study of the MRK Ad5 vaccine (HVTN 505) is being conducted among circumcised, Ad5 seronegative MSM to determine whether the MRK Ad5 vaccine is safe and immunogenic and reduces viral set point in patients with breakthrough HIV infections.

Some renewed optimism: The most recently completed HIV vaccine efficacy trial, RV144, was conducted in a low-HIV-prevalence setting in Thailand and utilized a prime-boost approach, with a viral vector (canarypox) to stimulate a T-cell response, followed by antibody boosting with recombinant gp-120. This is the first HIV-1 vaccine study to demonstrate efficacy, albeit modest, with just a 31% reduction in HIV-1 acquisition risk in the primary modified intent-to-treat analysis ($p = .04$) and 26% reduction in the per-protocol analysis (*N Engl J Med* 2009;361:2209). A surprising finding was the suggestion of increased efficacy among lower risk participants, although subgroup findings should be interpreted with caution given the relatively modest number of endpoints (51 and 74 endpoints in the vaccine and placebo arms, respectively), which limits the ability to evaluate the heterogeneity of vaccine protection. Initial analyses of potential immunologic correlates of protection have not identified a correlate.

The Thai RV144 trial has stimulated renewed optimism in the HIV vaccine field and identified multiple questions for research, including additional analyses of other potential immune correlates. Future priorities for the HIV vaccine field include evaluation of new HIV vaccine constructs, such as DNA, modified vaccinia vectors, and adenoviral mosaic vectors (e.g., Ad 25/35). Online updated lists of trials of HIV vaccines are maintained by the International AIDS Vaccine Initiative (www.iavi.org) and the HVTN (www.hvtn.org).

Treatment of Sexually Transmitted Infections

Increased susceptibility to HIV: STIs and other genital tract infections increase susceptibility to HIV. That STIs are important cofactors for HIV acquisition has been established by prospective studies from a variety of populations

examining risk factors for seroconversion. In such studies, women with genital ulcer disease, gonococcal or chlamydial cervicitis, or trichomoniasis were at twofold to fourfold increased risk for HIV infection. Several studies have demonstrated that disturbances in the normal microbial flora of the vagina—including bacterial vaginosis and vaginal candidiasis—may increase HIV risk, but randomized trials of vaginal infection treatment with an HIV endpoint have not been attempted to date. Even the best designed prospective studies have not been able to distinguish among STIs acquired at the same time as HIV infection and those already present that could have increased susceptibility.

STI interventions important to reduce risk, but treatment trials disappointing: Community trials of STI treatment have not found clear HIV reductions. Because of obvious ethical limitations, randomized trials that deny participants STI treatment cannot be conducted. As a result, community intervention trials of improved STI services or mass STI treatment have been conducted to determine the impact of STIs on population wide HIV transmission. Unfortunately, only one of six trials implementing STI treatment has shown a reduction in community HIV incidence. One principal reason is likely related to the stage of the epidemic: STIs play the greatest role in promoting HIV on a community level in early stages of an epidemic, when a core group of highest risk individuals, who are most likely to have concurrent STIs, contributes most to community HIV spread. Nevertheless, STIs clearly increase individual-level risk of HIV acquisition, and STI interventions should remain an important part of reducing HIV risk for individuals and populations, even where HIV is already well established.

Measures to reduce STIs:

- **Encourage** male and female condom use.
- **Encourage** early medical care for diagnosis and treatment of genital tract symptoms.
- **Provide** routine screening for genital tract infections among sexually active women.
- **Discourage** douching, which increases risk of bacterial vaginosis (BV) and pelvic inflammatory disease PID.
- **Teach** patients how to recognize genital herpes recurrences and prodromes; offer treatment to shorten/suppress recurrences.

For HIV infected persons, STI screening and treatment may reduce HIV infectiousness among those who are not taking ART and among those who are on therapy, because those infections may stimulate genital viral replication even in the context of good systemic HIV suppression.

Does suppression of HSV-2 reduce HIV transmission? Genital herpes may contribute substantially to HIV spread, but interventions to interrupt an effect of herpes on HIV risk have proved elusive. HSV-2 is common worldwide: Prevalence is approximately 20% among U.S. women and 50% or higher among populations in sub-Saharan Africa. A meta-analysis concluded that HSV-2 infection increased women's risk for HIV three-fold (*AIDS* 2006;20:73). Among HIV infected persons, symptomatic and asymptomatic HSV-2

reactivation increases HIV concentrations in the blood and genital tract, suggesting that HSV-2 activity enhances HIV infectiousness. Strong biologic plausibility exists for HSV-2 to enhance HIV susceptibility and infectiousness: HSV-2 causes genital ulcers that may serve as a portal for HIV entry or exit, and asymptomatic HSV-2 reactivation (occurring on average on 20% of days, without genital ulcers) may draw HIV target cells to the genital tract.

Acyclovir and the related compounds valacyclovir and famciclovir are routinely used as episodic treatment for symptomatic genital ulcer disease due to HSV-2 and as daily suppressive therapy to decrease the frequency of symptomatic HSV-2 reactivation and asymptomatic genital HSV-2 shedding. Unfortunately, two randomized trials of daily acyclovir HSV-2 suppressive therapy to reduce HIV acquisition and one trial of suppressive therapy to decrease HIV transmission from HIV infected persons to their sexual partners failed to demonstrate a protective effect of HSV-2 treatment. The results of these trials suggest that more potent and long-lasting HSV-2 suppressive therapies or, ultimately, a prophylactic HSV-2 vaccine might be needed to intervene in the relationship between HSV-2 and HIV.

While awaiting new HSV-2 prevention modalities, women with a history of genital herpes or with serologic evidence of HSV-2 infection should be taught how to recognize prodromes and recurrences. Suppressive herpes antiviral therapy should be considered in women with frequent recurrences, including those who report high-risk sexual behavior.

Antiretroviral-Based HIV Prevention Strategies

The role of ART in HIV prevention is a topic of significant public health interest. ART for HIV prevention comprises both treatment of HIV infected persons to decrease their infectiousness and post- or pre-exposure prophylaxis (PEP and PrEP, respectively) by HIV uninfected persons to prevent acquisition. Studies have now established potential efficacy for each of these approaches, although there is debate about how to implement preventive ART if it is proven to reduce HIV risk. Nonetheless, scientists and public health officials worldwide anticipate that ART-based prevention strategies may prove to be successful new ways to prevent HIV spread.

ART for Prevention

ART reduces HIV transmission risk: The amount of HIV in plasma is a primary determinant of the risk of sexual HIV transmission. In most people, ART reduces HIV plasma concentrations to undetectable levels within 6 months of initiation, and seminal and cervicovaginal HIV concentrations are also reduced to undetectable levels in most people as well. Use of ART during pregnancy, labor, and for the newborn has been responsible for the remarkable success in virtually eliminating mother-to-child HIV transmission in the United States.

Substantial reduction in the quantity of plasma and genital HIV in persons initiating ART translates into markedly reduced risk of HIV transmission to sexual partners. A meta-analysis of data from five prospective observational studies of HIV serodiscordant couples, some unpublished, found only five cases of HIV transmission to sexual partners in 1,098 person-years from HIV infected persons receiving ART; this finding is consistent with an infection rate of <1% per year (*AIDS* 2009:23:1397). Community-level data from Vancouver, British Columbia, has shown a significant decline in new HIV cases coincident with increased ART use (*Lancet* 2010;376:532).

Data from HPTN 052, a randomized clinical trial designed to evaluate ART for prevention of sexual transmission among serodiscordant couples, found that earlier initiation of ART (at CD4+ counts 350–550 cells/mm3) reduced HIV transmission to the uninfected partner by 96%. (*N Engl J Med* 2011;365(6):493–505). This study has major implications for the use of ART for prevention among serodiscordant couples, particularly those wishing to conceive or unable/unwilling to use safer sexual practices. The U.S. Department of Health and Human Services guidelines now recommend ART for all HIV-infected individuals for the prevention of transmission of HIV (both for heterosexual transmission and for other transmission risks). (Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Section accessed 5/16/13)

In the observational studies that have been reported to date, the follow-up time on ART was short relative to the lifetime duration of treatment that will be required of persons who start ART. Most patients who initiated ART did so at CD4+ counts <200 cells/mm^3, when clinical symptoms may have provided a greater impetus for adherence. It is essential to obtain reliable information about the comparative long-term transmission benefits and behavioral risks associated with ART, particularly when it is initiated at higher CD4+ cell levels.

ART does not eliminate transmission risk: An important research finding is that genital HIV shedding may not be fully suppressed among people receiving ART, even those with undetectable plasma viral loads, suggesting that ART may not completely eliminate transmission risk. In addition, the phenomenon of nonadherence means that not everyone prescribed ART will achieve reduced infectiousness. Healthcare providers should counsel patients on ART that the risk of transmission is not zero and that patients on ART have transmitted HIV to a partner, even when the patients had undetectable plasma HIV levels. Recommendations to women with HIV should stress the importance of consistent condom use to decrease HIV transmission risk.

Pre-exposure prophylaxis (PrEP) (see Table 3-9): The rationale for PrEP grows out of successful HIV prevention with use of ART prophylaxis for infants born to HIV-1–infected women and from nonhuman primate studies demonstrating that ARVs given prior to high-dose mucosal simian HIV challenge can provide partial or even full protection against infection (*PLoS Med* 2008:5:e28). PrEP offers advantages over post-exposure prophylaxis (PEP) for sexual and IDU exposures, because the efficacy of PEP declines rapidly if not initiated within

1 to 2 days after an exposure, and PEP is likely impractical for highest risk individuals (e.g., sex workers, members of HIV serodiscordant couples), who may have repeated exposures.

Providing ARVs orally to an uninfected female partner may offer some additional protection against HIV transmission from an infected male partner during attempts to conceive, but study results to date have been mixed.

A Phase III study of daily oral TDF/FTC in uninfected MSM (iPrEX) reported a 44% overall reduction in HIV acquisition compared with placebo; effectiveness was significantly affected by adherence (*N Engl J Med* 2010;363(27):2587; *N Engl J Med* 2010;363(27):2663). In the Partners PrEP study, conducted in Kenya and Uganda among more than 1400 HIV-serodiscordant couples, the use of daily TDF or daily TDF/FTC by the uninfected partner was found to have efficacy of 67% and 75%, respectively, compared with placebo in reducing HIV transmission (with reported 97% adherence by returned pill count, but only 81% of those assigned to the active-treatment arm had detectable blood levels of the study drug) (*N Engl J Med* 2012;367(5):399). Within a subgroup of those who received TDF/FTC and whose plasma drug levels were tested, measurable concentrations of TDF were associated with a 90% reduction in risk compared with placebo. In the TDF2 trial, conducted in Botswana, TDF/FTC given to 1200 HIV uninfected heterosexual men and women reduced transmission by 62% compared with placebo, with 84% adherence by returned pill count (*N Engl J Med* 2012;367(5):423).

However, the FEM-PrEP clinical trial conducted in high-risk uninfected African women, found no efficacy with daily oral TDF/FTC (*N Engl J Med* 2012;367(5):411; Microbicide Trials Network; 2011. Available at http://www.mtnstopshiv.org/node/3619. Accessed 9/3/2012). Medication adherence was very low in the FEM-PrEP trial; the study drug was detected in the blood of <27% of women who acquired HIV and in <38% of matched uninfected controls.

The VOICE (Vaginal and Oral Interventions to Control the Epidemic) Study was designed as a five-arm, double-blinded study in which heterosexually-active women were first randomized to receive either gel or oral PrEP, and then within each group, randomly assigned to either tenofovir 1% topical gel or placebo gel; or to oral TDF, oral TDF/FTC or oral placebo. Unfortunately, no study drug significantly reduced the risk of HIV acquisition and again adherence was low; detectable drug levels were found in less than one-third of those tested and randomized to active drug. (20th Conference on Retroviruses and opportunistic Infections, Atlanta, GA,Abstract 26LB, 2013; Microbicide Trials Network; 2011. Available at http://www.mtnstopshiv.org/node/3619. Accessed 9/3/2012). Therefore, it is likely that adherence is a key factor in the discrepant results of these studies (*AIDS* 2012;26(7):F13).

In studies of PrEP to date, safety and tolerability were excellent (although nausea and vomiting were more common in the first 1–2 months among those taking TDF/FTC) and limited resistance was observed in seroconverters. Twice-weekly and coital dosing of TDF/FTC, as well as longer-acting formulations, intravaginal rings, and new candidate ARVs, are currently being evaluated for PrEP.

In July 2012 the FDA approved a label indication for TDF/FTC for reduction of risk for sexual acquisition of HIV infection among adults, including heterosexual women. In August 2012 the CDC issued the following interim guidance for clinicians considering the use of PrEP for HIV prevention in heterosexually active adults, particularly those with known HIV-infected partners (*MMWR* 2012; 61(31):586): 1) TDF/FTC is contraindicated for PrEP in persons with unknown or positive HIV status; 2) in women and men at very high risk for acquiring HIV from penile-vaginal sex, daily doses of TDF/FTC can be safe and effective in reducing the risk of HIV infection; 3) PrEP use may be one of several options to help protect the HIV-negative partner in serodiscordant couples during attempts to conceive (*Am J Obstet Gynecol* 2011;204:488); and 4) women of reproductive age should have a documented pregnancy test before beginning PrEP and at regular intervals while being prescribed PrEP. If women become pregnant while being prescribed PrEP, providers should discuss currently available information regarding the potential risks and benefits of continuing PrEP to enable informed decision making. If a woman takes PrEP while pregnant, providers are encouraged to prospectively and anonymously submit information about the pregnancy to the Antiretroviral Use in Pregnancy Registry (http://www.apregistry.com/who.htm; accessed 9/4/2012). In addition, providers should counsel patients that the efficacy of PrEP is highly dependent on adherence and that its long-term safety in HIV-uninfected adults or following fetal exposure has not yet been determined.

PrEP should be delivered as part of a comprehensive set of prevention services, including risk-reduction and ready access to condoms. Table 3-10 summarizes current CDC guidance to health care providers providing PrEP for heterosexually active adults.

Nonoccupational Postexposure Prophylaxis

PEP may reduce likelihood of HIV infection after a high-risk exposure. Theoretically, PEP can prevent HIV transmission either by blocking initial viral infection of cells or by inhibiting viral dissemination, thereby allowing for immune clearance of a small number of already-infected cells. The data for efficacy of ARVs as PEP come primarily from a single case-control study of healthcare workers who experienced occupational HIV exposures, mostly through needlestick injuries. Those who received zidovudine had an 80% lower likelihood of becoming infected; this study, however, was limited by a small sample size, retrospective design, and other potential sources of bias. The rationale for PEP after sexual exposure is largely that the probability of infection after a single unprotected sexual exposure is similar to that after a needlestick exposure (i.e., ~0.1%; slightly higher for receptive anal intercourse). Animal models suggest that PEP may be effective for mucosal and needle exposures, particularly when used within 24–48 hours. Ethical and pragmatic considerations make it unlikely that a randomized trial of PEP will be conducted. The effectiveness of PEP is likely to be influenced by time to initiation of treatment, duration of treatment, size of inoculum, and drug resistance profile of the virus in the source individual. Although the risks and

benefits of PEP for sexual exposure remain to be fully defined, studies suggest that provision of PEP for nonoccupational exposures is feasible (*J Infect Dis* 2001;183:707).

Considerations: If approached by anxious patients who have recently had a high-risk sexual exposure, the healthcare provider must weigh the likelihood of HIV infection in the contact, ART history if the contact is known to be HIV infected, the specific nature and timing of the exposure (initiation of PEP within 48 hours is important, given findings from animal studies and breakthrough infections with later initiation), and the possible risks of drug toxicity or side effects. CDC guidelines recommend two or three ARV medications, depending on the intensity of the exposure, for 4 weeks for occupational and nonoccupational exposures having at least moderate HIV risk (Table 3-8 and *MMWR* 2005;54:1). Other considerations should include evaluation and consideration of empiric treatment for other STIs, emergency contraception when appropriate, and possible indication for hepatitis B vaccination. Informed consent is recommended when administering PEP.

Table 3-8

Elements of NonOccupational Postexposure Prophylaxis Against HIV Infection

Factors to Assess	Considerations	Recommendations
Exposure risk	**Substantial risk** for HIV exposure, defined as exposure of vagina, rectum, eye, mouth, nonintact skin, or percutaneous contact with blood, semen, vaginal secretions, rectal secretions, breast milk, or any bodily fluid contaminated with blood **Negligible risk** of HIV exposure if exposing fluid is urine, nasal secretions, saliva, sweat, or tears	**nPEP recommended** for exposures with substantial risk from a known HIV infected source **nPEP not recommended** for exposures with negligible risk, regardless of known or suspected HIV status of the source
Source of exposure	HIV infected vs. unknown HIV status (unknown HIV status of source frequently reported by persons seeking nPEP).	nPEP assessment on case-by-case basis for exposures with substantial risk from a source of unknown HIV status
Timing	nPEP efficacy for preventing HIV likely declines substantially as time since exposure elapses. Animal models indicate initiation should occur within 48–72 h	nPEP not recommended >72 h after exposure occurs

Table 3-8 continues on the next page

Table 3-8 *continued*

Elements of NonOccupational Postexposure Prophylaxis Against HIV Infection

Factors to Assess	Considerations	Recommendations
Initiate ARV nPEP	No evidence indicates that specific ARV agents improve efficacy for HIV prevention. In addition, no evidence indicates whether combinations of 2 vs 3 medications have different efficacy for preventing HIV. Recommended ARV medications for nPEP have been chosen on the basis of adherence and tolerability, subsequent to experience with their use for treatment of HIV infected persons.	Commonly used agents include • Efavirenz + lamivudine or emtricitabine + tenofovir or zidovudine • Atazanavir + lamivudine or emtricitabine + tenofovir (with ritonavir) or zidovudine • Lopinavir/ritonavir + lamivudine or emtricitabine + zidovudine
Testing	HIV testing at baseline is essential to confirm whether the person initiating nPEP is already HIV infected; however, nPEP should be initiated before results of HIV testing are obtained. HIV testing, including viral load and resistance testing of source, if available, should be done as well.	HIV testing at nPEP initiation and 4–6 wk, 3 mo, and 6 mo after exposure. Laboratory assessment of safety (complete blood count, liver enzymes, creatinine, as well as pregnancy testing) recommended at time of nPEP initiation and during nPEP. Additional testing for hepatitis B and C infection and STIs should be done.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Not a substitute for risk reduction: PEP should not be administered for exposures with low transmission risk or when care is sought beyond the period of 72 hours postexposure. PEP should be considered strongly for persons who have been sexually assaulted or when a condom break during sex occurs in an HIV serodiscordant couple (especially if the positive partner is not on antiretroviral treatment or does not have an undetectable viral load). PEP is not a substitute for risk reduction and should not be considered a form of primary HIV prevention. Patients presenting for possible PEP should have reinforcement of the importance of initiating, resuming, or improving risk reduction activities.

Table 3-9

Efficacy Trials of Oral and Topical Pre-Exposure Prophylaxis

	Study Population	Location	Intervention	Outcome	Comments
CAPRISA 004	900 sexually active women	South Africa	1% topical TFV gel (dosed coitally)	39% protection with TFV gel	54% effectiveness with >80% gel adherence; high vaginal TFV concentrations needed at exposure (*Lancet* 2011; 378:279)
TDF2	1219 sexually active adults; 55% male, 45% female; 94 % unmarried; approximately 90% age 21–29 years	Botswana	Daily oral TDF/FTC	63% protection	>30% did not complete study; cannot draw definitive conclusions for women and men separately
Partners PrEP	4758 heterosexual serodiscordant couples; 38% negative-female, 68% negative-male partner; 98% married; median age 33 years	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF or TDF/FTC	67% protection with TDF alone; 75% protection with TDF/FTC	Discordant couples may be a distinct, unique population
FEM-PrEP	1951 heterosexual women at high risk of infection aged 18–35 years	Kenya, South Africa, Tanzania	Daily oral TDF/FTC	Trial discontinued for futility in April, 2011	Adherence assessment with monthly clinical samples to measure drug concentration is pending
VOICE (MTN-003)	5029 heterosexual women aged 18–45 years in high-prevalence areas	Uganda, South Africa, Zimbabwe	Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel	No study drug significantly reduced the risk of HIV acquisition: HIV incidence was 5.7 per 100 person years. Effectiveness was –48.8% for TDF; –4.2% for TDF/FTC; and 14.7% for TDF gel.	Adherence to study drugs was low: TFV was detected in 30% of the oral TDF arm; 29% in the oral TDF/FTC arm; and 25% in the TDF gel arm.

Table 3-9 continues on the next page

Table 3-9 *continued*

Efficacy Trials of Oral and Topical Pre-Exposure Prophylaxis

	Study Population	Location	Intervention	Outcome	Comments
HPTN 052	1763 heterosexual serodiscordant couples; 50% negative-female, 50% negative-male partner; 94% married; 61% aged 26–40 years	Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand	Immediate or delayed ART in HIV-infected partner	96% protection	Suppression of viraemia on therapy assured by routine monitoring

TDF = tenofovir disoproxil fumarate. TFV = tenofovir. TFV-DP = tenofovir diphosphate. FTC = emtricitabine. ART = antiretroviral therapy.

Adapted from Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States. (Note: only trials including women were included).

Table 3-10

Interim guidance for provision of PrEP for the prevention of HIV infection in heterosexually active adults who are at ongoing, very high risk for sexual acquisition of HIV infection*

Before initiating PrEP

Determine eligibility

- Document negative HIV antibody test immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection or reports unprotected sex with an HIV-positive person in the preceding month.
- Determine if women are planning to become pregnant, are currently pregnant, or are breastfeeding.
- Confirm that patient is at ongoing, very high risk for acquiring HIV infection.
- If any sexual partner is known to be HIV-infected, determine whether receiving antiretroviral therapy; assist with linkage to care if not in care or not receiving antiretroviral therapy.
- Confirm that calculated creatinine clearance is ≥60 mL per minute (Cockcroft-Gault formula). [*Nephron* 1976;16:31]).

Other recommended actions

- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision regarding prescribing PrEP.
- Screen and treat as needed for sexually transmitted infections (STIs).
- Disclose to women that safety for infants exposed during pregnancy is not fully assessed but no harm has been reported.
- Do not prescribe PrEP to women who are breastfeeding.

Beginning PrEP medication regimen

- Prescribe TDF/FTC (300 mg/200 mg) daily
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected. For women, ensure that pregnancy test is negative or, if pregnant, that the patient has been informed about use during pregnancy.
- If active hepatitis B infection is diagnosed, consider using TDF/FTC, which may serve as both treatment of active hepatitis B infection and HIV prevention.
- Provide risk-reduction and PrEP medication–adherence counseling and condoms.

Follow-up while PrEP medication is being taken

- Every 2–3 months, perform an HIV antibody test (or fourth generation antibody/antigen test) and document negative result.
- At each follow-up visit for women, conduct a pregnancy test and document results; if pregnant, discuss continued use of PrEP with patient and prenatal-care provider.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
- Every 2–3 months, assess risk behaviors and provide risk-reduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STIs as needed.
- Every 6 months, test for bacterial STIs, even if asymptomatic, and treat as needed.
- Three months after initiation, then every 6 months while on PrEP medication, check serum creatinine and calculate creatinine clearance.

Table 3-10 continues on the next page

Table 3-10 *continued*

Interim guidance for provision of PrEP for the prevention of HIV infection in heterosexually active adults who are at ongoing, very high risk for sexual acquisition of HIV infection*

On discontinuing PrEP (at patient request, for safety concerns, or if HIV infection is acquired)

- Perform HIV test(s) to confirm whether HIV infection has occurred.
- If HIV-positive, order and document results of resistance testing, establish linkage to HIV care.
- If HIV-negative, establish linkage to risk reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B infection.
- If pregnant, inform prenatal-care provider of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and breastfeeding.

*E.g., those with partners known to have HIV infection.

MMWR 2012;61(31);586–589

Possibilities and Challenges of ART-Based Prevention

A question of resources: During the past decade, ART has become available to populations worldwide—a tremendous health advance that has resulted in substantial decreases in morbidity and mortality risk for those on therapy. Nonetheless, in 2006, for each person started on ART worldwide, four were newly infected. Moreover, finite resources have limited ART availability worldwide, even for infected persons with clinical AIDS, who are most desperately at need. Implementing ART-based prevention strategies will require sufficient resources and targeted delivery to achieve a population-level impact. Pharmacovigilance systems to monitor ARV resistance will be critical for persons who become infected despite PEP or PrEP and might develop resistant virus and for those who are nonadherent to PrEP or ART.

Combination Strategies for HIV Prevention

Maximizing prevention efforts: No single standalone HIV prevention intervention is a panacea, and in the absence of a fully protective prophylactic vaccine, it is not likely that a single intervention will reverse the global epidemic. However, a number of HIV prevention strategies have been demonstrated to provide some protection against infection, thereby offering the possibility that combining several partially protective strategies might have additive or synergistic effects in reducing HIV on a population level. Analogous to the need for combination ART for treatment, researchers and clinicians are increasingly recognizing that combination HIV prevention strategies might maximize HIV prevention effects. Multicomponent packages of evidence-based biomedical, behavioral, and structural interventions must be appropriate, acceptable, and deliverable to priority subpopulations.

Population-level prevention: A core tenet of combination HIV prevention is that understanding the patterns and risks for HIV transmission at a population level guides the design of an optimal package of prevention interventions. On a population level, a combination prevention package that brings together interventions that target both HIV uninfected persons (e.g., behavioral risk reduction) and HIV infected persons (e.g., ART initiation and adherence) may achieve the greatest benefits. A key component of combination HIV prevention is increasing knowledge of HIV serostatus. For HIV infected persons, a strategy combining universal HIV testing with immediate linkage to ART has been named *Test and Linkage to Care*.

Interest in this approach was stimulated in large part by publication of a hypothetical modeling exercise in a high-prevalence African country. The results indicated that near-universal uptake of ART and optimal adherence, regardless of CD4+ cell levels, could reduce HIV incidence to <1 case per 1,000 population within 10 years of full implementation of the strategy and reduce HIV prevalence to <1% within 50 years (*Lancet* 2009;373:48).The feasibility of implementing such an approach and the realism of the original model's assumptions have been widely debated, given the challenges to date in (1) achieving high testing rates, particularly among some hard-to-reach populations; (2) addressing barriers to linking patients with HIV care; and (3) finding resources for increased testing and ART. Ongoing HIV epidemics in the United States and other high-income countries that have approximately 15 years of widely available ART are a reminder of the continued need to identify barriers to reaching HIV infected individuals who are not aware of their status. Also needed is a focus on secondary transmission risk behaviors, because ART availability alone will not curb the epidemic. Demonstration projects to increase HIV testing and triage to HIV care on a population scale are being evaluated in the Bronx, NY, and Washington, DC, as well as in international settings.

Conclusion

Prevention of HIV Remains a Critical Priority

The most effective available strategies for prevention are HIV counseling and testing, behavioral interventions that support abstinence or reduce risk taking, and condom use. While new strategies are being tested, healthcare providers must continue to assess and identify women at risk for acquiring or transmitting HIV and assist them in reducing their risk by setting and following through on achievable risk reduction plans.

Chapter 4:
Primary Medical Care

Judith Feinberg, MD
Professor of Medicine
University of Cincinnati College of Medicine

The author declares no conflict of interest

Chapter 4: Primary Medical Care

Chapter 4 at a Glance

Essential Principles of Care for the HIV Infected Woman

This chapter focuses on the essential principles of care for the HIV infected woman. Cutting-edge treatment strategies currently being studied will be mentioned but not described in detail. To be truly useful, we indicate the general directions in which this field is moving and how to access updated information.

Several studies have demonstrated that positive clinical outcomes are a function of the clinician's experience in caring for HIV infected patients (*Cochrane Database Syst Rev* 2011;6:CD003938). Nonspecialists are urged to seek expert advice and consultation whenever there is any question about the best way to manage a specific patient. This is especially important in the settings of antiretroviral (ARV) treatment failure and advanced HIV disease when patients are vulnerable to multiple simultaneous opportunistic processes.

There is as yet no compelling evidence that the clinical course of HIV infection in women differs significantly from that in men, with the obvious exception of the associated gynecologic conditions and obstetric issues (described in Chapters 6 and 8). Although recent data have indicated that women may have lower HIV viral loads (VLs) than men with an equivalent degree of immunosuppression, this does not appear to confer benefit in terms of either overall survival or complication-free survival. At present, the approach to the management of HIV infected women is the same as for men. With prolonged survival now possible, general preventive and health maintenance strategies, such as smoking cessation, control of hypertension, reduction of cardiovascular (CV) risk factors, and routine screening for malignancy (cervical, breast, colon), are all part of routine care for HIV infected women.

Initial and Ongoing Evaluation

History and Counseling/Education

A comprehensive database is valuable to the primary caregiver in assessing a patient's current status and in formulating a management plan. At their initial encounter for HIV care, most patients are anxious and frightened. The ability to empathize, share knowledge without being patronizing, provide reassurance, and remain nonjudgmental are essential to gaining a patient's trust and obtaining accurate information (see Chapter 2, **Approach to the Patient**). The areas of exploration detailed in Table 4-1 are of particular importance in caring for patients with HIV disease and deserve special attention.

Table 4-1

Initial HIV History

Areas of Focus	Areas of Exploration and Key Points
HIV diagnosis	• When was first positive HIV test? Why was test done? • Can source of HIV infection be identified? Has source patient been treated for HIV? If so, are HIV medicines known? (Valuable if patient has acquired drug-resistant infection) • IDU? Sex with IDU or bisexual male? Trading sex for drugs, money, or shelter? Current partner(s) HIV infected or at risk? (Many women are unaware of partner's risk or HIV status.) • Previously tested for HIV? If prior test(s) negative, look for evidence of acute seroconversion syndrome within past 6–9 mo (e.g., flu-like syndrome, rash, lymphadenopathy).
HIV treatment history	• Pre-therapy CD4+ cell count and HIV RNA PCR quantification (i.e., VL) • Specific treatment history, including during pregnancy: specific drugs and regimen changes (when/why), problems with adherence, response to therapy, adverse effects, history of treatment-limiting tolerance to any agent, other barriers to taking ARVs, treatment interruptions (including after delivery) • History of resistance testing and availability of results • Past OI prophylaxis • HIV-related hospitalizations or any HIV-associated diagnoses
Other infectious diseases history	• Identify history of STIs: syphilis, gonorrhea, chlamydia, HSV, PID, trichomoniasis, anogenital warts • Identify history of other infectious diseases: TB, HAV, HBV, HCV, history of chicken pox or shingles • Vaccination history: usual childhood illnesses, HAV and/or HBV, pneumococcal infection and influenza, HPV
OB-GYN history (see Chapter 6)	• Date of most recent evaluation and results • Pap smear: history of abnormal results, date of most recent • Menstrual history/LMP • History of gynecologic problems (e.g., fibroids, endometriosis, recurrent yeast infections), previous gynecologic surgery (e.g., hysterectomy, tubal ligation, LEEP, cervical conization) • History of infertility or difficulty getting pregnant • OB history: dates and outcomes of pregnancies, OB complications, future childbearing plans and/or desires • Menopause: vasomotor symptoms, vaginal dryness, post-menopausal bleeding • Last mammogram, history of abnormal mammogram
Other pertinent medical history	• Hypertension • Chronic kidney disease • Diabetes • Cardiovascular disease • Thromboembolic disease • Asthma or COPD • Premalignant or malignant conditions (e.g., cervical, breast, colon, ovary) • Osteopenia and/or osteoporosis
Surgical history	• Prior surgical procedures, indications, complications

Table 4-1 *continued*

Initial HIV History	
Areas of Focus	**Areas of Exploration and Key Points**
Sexual practices	• Use of condoms (male and/or female) • Use of contraception other than condoms • Consistency of use of condoms and other contraception • Number of current sexual partners and their HIV status (if known) • Sexual activity with men, women, or both • History of anal sex
Current medications	• Prescription • OTC remedies • History of and attitude toward regular medication use • Use of nontraditional medications for HIV or other conditions • Drug allergies
Mental health history	• Past and current problems • Depression (trouble sleeping, early awakening, change in appetite, loss of interest in usual activities, anhedonia)
Family history	• Age and health of children, including HIV test results, if performed • HIV in other family members • Other medical diagnoses in family (see above list)
Social history	• Where was patient born and raised? • Where and with whom does patient live? Relationship to others in the household? • Food or housing insecurity • Childcare responsibilities • History of or current domestic violence • Presence of pets, especially reptiles (salmonellosis) and kittens (toxoplasmosis) • Extent of formal education • Occupational history and potential toxic exposures • Travel history • Cigarette, alcohol, and illicit drug use, past and current; misuse of prescription drugs
Sources of support	• To whom has the patient disclosed her diagnosis? What were the reactions? • Does the patient have friends or family to whom disclosure seems possible either now or in the future? • Other HIV infected family members or friends? • Are family or friends able to care for the patient's children in the event of acute illness? • Is the patient employed, and, if so, full or part time? Able to confide in supervisor? • Does the patient have health insurance?

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Counseling and education are important elements of the therapeutic bond; the information about HIV that the clinician shares with the patient is just as important as the information the clinician learns about the patient in the history-taking process. Because education about HIV entails conveying a large amount of information, it is best broached initially and then reintroduced and reinforced at appropriate intervals. Many patients are in a state of shock following their diagnosis or may be suffering from situational depression or fear of a partner's response. Clinicians should be kind and patient and should take adequate time with the patient; schedule at least an hour for the initial visit and schedule an early second visit. Assure patients that they will be supported and cared for. Encourage patients to develop good relationships with the office or clinic nurse and ensure that patients are able to reach someone when they have questions, complaints, or symptoms, especially when starting antiretroviral therapy (ART). Convey information in lay language at a level of complexity appropriate to the patient's ability to comprehend. Remember that a patient's formal educational level may not necessarily correlate with her ability to understand complicated medical concepts. Concepts of particular importance for review with a new patient are described in Table 4-2.

Table 4-2

HIV Information for New Patients

Topic	Areas of Discussion
HIV pathogenesis	• What are CD4+ lymphocytes and why are they important? • How does HIV infection affect CD4+ cells?
Natural history of HIV disease	• How is "AIDS" different from "HIV infection" or "HIV disease"? • Without therapy, what is the typical time course between acquisition of HIV and the development of HIV-associated problems and/or AIDS?
Monitoring activity of HIV disease	• What do CD4+ cell counts and HIV VL tests measure? • How are they used and how often will they be repeated?
Goals of HIV disease management	• What does "maintain or improve the immune system" mean and why is it a goal of therapy? • How is HIV replication controlled and why is this important? • How can medication side effects be avoided or minimized? • What are OIs and how are they prevented or treated?
Principles of HIV treatment	• Describe the value of combination therapy in preserving health and prolonging life • Underscore the importance of adherence to avoid treatment failure and the development of resistance • Discuss decision-making about starting treatment

Table 4-2 *continued*

HIV Information for New Patients

Topic	Areas of Discussion
Preventing spread of HIV infection	• Notification of sexual partners and drug use contacts • Practicing safe sex • Safer injection drug use practices, including needle exchange programs and the use of diluted bleach to sterilize injection equipment • Be informed of the prevention benefit of ART, namely, that if taken as prescribed it can substantially reduce their risk of transmitting uninfected sexual (and likely also needle-sharing) partners • Be informed about PEP and PrEP for HIV-uninfected sexual partners and under what circumstances they might consider employing either strategy
"Prevention for Positives"	• Keep bleach readily available in the household to clean up blood from accidents • Describe appropriate wound care for injuries • Reassure the patient about the difficulty of transmitting HIV to casual contacts and to family members, even in the close context of everyday family life
Health maintenance	• Cancer screening (Pap smear, mammogram, colonoscopy) • Immunizations • TB screening • Smoking cessation • Lipid screening • Diet, exercise, weight management • Dental and eye care • Bone density screening

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Lastly, because HIV is a chronic, life-threatening disease that still carries a social stigma, the clinician plays a key role in exploring mental health and psychosocial needs; helping patients identify potential sources of support; and referring patients for additional medical, psychiatric, and/or social services.

Depending on the initial history, a variety of issues may need to be explored in an ongoing fashion (at each visit or periodically). Such issues include new or worsening symptoms; interval sexual practices and other risk behaviors; interval menstrual history; a review of all medications, including complementary or over-the-counter products; adherence to ART; disclosure and/or social support issues; and others as indicated.

Physical Examination

The examination may yield clues to specific HIV-associated conditions. Perform a complete physical examination and track vital signs, particularly temperature and weight. Pay special attention to the areas outlined in Table 4-3.

Table 4-3

Physical Examination of the HIV Infected Woman

Area	Key Focal Points
General	• Evidence of wasting, often prominent at the temples • Fat redistribution syndromes, including buffalo hump, fatty deposits in neck, enlarged breasts, and truncal (visceral) obesity; may coexist with or be separate from marked subcutaneous fat loss in the extremities, face, and buttocks
Eyes	• Purplish spots of KS on conjunctival surfaces (rare in women) • Petechiae • Funduscopy: "cotton wool" spots, i.e., microinfarcts of the retinal nerve fiber layer due to occlusion of retinal capillaries • CMV retinitis: typical "eggs and ketchup" appearance of infiltrates and hemorrhages in advanced HIV disease • Visual-field deficits, common in CMV retinitis, may be uncovered with simple field testing by confrontation
Oropharynx	• No examination of an HIV infected person, regardless of disease stage, should be considered complete without a careful oral exam, which often yields the earliest physical evidence of HIV infection • Thrush: white plaques on buccal mucosa, palate, tongue, or posterior pharynx that are readily scraped off with tongue blade • Oral hairy leukoplakia: furry white plaques most often found on the lateral margins of the tongue that cannot be scraped off • Purplish spots or plaques on mucosal surfaces consistent with KS and with bacillary angiomatosis • Ulcers (HSV, CMV, aphthous)
Lymph nodes	• Generalized adenopathy: nontender or minimally tender; may wax and wane; most often related to HIV infection itself, but may also indicate lymphoma or disseminated OIs • Localized adenopathy: may be sign of malignancy or infection, e.g., enlarged axillary nodes in breast cancer, inguinal adenopathy in vulvar cancer or LGV • MAC • Extremely tender or unilaterally enlarged lymph nodes: should trigger an evaluation for specific etiology
Heart	• S3 gallop: may indicate heart failure, possible cardiomyopathy
Lungs	• Fine, dry "cellophane" rales: classic for PCP, but are a late finding and may be absent
Abdomen	• Organomegaly: may reflect disseminated infection with MAC, TB, disseminated endemic mycoses such as histoplasmosis, or lymphoma • Splenomegaly: may be associated with ITP
Pelvic examination (including digital rectal exam) (see Chapter 6)	• Genital ulcers: may reflect HSV; syphilis; other infections, including CMV, TB; aphthous or invasive vulvar cancer • Genital warts: HPV • Abnormal vaginal discharge: generally caused by infectious vaginitis (candidiasis, bacterial vaginosis, trichomoniasis)

Table 4-3 *continued*

Physical Examination of the HIV Infected Woman

Area	Key Focal Points
Neurologic	• Motor deficits: may reflect space-occupying lesions of the CNS, e.g., toxoplasmosis, CNS lymphoma, PML; may be due to neurosyphilis • Symmetrical, distal sensory deficits (especially decrease or loss of vibratory or proprioceptive sensation): typically affect feet more than hands; indicate peripheral neuropathy due to either HIV disease or drug toxicity from some nucleoside analogs (e.g., ddI or d4T) • Poor short-term memory, diminished concentration, sensorimotor retardation: hallmarks of AIDS dementia complex (HIV encephalopathy) • Dysphoric mood and flat affect: may be signs of depression
Skin	• Careful examination of skin often yields early clues about HIV infection and should be performed regularly • Pruritic papular eruptions: early manifestation; may be sign of bacterial folliculitis, eosinophilic folliculitis, or scabies • Pearly papules with central umbilication: typical of *Molluscum contagiosum* • Painful vesicular rash: may be HSV; in a dermatomal distribution is usually shingles (VZV) • Seborrheic dermatitis: may be severe; appears as greasy, scaly white, and/or erythematous areas on face, especially nasolabial fold and eyebrows; may be confined to scalp and hairline • Psoriasis: common scaling lesion • Purplish macules or plaques: may be either KS or bacillary angiomatosis; similar to appearance on mucosal surfaces; in dark-skinned individuals KS may appear more brown than purple

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Laboratory Testing and Other Monitoring

Initial HIV Diagnosis

The U.S. Centers for Disease Control and Prevention (CDC) recommends that voluntary, opt-out HIV testing be made a routine part of medical care for all patients aged 13–64 years who have been sexually active (*MMWR Recomm Rep* 2006;55(RR-14):1). Under current CDC recommendations, a separate signed consent and more extensive pretest counseling are not considered necessary. These changes are meant to simplify the process and promote universal testing; however, the need for specific consent or counseling is ultimately determined by relevant state laws.

HIV antibody tests: Standard HIV screening involves detecting antibodies to HIV, generally with an enzyme immunoassay (EIA). A reactive EIA should be followed by a confirmatory test, most commonly Western blot or, less commonly, immunofluorescence assay (IFA), which detects specific antibodies to HIV-1 proteins. CDC criteria for a positive Western blot are a band pattern indicating antibodies to two of the following proteins: p24, gp41, and gp120/160. A final diagnosis of HIV should not be given unless both screening and confirmatory tests are positive or reactive; with EIA alone the false-positive rate is 2%. In patients with infection >12 weeks after transmission, the sensitivity of this screening algorithm is 99.5%; specificity is 99.99% (*Am J Med* 2000;109(7):568).The average time from transmission to a reactive EIA is 10–14 days; seroconversion may be delayed to 3–4 weeks or longer in rare circumstances, but essentially all HIV-1 infected patients will seroconvert within 6 months (*Am J Med* 2000;109(7):568). A false-negative test can occur if testing is performed in the window period (i.e., after infection occurs but prior to the development of detectable antibodies). Agammaglobulinemia is a rare cause of a false-negative test.

The test may be reported as indeterminate if the EIA is positive but only a single band is detected by Western blot. Although the logical concern is that this result represents testing during the process of seroconversion, in most cases—particularly in low-risk individuals and low-prevalence areas—it represents the presence of cross-reactive nonspecific antibodies. With evolving seroconversion, antibody to p24 is usually the first to appear; in its absence, seroconversion is unlikely. Causes of indeterminate test results include

- Seroconversion, which can be confirmed by a quantitative virologic test with a PCR-based assay (see below);
- Advanced HIV infection with decreased titers of p24 antibodies (seroreversion is rare);
- Autoantibodies due to autoimmune or collagen vascular diseases or malignancy;
- Cross-reactive allo-antibodies from pregnancy, blood transfusions, or organ transplantation; and
- Previous receipt of an experimental HIV vaccine.

For a woman with indeterminate test results, repeat serology at 1, 2, and 6 months is recommended. Until seroconversion is ruled out, precautions should be taken to prevent HIV transmission to others. Typically, a woman in the process of seroconversion will develop a positive Western blot within 1 month. In high-risk patients or in other situations where acute infection is suspected, HIV RNA level (i.e., VL) should be obtained; this test has high sensitivity because of the generally high levels of viremia during acute infection.

HIV antigen/antibody tests: Two combination HIV antigen/antibody tests (ARCHITECT and Bio-Rad GS) have now been licensed by the U.S. Food and Drug Administration (FDA), and may be used for this purpose.

Rapid tests: Six FDA-approved rapid serologic tests are now available and usually provide results within 15–30 minutes (*FDA-Approved Rapid HIV Antibody Screening Tests*. CDC. 2008; http://www.cdc.gov/hiv/topics/testing/rapid/rt-comparison.htm. Accessed 8/1/2012). Three of the rapid tests are Clinical Laboratory Improvement Amendment (CLIA) waived, allowing point-of-care testing in clinical settings, which is particularly useful in settings where patients typically do not return for results, such as sexually transmitted infection (STI) clinics and emergency rooms, and during labor and delivery. Sensitivity and specificity are consistently >99% but positive predictive value varies depending on HIV prevalence. For this reason, positive results are considered preliminary and should always be confirmed with Western blot or IFA. For women who present to labor and delivery with undocumented HIV status and positive rapid test results, however, ARV prophylaxis should be given without delay to reduce the risk of perinatal transmission (ACOG Committee Opinion No. 418; *Obstet Gynecol* 2008;112(3):739).

In July 2012 the FDA approved the OraQuick In-Home HIV Test, a rapid home-use HIV test kit that provides a test result in 20–40 minutes and is approved for sale in stores and online to those 17 years and older. As with other rapid tests, positive tests must be confirmed by follow-up laboratory-based testing. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310542.htm) (http://www.oraquick.com/)

Urine test: The only currently available urine test (Calypte HIV-1 Urine EIA) is licensed for screening only and must be administered by a physician; a positive result requires confirmation by another method.

Virologic tests: Nucleic acid amplification tests—HIV DNA (qualitative) or HIV RNA (quantitative)—are used to diagnose acute HIV infection, confirm the diagnosis during the window period, and diagnose neonatal infection. HIV RNA testing is ***not*** recommended as a routine screening test for HIV because 2%–9% of people without HIV infection will have false-positive results, virtually always with low HIV RNA levels (i.e., <10,000 copies/mL [c/mL]) (*Ann Intern Med* 1999;130(1):37). Patients with acute HIV infection diagnosed by a virologic test while still antibody negative or indeterminate should undergo confirmatory serologic testing over the next 3 months. (See further discussion of HIV RNA testing on p. 92.)

Acute HIV infection should be suspected in patients with typical symptoms, including fever, pharyngitis, lymphadenopathy, and rash, particularly if these symptoms are accompanied by a high-risk exposure during the previous 3–4 weeks. Women may be less likely to perceive an exposure as high risk, particularly if they are in what they believe to be a mutually monogamous relationship.

There is evidence that pregnancy may be a time of increased risk for HIV acquisition (*Lancet* 2005;366(9492):1182). Obstetrical providers should therefore have a low threshold for retesting in pregnancy when there is concern for possible acute HIV infection. In this situation both HIV VL and HIV serology should be obtained because serology may be negative or

indeterminate. An antibody/antigen test would be appropriate to use in this circumstance as well, since the woman may be antibody negative but antigen positive.

- HIV DNA is a qualitative test used to detect intracellular virus; it is used primarily to diagnose neonatal infection. Sensitivity is >99% at all stages of infection and specificity is approximately 98%.
- Viral isolation: qualitative or quantitative cultures have been used primarily to diagnose neonatal HIV infection, but they are expensive and labor intensive and have been largely replaced by HIV DNA or HIV RNA assays.

Baseline and Interval Laboratory Evaluation

Baseline laboratory evaluation is used to establish the stage of HIV disease and determine exposure to other infectious diseases, need for vaccinations, and the presence of comorbidities that may affect the choice of HIV therapy or require specific management. Ongoing laboratory testing is needed to assess the response to therapy and monitor for adverse effects. A flow sheet, whether part of an electronic or paper health record, is an essential tool for tracking important test results and key clinical data over time. Table 4-4 outlines baseline and interval laboratory and other monitoring for women with HIV infection.

Table 4-4

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/ Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
HIV DISEASE TESTS										
CD4+ cell count	X	q 3–6 mo	X		X	q 6–12 mo in clinically stable patients with NDVL		X	X	
HIV RNA (VL)	X	q 3–6 mo	X	X	X	X		X	X	If VL is detectable at 2–8 wk, repeat q 4–8 wk until <200 c/mL, then q 3–6 mo. Interval for monitoring can be extended to q 6 mo if patient is ART adherent, has NDVL, and is clinically and immunologically stable for >2–3 y.
Resistance testing	X		X					X	X	If RT is performed at entry into care, repeat testing is optional if patient is ART naïve. RT is not possible with viral suppression and an ART switch that is due only to toxicity or for convenience.
Tropism testing			X					X	X	Perform if considering CCR5 antagonist therapy or for failure of CCR5 antagonist therapy
SAFETY/TOXICITY MONITORING										
CBC w/ differential	X	q 3–6 mo	X	If on ZDV	X				X	

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/ Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
Electrolytes, BUN, creatinine	X	q 3–6 mo	X	X	X				X	Some experts recommend phosphorus measure while on TDF. Renal function assessment should include estimation of CrCl or GFR.
ALT, AST, bilirubin	X	q 3–6 mo	X	X	X				X	
Fasting glucose or hemoglobin A1C	X	If normal, q 12 mo	X		If last measure abnormal	If last measure normal			X	See *Diabetes Care* 2006;29:1963 for consensus guidelines for management of hyperglycemia in Type 2 DM
Fasting lipid profile	X	If normal, q 12 mo	X	Consider 4–8 wk after starting new ART		If last measure abnormal	If last measure normal		X	
Urinalysis: RBC, WBC, proteinuria, sediment levels	X		X			If on TDF	X		X	More-frequent monitoring indicated for patients with increased risk of renal insufficiency (e.g., DM, HTN)
Calculated creatinine clearance	X		Prior to initiating TDF or IDV						X	Consider at baseline, especially in Black patients, due to increased risk of HIVAN
Albumin level	X	q 12 mo					X		X	

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/ Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
Alkaline phosphatase level	X	q 12 mo					X		X	
Pregnancy test			If starting EFV						X	
G6PD	X									Screen for deficiency in appropriate racial or ethnic groups
HLA-B*5701 testing			If considering ABC							
COINFECTION AND COMORBIDITY TESTING										
Viral hepatitis screening (HAV, HBV, HCV)	X		If not performed at entry; if patient is not HBV immune or vaccinated						X	If HBV nonimmune, administer HBV vaccine series. Administer HAV vaccine if patient has HBsAg+ or HCV infection, is planning travel to endemic areas, is IDU, or in presence of HAV community outbreaks.
TB screening	X						X		X	Test with PPD or interferon-gamma release assay; no need to repeat if prior (+) PPD. Other testing may be indicated with potential exposure.
Syphilis serology	X						X		X	More-frequent testing may be indicated if patient engages in high-risk behavior

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/ Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
CMV and other herpes virus screening	X									CMV screening if at low risk for CMV; VZV screening if no history of chicken pox or shingles. Some experts recommend HSV-2 screening.
Toxoplasma serology	X									
STI screening (GC, chlamydia, trichomoniasis) (see http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm for detail on indications for more frequent testing and which testing modalities to use)	X						X		X	More-frequent testing may be indicated if patient engages in high-risk behavior
Chest X-ray	X								X	Indicated for patients with positive TB screening results. Consider at baseline in presence of underlying lung disease.
HEALTH MAINTENANCE SCREENING										
Cervical cytology	X	2x in first y of care					X			More-frequent screening is indicated if abnormal results are obtained and/or after treatment

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/ Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
Anal cytology/ digital rectal exam	X	2x in first y of care					X			Not currently considered standard of care, but some experts recommend a screening schedule similar to that for cervical cytology. Consider anal Pap smear in women with genital warts or abnormal cervical cytology. Evaluate abnormal results with high-resolution anoscopy.
Ophthalmologic screening						Perform dilated exam q 6–12 mo in patient with CD4+ cell count <50 cells/mm^3			X	
Depression screening	X						X		X	
Domestic violence screening	X						X		X	
Alcohol and drug use	X						X		X	
Tobacco use	X						X		X	

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

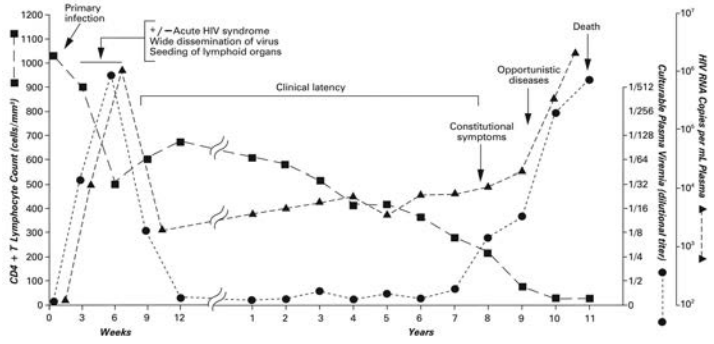
	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/ Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
Colonoscopy	X								X	Initiate screening at age 50; perform every 10 y, but earlier or more often if indicated by family history or prior findings
Mammography	X						X			Baseline screening at age 40 and annually thereafter (ACOG Practice Bulletin #122; *Obstet Gynecol* 2011;118(2 Pt 1):372). Perform individualized, periodic assessment of breast cancer risk.
Bone densitometry	X									Initiate screening at age 65; consider at age 50+ if patient has one or more risk factors for premature bone loss. Perform periodically based on prior results and ongoing risk factors for bone loss.
Global assessment for frailty, functionality, fall risk	X						X		X	Initiate screening at age 65

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: Adapted from *Primary Care Guidelines for the Management of Persons Infected With Human Immunodeficiency Virus*: 2009 *Update by the HIV Medicine Association of the Infectious Diseases Society of America* (*Clin Infect Dis* 2009;49:651)

CD4+ lymphocyte count (CD4+ % and absolute CD4+ cell count): This is a key indicator of immune function in HIV infected patients. The normal laboratory range for the CD4+ lymphocyte percentage is 33%–60% and a normal CD4+ cell count is 700–1400 cells/mm^3. CD4+ cell counts often drop precipitously at the time of primary HIV infection, then usually rebound to near-baseline levels. The natural history of HIV infection, illustrated in Figure 4-1, involves a progressive loss of CD4+ cells (approximately 60 cells per year), with the risk of opportunistic infections (OIs) increasing as CD4+ cell counts decrease. An adequate CD4+ response to therapy is defined as an increase in the range of 50–150 cells/mm^3 per year until a steady-state level is reached. If therapy is initiated at a low CD4+ cell count or at an older age, the increase may be blunted, even with appropriate virologic suppression.

Figure 4-1
Natural History of HIV Infection without the Use of Antiretroviral Therapy



Source: © *N Engl J Med* 1993;328:327. Reprinted with permission.

The baseline CD4+ cell count is important in decisions regarding the initiation of ART and the need for prophylaxis against specific OIs. Follow-up CD4+ cell count testing is important for determining when to start ART in untreated patients, assessing the immunologic response to ART, and informing decisions about the initiation or discontinuation of OI prophylaxis.

Because the CD4+ percentage is measured directly and the absolute CD4+ cell count is a calculated value, it is more useful and accurate when assessing trends over time to focus on changes in the CD4+ percentage. Most clinicians, however, use the absolute CD4+ cell count in clinical decision making.

Several factors may cause decreases in the absolute CD4+ cell count, including pregnancy (due to hemodilution; the CD4+ percentage remains relatively stable), corticosteroid use, intercurrent illness, bone-marrow suppressive medications, and recent vaccination. HTLV-1 infection may increase the CD4+ cell count.

In general, the same laboratory should be used for serial CD4+ measurement and any value that indicates a change in patient management should trigger a retest. A 30% change in the absolute CD4+ cell count or a 3-point change (increase or decrease) in the CD4+ percentage between one test and the next is significant (i.e., a change of two standard deviations or more).

Plasma HIV RNA (VL): At baseline, VL reflects the rapidity with which HIV disease is likely to progress. Higher VLs have been repeatedly associated with a more rapid rate of disease progression.

VL is used routinely to monitor a patient's response to treatment of HIV infection, with the goal of achieving and maintaining an undetectable VL as measured by ultrasensitive assays (<20–75 c/mL, depending on the assay); however, isolated "blips" (i.e., VLs transiently detectable at low levels) can be seen in successfully treated patients and are not thought to represent viral replication or to predict virologic failure (*JAMA* 2001;286(2):171). A repeat test should be performed as quickly as possible if a patient on ART with previously undetectable VL suddenly has quantifiable virus. The U.S. Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* defines virologic failure as a confirmed VL of >200 c/mL, which eliminates most cases of apparent viremia caused by blips or assay variability (http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 5/16/2013).

Acute illness (e.g., bacterial pneumonia, tuberculosis (TB), herpes simplex virus (HSV), *Pneumocystis jirovecii* pneumonia [PCP]) and immunizations can cause transient increases in plasma HIV RNA for 2–4 weeks; testing should not be performed during this time. Plasma HIV RNA results usually should be verified with a repeat determination before making changes in therapy. The most frequent reason for an increase in viral load is poor adherence and any increase in viral load should prompt assessment of the patient's adherence to the prescribed ART regimen. Recent studies have shown that women have lower VLs than men at comparable CD4+ cell counts, although these VL differences tend to disappear several years after seroconversion and have not been associated with slower disease progression or longer survival (see Chapter 1, ***Epidemiology***).

Several different VL assays and methodologies (e.g., reverse transcriptase PCR, branched DNA, nucleic acid sequence-based amplification) are available. The variability of VL assays is 0.3–0.5 log. Although the results of different assays correlate, absolute values differ and no standard multiplication factor exists to translate among different assays. For this reason, the same VL assay should be used to follow an individual patient longitudinally.

HIV drug-resistance testing (see also p. 110): Genotypic and phenotypic resistance assays are used to provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs); tests for integrase and fusion inhibitor resistance are available separately from several commercial laboratories. A genotypic tropism assay for predicting HIV co-receptor usage is now commercially available and may be used as an alternative to a

phenotypic tropism assay before initiation of a CCR5 antagonist-containing regimen and for evaluation of virologic failure while taking CCR5 inhibitors. The purpose of resistance assays is to inform treatment decisions in the case of possible transmitted drug resistance, virologic failure, or suboptimal VL reduction.

Resistance testing should be performed in the following circumstances:

- With acute HIV infection; 6%–16% of transmitted virus is resistant to at least one ARV, and 3%–5% is resistant to drugs from more than one ARV class (*AIDS* 2010;24(8):1203; *HIV Clin Trials* 2007;8(1):1)
- At entry into HIV care; some drug-resistance mutations can remain detectable for years in untreated infected patients (*Clin Infect Dis* 2005;40(3):468; *J Virol* 2008;82(11):5510)
- Upon initiation of ART, because of the possibility of superinfection (optional)
- At entry into prenatal care; test prior to the initiation of ART and in patients who are on therapy and have detectable VL
- If virologic failure occurs, test before or within 4 weeks of discontinuing the failing drug regimen
- If VL reduction if suboptimal

In most situations, genotypic testing is preferred over phenotypic testing because of faster turnaround time, lower cost, better sensitivity for detecting mixtures of wild-type and resistant virus, and relative ease of interpretation. Adding phenotypic to genotypic testing is generally preferred for patients with known or suspected complex drug-resistance mutation patterns, particularly to PIs. In general, resistance testing should be performed with VL >1000 c/mL. With VL >500 but <1000 c/mL, testing may be unsuccessful but should still be considered. Testing is not recommended with VL <500 c/mL because resistance assays cannot be performed consistently at such low VLs.

Hematology and chemistry panels: The effects of HIV, associated conditions, and adverse effects of drugs may involve hematologic, renal, or hepatic abnormalities.

- Complete blood count (CBC): look for leukopenia, anemia, and thrombocytopenia; lymphocyte count is needed to calculate the absolute CD4+ cell count
- Serum creatinine: increased levels may indicate HIV-associated nephropathy (HIVAN) or drug toxicity
- Abnormal liver function tests (LFTs): may reflect viral hepatitis, alcohol abuse, or drug toxicity. Abnormalities may have an impact on options for ART.

Syphilis serology: High rates of coinfection necessitate routine testing in all HIV infected patients. A reactive nontreponemal assay (rapid plasma reagin [RPR] or venereal disease reaction level [VDRL]) must be confirmed with a treponemal-specific assay (fluorescent treponemal antibody absorption test [FTA] or methoxy trifluoromethyl phenyl acetic acid).

Toxoplasmosis serology (*MMWR Recomm Rep* 2009;58(RR-4):1): Latent toxoplasmosis infection, as indicated by the presence of *Toxoplasma gondii* immunoglobulin G (IgG), may be relevant to decisions on prophylaxis and avoidance of exposure in those who are IgG negative (e.g., avoiding raw or undercooked meat, cat litter). Repeat serology is recommended in patients who were previously IgG negative and have immune reconstitution to a CD4+ cell count >100 cells/mm^3. Also repeat with a decrease in the CD4+ cell count to 100 cells/mm^3, especially if the patient is not receiving *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis, which is active against toxoplasmosis. The prevalence of latent toxoplasma infection varies significantly worldwide; in the United States, the rate is approximately 30%.

CMV serology (IgG): Most HIV infected adults have latent cytomegalovirus (CMV) infection. Knowledge of CMV antibody status can guide the clinician to use CMV-negative blood products if the patient is CMV IgG negative and transfusions are required. Check serology in patients at lower risk for CMV (e.g., non-injection drug users [IDUs]) upon initiation of care (*MMWR Recomm Rep* 2009;58(RR-4):1).

Varicella serology (IgG): Check serology in patients who do not have a history of chicken pox or shingles. If the patient is varicella IgG-negative and is subsequently exposed, administer postexposure prophylaxis with varicella immune globulin (*MMWR Recomm Rep* 2009;58(RR-4):1). Consider varicella vaccination for seronegative patients at increased risk for exposure to VZV.

Hepatitis A, B, C serology (*MMWR Recomm Rep* 2009;58(RR-4):1): Hepatitis A and B serologies will identify those who are not immune and are therefore candidates for vaccination. Laboratory tests for the hepatitis viruses are listed in Table 4-5.

Table 4-5

Laboratory Tests for Hepatitis Viruses

Hepatitis Virus	Laboratory Test	Interpretation
A	HAV IgM Ab	Current or recent HAV infection
	HAV IgG Ab	Immunity to HAV (past infection or after vaccination)
B	HBsAg	Current (acute or chronic) HBV infection
	HBeAg	Current HBV infection with high risk of infectivity
	HBcAb	Past or present HBV infection
	HBsAb	Immunity to HBV (past infection or after vaccination)
C	HCV IgG Ab (ELISA)	Past or present HCV infection
	HCV IgG Ab (RIBA)	Confirms HCV ELISA
	HCV RNA PCR (qualitative, quantitative)	Current HCV infection
	HCV genotype in PCR+s	Useful in determining prognosis, duration of treatment of anti-HCV therapy

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Recommendations are as follows:

Hepatitis A

- Vaccinate HAV Ab-negative IDUs, women with chronic liver disease, and patients infected with hepatitis B or C
- Consider vaccine for all other HIV infected patients without prior exposure by serology
- Vaccine may not produce an adequate immune response in patients with CD4+ cell counts <350 cells/mm^3

Hepatitis B

- Provide vaccine for patients who are susceptible to infection (i.e., patients who are negative for the hepatitis B surface antigen (HbsAg), surface antibody (HbsAb), and core antibody (HBcAb)
- Offer vaccine to sex partners of persons who are HBsAg positive
- Vaccine may not produce an adequate immune response in patients with CD4+ cell counts <350 cells/mm^3
- Consider HBV DNA PCR for patients who are HBcAb positive but HBsAg and/or HBsAb negative. Most of those with isolated HBcAb are not immune and should receive a complete primary vaccination series.

- Choose ART or other potentially hepatotoxic agents carefully for women with chronic HBV (i.e., HBsAg positive or HBsAg negative but HBcAb positive with detectable HBV DNA) infection because of potential increased hepatic toxicity and the need for more-frequent assessment of LFTs
- For patients who are HBsAg positive, ART should include TDF + (FTC or 3TC) to treat both HIV and HBV infections
- In patients with HBV infection and documented cirrhosis, perform alpha-fetoprotein (AFP) and hepatic ultrasound annually to screen for hepatocellular carcinoma

Hepatitis C

- Infection status is needed to guide therapeutic decisions for possible HCV treatment
- Perform HCV antibody test at initiation of care and confirm positive HCV Ab with quantitative HCV RNA
- HIV/HCV coinfected patients may not manifest HCV antibody; consider a qualitative HCV RNA PCR test when HCV is suspected (i.e., with abnormal LFTs and negative serology)
- Women with detectable HCV should be tested for the HCV genotype
- Choose ART or other potentially hepatotoxic agents carefully for women with chronic HCV infection because of potentially increased hepatic toxicity and the need for more frequent assessment of LFTs
- Infants born to HCV infected women should be tested for HCV
- In patients with HCV infection and documented cirrhosis, perform an annual AFP and hepatic ultrasound to screen for hepatocellular carcinoma

Tuberculosis testing (*MMWR Recomm Rep* 2009;58(RR-4):1): A baseline purified protein derivative (PPD) or interferon-gamma release assay should be obtained for all patients who do not have a past history of a positive PPD. Patients who do have a history of a positive PPD should get a baseline chest X-ray (CXR). Note the following:

- A positive PPD in the setting of HIV infection is defined as >5 mm induration
- Anergy testing is not recommended
- Prior bCG vaccination is not a contraindication for PPD but may produce a positive PPD. Evaluate the patient for active TB and consider therapy for latent infection.
- With a positive PPD or interferon-gamma release assay, treat for latent TB after excluding active TB
- Repeat testing in patients with advanced HIV who were initially PPD negative but have subsequent immune reconstitution to a CD4+ cell count >200 cells/mm^3
- Close contacts of persons with active TB should be treated for latent

TB, regardless of PPD results or prior treatment for TB, but active TB must first be ruled out

Other Laboratory Testing

Glucose-6-phosphate dehydrogenase deficiency: A relative deficiency of glucose-6-phosphate dehydrogenase (G6PD) may be found in up to 2% of African Americans and is not usually clinically significant. An absolute G6PD deficiency is occasionally found in women of Mediterranean ancestry and predisposes to hemolytic anemia with the use of certain medications, including dapsone and sulfonamides. Baseline testing will permit safe use of these drugs when needed.

Fasting blood sugar or hemoglobin A1C and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein): Both HIV and many ARVs have been associated with the development of hypertriglyceridemia and hypercholesterolemia; PIs have been linked to both new onset of and worsening of existing diabetes. Abnormal lipids should trigger a review of diet and exercise and the patient should be encouraged to make appropriate lifestyle changes. Also consider a change of HIV medications and/or anti-lipid therapy. (See *Circulation* 2005;112:3184 for the most recent recommendations.)

Urinalysis/calculated creatinine clearance: Because of an increased risk of HIV-associated nephropathy, this test is particularly important for Black HIV infected patients and patients with advanced disease or comorbid conditions. Perform prior to initiating TDF, IDV, ATV or other drugs with potential for nephrotoxicity.

Pap smear/STI screening: A Pap smear should be obtained (along with screening for gonorrhea, chlamydia and trichomoniasis) at baseline and periodically, with intervals based on prior results and/or treatment for an abnormal Pap, risk behaviors, and signs or symptoms or a diagnosis of STI (see Chapter 6, ***Gynecologic Problems***).

Antiretroviral Therapy

DHHS supports several working groups of the Office of AIDS Research Advisory Council to develop and continuously update ARV treatment guidelines for adults and adolescents, children, and pregnant women. Updated recommendations are available at http://www.aidsinfo.nih.gov. The primary areas of attention in the adult and adolescent guidelines include baseline assessment, treatment goals, indications for initiation of ART, choice of the initial regimen in ART-naïve patients, drugs or combinations to be avoided, management of adverse effects and drug-drug interactions, management of treatment failure, and special ART-related considerations in specific patient populations.

This section provides an overview of the general principles of ARV treatment; current evolution of and rationale for recommendations for earlier initiation of ART; current recommendations for initiating therapy in ART-naïve individuals, with special considerations for women; and management of ART-experienced patients. For detailed information on specific ARV agents now available in the U.S., see Table 8-7 (pp. 285–298 in Chapter 8, ***Pregnancy***) and Tables 13-7 to 13-9 (pp. 491–512) in Chapter 13, ***Pharmacology***).

Goals of Antiretroviral Therapy

Eradication of HIV infection cannot be achieved with currently available ARV drug regimens, largely because a pool of latently infected CD4+ cells is established very early after acute infection (*Proc Natl Acad Sci USA* 1998;95(15):8869) and persists despite prolonged suppression of plasma viremia (*Nat Med* 2003;9(6):727; *Nat Med* 1999;5(5):512). Therefore, the primary goals of ART are to 1) reduce morbidity and mortality associated with HIV infection and improve quality of life; 2) restore and preserve immune function; 3) maximally and durably suppress HIV VL; and 4) prevent HIV transmission (DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012).

Three characteristics of HIV infection have significant implications for ART:

- **Progressive immune damage:** Between the time of initial infection and the development of clinical disease, progressive immune-system damage occurs, as evidenced by a decline in CD4+ lymphocyte counts as well as by ongoing inflammation and immune activation. These changes ultimately result in vulnerability to OIs and other AIDS-defining conditions as well as in higher rates of cardiovascular and other end-organ damage. Interrupting this progression provides a major rationale for the early initiation of ART.
- **Rapid viral replication:** The half-life of HIV in plasma is less than 48 hours and turnover occurs at a rate of up to 1 billion virions per day (*Nature* 1995;373(6510):123). Lifelong therapy must be maintained to suppress viral replication and prevent disease progression.
- **High degree of inherent genetic mutability:** Mutations may develop rapidly when patients are not adherent to therapy; single mutations may confer high-level resistance to some ARV drugs and/or drug classes. Combination ART, consisting of at least two and preferably three active drugs from at least two drug classes, has been shown to have superior effectiveness in controlling viral replication, limiting the emergence of resistant virus, and reducing the risk of HIV progression and death.

When to Initiate Antiretroviral Therapy

It is now recommended that ART be initiated in all HIV-infected individuals regardless of CD4 cell count to reduce the risk of disease progression ART and to prevent of transmission of HIV. These recommendations are based on

the results of randomized controlled trials and cumulative observational cohort data that demonstrate the benefits of ART in reducing AIDS and non-AIDS associated morbidity and mortality as well as on increasing awareness that HIV-related morbidity and mortality result not only from immune deficiency but also from both the direct effects of HIV on specific organs and the indirect effects of HIV-associated inflammation on those organs. The benefit of ART in reducing transmission to others should also be considered in decisions about when to initiate therapy. The benefits of starting ART with high CD4+ cell counts and/or low viral set points should be balanced against considerations of short- or long-term adverse drug effects and the need for good adherence to lifelong therapy to prevent the development of resistance (DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 5/16/2013).

Available data indicate the following:

- Untreated HIV infection may have detrimental effects at all stages of infection
- Treatment is beneficial, even when initiated later in infection; however, later initiation may not fully reverse damage related to viral replication in the early stages of infection
- Earlier treatment may prevent the damage associated with HIV replication in early infection
- Earlier ART treatment is associated with reduced transmission to uninfected partners (*N Engl J Med* 2011; 365:493)
- Sustained viral suppression and maintenance of higher CD4+ cell counts may delay or prevent some HIV-associated but non-AIDS defining complications. Complications that may be delayed or prevented with ART include the following:
  - HIVAN: ART is associated with preserved renal function and prolonged survival (*Nephrol Dial Transplant* 2006;21(10):2809; *AIDS* 2008;22(4):481; *J Am Soc Nephrol* 2005;16(8):2412)
  - Progression of HBV/HCV infection (*Hepatology* 2009;50:1056; *BMC Res Notes* 2008;1:46; *Hepatology* 2008;48:1062)
  - CV disease: Several studies suggest that untreated HIV and viral replication may be associated with endothelial dysfunction and inflammation; that increased markers of inflammation and coagulation, as well as risk of CV events, occur with treatment interruption; and that CV disease is associated with CD4+ cell depletion. Evidence also suggests that ART may result in significant improvement of parameters associated with CV disease, including markers of inflammation, high-sensitivity C-reactive protein, and endothelial dysfunction (*J Acquir Immune Defic Syndr* 2009;52(1):25; *AIDS* 2009;23:929; *J Am Coll Cardiol* 2008;52:569; *PLoS Med* 2008;5:e203; *N Engl J Med* 2006;355:2283; *AIDS* 2009;23:1743; *AIDS* 2008;22:2409).
  - Cancer: Incidence of AIDS- and non-AIDS malignancies is increased as CD4+ cell count decreases to <350–500 cells/mm^3. Regardless of CD4+ cell count, there appears to be a protective effect of ART for HIV-associated malignancies (*J Acquir Immune Defic Syndr*

2009;52(1):25; *AIDS* 2009;23:1743; *AIDS* 2008;22:2143; *Clin Infect Dis* 2009;49:1109; *Lancet Oncol* 2009;10:1152).

- Neurocognitive decline: CD4+ cell count <350 cells/mm^3 is associated with higher risk for HIV-associated dementia and more-severe neurologic complications (*Ann Neurol* 2008;63:213; AIDS 2007;21:1915-1921; *AIDS Res Hum Retroviruses* 2008;24:1301)

Current recommendations for ART initiation (adapted from DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents;* http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/10/initiating-art-in-treatment-naive-patients. Accessed 5/16/2013):

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression. The strength and evidence for this recommendation vary by pretreatment CD4 cell count: CD4 count <350 cells/mm^3 (strong recommendation); CD4 count 350–500 cells/mm^3 (strong recommendation); CD4 count >500 cells/mm^3 (moderate recommendation).

- ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV (strong recommendation).

- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence (strong recommendation). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Choosing an Initial Regimen

Factors to consider include the following (DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- Comorbid conditions (e.g., cardiovascular disease, chemical dependency, liver disease, psychiatric disease, renal diseases, TB)
- Potential adverse drug effects
- Potential drug interactions with other medications
- Pregnancy or pregnancy potential
- Results of genotypic drug-resistance testing
- Female gender and pretreatment CD4+ cell count if considering NVP
- HLA-B*5701 testing if considering ABC
- Coreceptor tropism assay if considering MVC
- Patient adherence potential
- Convenience (e.g., pill burden, dosing frequency, food and fluid considerations)

The current guidelines for managing HIV in adults and adolescents offer four preferred regimens for initial therapy in ARV-naïve patients:

- Efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC)
- Ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC)
- Ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC)
- Raltegravir + tenofovir/emtricitabine (RAL + TDF/FTC)

The DHHS guidelines also describe alternative and acceptable regimens, as well as combinations for which more data are needed and combinations that should be avoided. Chapter 8 of the current book covers recommendations for ART in pregnancy. Consultation with an HIV specialist is recommended for questions about treatment in specific patient situations.

In an ART-naïve patient, VL reduction to levels below the limits of assay detection usually occurs within the first 12–24 weeks of therapy. Predictors of virologic success include use of a high-potency ARV regimen, patient adherence to the treatment regimen, low baseline VL, higher baseline CD4+ cell count (>200 cells/mm^3), and rapid reduction of VL in response to treatment.

In general, studies to date have not shown differences in the virologic efficacy of ART by gender (*AIDS* 2007;21(7):835; *HIV Med* 2006;7(8):520; *Ann Intern Med* 2010;153(6):349), although several studies have suggested that gender may influence the frequency, presentation, and severity of selected ARV-related adverse events (*Expert Rev Anti Infect Ther* 2005;3(2):213). Although data are limited, evidence also suggests that women may metabolize and respond to specific medications, including ARV drugs, differently from men (*Annu Rev Pharmacol Toxicol* 2004;44:499; *Pharmacol Res* 2008;58(3-4):173; *Gend Med* 2007;4(2):106).

Results of a few studies examining metabolic complications associated with ARV use indicate that HIV infected women on ART are more likely than men to experience increases in central fat deposition and less likely than men to have triglyceride elevations (*HIV Med* 2001;2(2):84; *J Acquir Immune Defic Syndr* 2003;34(1):58). Compared with men, women have an increased risk of osteopenia and/or osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and ART (*Osteoporos Int* 2005;16(11):1345; *AIDS* 2007;21(13):1830). None of these differences, however, currently requires a change in the recommendations for treatment or monitoring in women.

Antiretroviral Agents

See Table 8-7 in Chapter 8, ***HIV and Pregnancy***, for ARVs (including co-formulations) currently licensed in the United States, including formulations, dosing, and adverse effects. See Chapter 13, ***Pharmacologic Considerations in HIV Infected Pregnant Patients***, for drug interactions and recommended dose adjustments with ARVs.

ARVs are now divided into six classes on the basis of their mechanism of action: NRTIs, NNRTIs, PIs, fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTIs). It is helpful to understand how these drug classes inhibit HIV as components of a successful combination regimen.

Nucleoside reverse transcriptase inhibitors: NRTIs were the first class of agents shown to be effective in the treatment of HIV infection. The target enzyme for this group of drugs is HIV reverse transcriptase, an RNA-dependent DNA polymerase. Class-wide adverse effects include lactic acidosis, which appears to have a female predominance. Lactic acidosis is a rare but potentially life-threatening toxicity thought to be due to mitochondrial toxicity and associated with prolonged exposure to NRTIs. It is most common with stavudine, didanosine, and zidovudine; however, it can occur with other NRTIs (*AIDS* 2007;21(18):2455).

Non-nucleoside reverse transcriptase inhibitors: NNRTIs noncompetitively inhibit HIV reverse transcriptase by binding to a site distant from the enzyme's active site. There are three first-generation NNRTIs: nevirapine, delavirdine, and efavirenz. The two second-generation agents, etravirine and rilpivirine, work against HIV that has developed some mutations to the older drugs in this class. NNRTIs are both metabolized by and induce the hepatic cytochrome P450 (CYP) enzyme system, resulting in multiple drug-drug interactions. All NNRTIs are associated with potential rash, which typically appears in the second week of dosing, usually around days 9–11. Dosing can be continued unless there is mucosal involvement, and the rash will resolve. NVP has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among ARV-naïve individuals; women with higher CD4+ cell counts (>250 cells/mm^3) and/or elevated baseline transaminases appear to be at the greatest risk (*J Acquir Immune Defic Syndr* 2004;35(5):538; *Clin Infect Dis* 2008;46(6):933; *Clin Infect Dis* 2004;38 Suppl 2:S80; *J Infect Dis* 2005;192(3):545). It is not generally recommended that NVP be prescribed for ARV-naïve women who have CD4+ cell counts >250 cells/mm^3 unless there is no alternative and the benefit from NVP outweighs the risk of hepatotoxicity.

Protease inhibitors: PIs prevent maturation of virus proteins by competitively inhibiting HIV protease, an enzyme essential for cleavage of the HIV polyprotein into its separate active structural proteins; three viral enzymes (reverse transcriptase, integrase, and protease); and surface glycoproteins. When this enzyme is blocked, immature, noninfectious virus particles are produced. The other important properties of PIs are limited CNS penetration; metabolism by and complex effects on the CYP enzyme system, resulting in multiple drug-drug interactions; and an increased incidence of new diagnoses of diabetes or worsening of pre-existing diabetes.

Ritonavir, an early PI that was very difficult to tolerate at full dose, has more recently been used to enhance or boost the pharmacokinetic profiles of other PIs and other ARVs primarily metabolized by CYP 3A4, such as the CCR5 antagonist maraviroc, because it is such an effective inhibitor of CYP 3A4. RTV-boosted PI regimens that permit fewer doses and/or fewer pills

per day while achieving high PI drug levels are preferred over unboosted dosing regimens. Boosting thus facilitates adherence and helps prevent the development of resistance.

All PIs are associated with variable degrees of gastrointestinal adverse effects (nausea, diarrhea, abdominal discomfort), hyperlipidemia, hyperglycemia, and fat maldistribution (central adiposity and/or peripheral lipoatrophy). All boosted PIs should be taken with food.

Fusion inhibitors: FIs interact with HIV directly, rather than with the host cell. This interaction prevents the fusion of HIV to the cell. Because it is a protein, enfuvirtide, the first drug in this class, must be given by subcutaneous injection twice daily. The most common side effect is local injection-site reactions.

CCR5 antagonists: This is the only drug class that targets a host cellular protein rather than a viral protein. To gain access to a CD4+ cell, HIV must first bind to the CD4+ receptor, undergo a conformational change, and then bind to the CCR5 coreceptor as a prelude to virus-cell fusion. MVC, the first drug in this class, is very well tolerated but is effective only against virus that solely utilizes CCR5; it is not effective against virus that can bind to both CCR5 and the CXC chemokine receptor type 4 (CXCR4), or solely to CXCR4. A tropism assay can determine whether MVC will be effective.

Integrase strand transfer inhibitors: This is the most recently approved class of ARVs. INSTIs prevent the covalent integration of proviral DNA into cellular DNA, thus preventing the manufacture of the constituent parts of new virions by an infected cell. Raltegravir, the first drug in this class, is well tolerated and at a dose of 400 mg twice daily produces a very rapid decrease in HIV VL within the first few weeks of treatment. It has no effect on CYP 450 and therefore produces minimal drug-drug interactions. It inhibits another hepatic enzyme, UGT1, that is involved in glucuronidation. A second INSTI, elvitegravir, has been FDA approved for ART-naïve patients; it is available in a co-formulated tablet with FTC, TDF and cobicistat (a pharmokinetic enhancer) and is given once daily. Approval of a third INSTI, dolutegravir, is anticipated in the near future.

Adherence

Medication adherence is the crucial element in successful HIV treatment. (See Chapter 5, ***Adherence***.) Studies have shown that healthcare professionals are poor judges of who will and will not be adherent. For this reason, all patients initiating therapy should be educated about the importance of adherence, and adherence should be discussed repeatedly over the course of treatment to offset the effects of treatment fatigue. The most frequent reason for an increase in viral load is poor adherence and any increase in viral load should prompt assessment of the patient's adherence to the prescribed ART regimen. A potential reason for poor adherence in pregnancy is concern on the patient's or the provider's part that ARV drugs are dangerous in early pregnancy. Although multiple strategies have been employed to support and promote adherence, no data indicate which strategies are most effective.

Adverse Events Associated with Antiretroviral Therapy

Complications of particular clinical significance or concern are included in Table 4-6, with additional key information noted below. In general, decisions about management, including changes in ART, should be made in consultation with an HIV specialist.

Table 4-6

Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects

Adverse Effect	Antiretroviral Agent(s)
Bleeding events	• All PIs: ↑ spontaneous bleeding • TPV: Reports of intracranial hemorrhage. Risk factors include CNS lesions; trauma; surgery; hypertension; alcohol abuse; coagulopathy; use of anticoagulant or antiplatelet agents, including vitamin E.
Bone marrow suppression	• ZDV: Anemia, neutropenia
Cardiovascular disease	• ABC and ddI: Associated with MI in some cohort studies. Risk greatest among those with traditional CVD risk factors. • PIs: Associated with MI and stroke in some cohort studies. Risk greatest among those with traditional CVD risk factors. Limited data on newer PIs (ATV, DRV, TPV). • SQV/r, ATV/r, and LPV/r: PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and coadministration with other drugs that prolong PR interval. • SQV/r: QT interval prolongation in a study of healthy volunteers. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG is recommended prior to SQV initiation and should also be considered during therapy.
CNS effects	• d4T: Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare) • EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation. Most symptoms subside or diminish after 2–4 wk. Bedtime dosing may reduce symptoms. Risk factors include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and ↑ plasma EFV concentrations due to genetic factors or absorption (i.e., with food).
Diabetes mellitus, Insulin resistance hyperglycemia	• ZDV, d4T, and ddI • Reported for some PIs (IDV, LPV/r), but not all PIs studied • ATV +/- RTV not found to alter insulin sensitivity
Hyperlipidemia	• d4T > ZDV > ABC: ↑ LDL and TG • EFV: ↑TG, ↑LDL, ↑HDL • All RTV-boosted PIs: ↑LDL, ↑TG, ↑HDL • LPV/r = FPV/r and LPV/r > DRV/r and ATV/r

Table 4-6 *continued*

Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects

Adverse Effect	Antiretroviral Agent(s)
Gastrointestinal	• ddI, ZDV > other NRTIs: Nausea and vomiting • ddI: Pancreatitis • PIs: Diarrhea, nausea, vomiting • LPV/r > DRV/r and ATV/r; NFV (common): Diarrhea • ATV: cholelithiasis
Hepatic toxicity	• NRTIs: Reported for most - ddI: Prolonged exposure linked to noncirrhotic portal hypertension, in some cases with esophageal varices - ZDV, d4T, ddI: Most commonly associated with steatosis - TDF, 3TC, FTC: When withdrawn, HBV coinfected patients may develop severe hepatic flare (also when HBV resistance develops) • NNRTIs: NVP > other NNRTIs - NVP: Severe hepatic toxicity with NVP is often associated with skin rash or symptoms of hypersensitivity. For ARV-naïve patients, risk is greater for women with pre-NVP CD4+ cell count >250 cells/mm^3. Overall risk is higher for women. Risk is greatest during first few months of treatment. 2-wk dose escalation of NVP reduces risk of rash and may reduce hepatotoxicity if related to hypersensitivity. NVP is contraindicated in patients with moderate to severe liver disease (Child-Pugh classification B or C). • All PIs: Varying degrees of drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs - TPV/r has a higher frequency of hepatic events than other PIs - IDV, ATV: Jaundice due to indirect hyperbilirubinemia - TPV/r: Contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C) • CCR5 antagonist: MVC
Hypersensitivity reaction (excluding rash alone or Stevens–Johnson syndrome)	• ABC: Screen for HLA-B*5701 prior to initiation; do not start ABC therapy if HLA-B*5701 is positive. Symptoms of HSR include (in descending order of frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms. HSR worsens with continuation of ABC. Median onset, 9 d; ~90% of reactions occur within first 6 wk. Onset of rechallenge reactions is within hours of rechallenge dose. Patients, regardless of HLA-B*5701 status, should not be rechallenged with ABC if HSR is suspected. • NVP: Hypersensitivity syndrome of hepatic toxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction. For ARV-naïve patients, risk is greater for women with pre-NVP CD4+ cell count >250 cells/mm^3. Risk is higher for women. 2-wk dose escalation of NVP reduces risk. • RAL: Rash, constitutional findings and sometimes organ dysfunction • MVC: Reported as part of a syndrome related to hepatotoxicity

Table 4-6 *continued*

Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects

Adverse Effect	Antiretroviral Agent(s)
Lactic acidosis	• NRTIs, especially d4T, ZDV, and ddI: Insidious onset with GI prodrome, weight loss, and fatigue. May be rapidly progressive, with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes, respiratory distress, pancreatitis, and organ failure. Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L. Increased risk: female sex, obesity. • Laboratory findings: ↑ lactate (2–5 mmol/L: correlate with symptoms; >5 mmol/L abnormal), anion gap, AST, ALT, PT, bilirubin; ↑ amylase and lipase in patients with pancreatitis; ↓ arterial pH, serum bicarbonate, serum albumin • Upon diagnosis, stop all ARV drugs until recovery
Lipodystrophy (fat maldistribution syndromes)	• Thymidine analogs (d4T > ZDV): Lipoatrophy; may be more likely when combined with EFV vs. boosted PI • EFV-, PI-, and RAL-containing regimens: Lipohypertophy (trunk fat increase) has been observed; however, a causal relationship has not been established
Myopathy and/or elevated CPK	• ZDV: Myopathy • RAL: ↑ CPK, muscle weakness, rhabdomyolysis
Nephrotoxicity and/or urolithiasis	• TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis; concurrent use of PI may increase risk • IDV: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy • IDV, ATV: Stone, crystal formation; adequate hydration may reduce risk • EVG (co-formulated with cobicistat): potential for new or worsening renal impairment
Osteopenia and/or osteoporosis	• TDF: Associated with greater loss of bone mineral density compared with ZDV, d4T, and ABC • Decreases in bone mineral density observed in studies of regimens containing different NRTIs combined with either NNRTIs or PIs
Peripheral neuropathy	• d4T > ddI, ddC: Peripheral neuropathy (pain and/or paresthesias, lower extremities > upper extremities); can be irreversible
Rash	• All NNRTIs • ATV, DRV, FPV • RAL: Uncommon • MVC
Stevens–Johnson syndrome and/or toxic epidermal necrolysis	• ddI, ZDV: Reported cases • NVP > DLV, EFV, ETR, RPV; females at greater risk than males • FPV, DRV, IDV, LPV/r, ATV: Reported cases • RAL: Reported cases

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*

Hepatotoxicity: Hepatotoxicity, generally defined as a three- to fivefold increase in serum transaminases, may occur with or without clinical hepatitis. NVP has the greatest potential for causing hepatotoxicity (up to 12%). Approximately two-thirds of NVP-associated cases of clinical hepatitis occur within the first 12 weeks of treatment; however, risk continues after this time and patients should be monitored closely for the first 18 weeks of treatment.

The initial presentation may include nonspecific gastrointestinal and flu-like symptoms. Although liver-enzyme abnormalities may or may not be present initially, this syndrome can progress rapidly to fulminant hepatic failure. Risk factors for hepatic toxicity include HBV or HCV coinfection, alcohol abuse, baseline elevated liver enzymes, and concomitant use of other hepatotoxic agents (*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*).

Lactic acidosis: Lactic acidosis is usually seen with long-term NRTI exposure. Because the initial signs and symptoms are nonspecific, clinicians should have a high level of suspicion for this adverse effect. Routine lactate testing is not recommended; however,testing should be performed with signs or symptoms of possible lactic acidosis. ART should be stopped if clinical and laboratory manifestations are consistent with lactic acidosis. A new regimen should commence after recovery, which can take months.

Lipodystrophy (fat maldistribution syndromes): Fat accumulation is most commonly seen in the abdomen, neck (dorsocervical fat pad), and breasts. Lipoatrophy most commonly affects the face, buttocks, and extremities; risk has been associated with d4T use in particular. Women seem particularly prone to developing truncal obesity (i.e., increased abdominal girth, increased breast size). Women who perceive adverse changes in body habitus related to their ARV regimens may be at increased risk for nonadherence. It may be useful to obtain some standard measurements, such as minimum waist, maximum hip, and neck circumference at an early visit, before ART is started, and to question the patient at regular intervals about any perceived changes in body shape or changes in clothing and brassiere size. Such measurements, while inexact, are inexpensive and easier to obtain than anthropomorphic measurements, dual-emission X-ray absorptiometry, or computed tomography (CT) scans.

Management of the Treatment-Experienced Patient

In general, a distinction is made between patients with limited prior treatment and those with extensive prior treatment because those with more limited ARV experience have a greater likelihood of achieving maximal viral suppression with an appropriate change in regimen. Assessing and managing a patient with extensive prior ARV experience and treatment regimen failure is complex and expert advice is critical. Changing therapy sooner rather than later is recommended to minimize the continued selection of resistance mutations.

The DHHS Guideline Panel's overall recommendations for management of the patient whose current therapy is failing are as follows: (adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012)

- **Evaluate virologic failure** (defined as the inability to achieve or maintain suppression of viral replication <200 c/mL): Assess the severity of the patient's HIV disease, ART history, use of concomitant medications (with consideration of possible adverse drug interactions with ARV agents), HIV RNA and CD4+ cell count trends over time, and prior drug-resistance testing results.
- **Perform drug-resistance testing:** Test for drug resistance while the patient is taking the failing ARV regimen (or within 4 weeks of treatment discontinuation). To avoid false-negative results in patients who have discontinued their treatment regimen, it may be helpful to have them restart their medications for a week or so and then obtain a resistance test.
- **Re-establish virologic suppression:** The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA below the current limit of detection).
- **Design a new regimen:** Use the patient's treatment history and past and current resistance test results to identify at least two, and preferably three, fully active agents to combine with an optimized background ARV regimen. A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, the results of drug-resistance testing, and/or the presence of a novel mechanism of action.
- **Do not add just one ARV:** In general, adding only a single, fully active ARV to a new regimen is not recommended because of the risk that resistance to this agent will develop rapidly. In patients with a high likelihood of clinical progression (e.g. CD4+ cell count <100 cells/mm^3) and limited drug options, however, adding a single drug may reduce the risk of immediate clinical progression because even transient decreases in HIV RNA and/or transient increases in CD4+ cell counts have been associated with clinical benefits.
- **Adjust goals:** For some highly ART-experienced patients, maximal virologic suppression is not possible. In these cases, ART should be continued with regimens designed to minimize toxicity, preserve CD4+ cell counts, and avoid clinical progression.
- **Avoid interruption:** Discontinuing or even briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4+ cell count and increases the risk of clinical progression (*N Engl J Med.* 2001;344(7):472; *N Engl J Med.* 2003;349(9):837). Therefore, this strategy is not recommended.
- In the setting of virologic suppression, no consensus exists on how to define or treat immunologic failure.

Other important clinical situations besides overt virologic failure are not necessarily linked to the development of resistance, such as

- Incomplete virologic response: defined as two consecutive plasma HIV RNA levels >200 c/mL after 24 weeks; the baseline HIV RNA level may affect the time course of response and some regimens take longer than others to suppress HIV RNA levels

- Virologic rebound: defined as a confirmed detectable HIV RNA (to >200 c/mL) after virologic suppression

Treatment failure may occur for several reasons. It is important to try to distinguish among these reasons because approaches to the management of treatment failure will vary depending on the reason. In addition to patient and regimen characteristics, provider characteristics, such as inexperience in treating HIV disease, may also come into play. In some cases, the cause of treatment failure may be unknown.

Patient characteristics:	ARV regimen characteristics:
• Higher pretreatment or baseline VL • Lower pretreatment or nadir CD4+ cell count • Prior AIDS diagnosis • Comorbidities (e.g., active substance abuse, depression) • Presence of drug-resistant virus, either transmitted or acquired • Prior treatment failure • Incomplete medication adherence and missed clinic appointments	• Drug side effects and toxicities • Suboptimal pharmacokinetics (variable absorption, metabolism, or [theoretically] penetration into reservoirs) • Food and/or fasting requirements • Bedtime dosing problems (e.g. falling asleep early, sleeping at different location from where medications are kept) • Adverse drug-drug interactions with concomitant medications • Suboptimal potency • Prescription errors

To assess virologic failure, the clinician should evaluate the following (adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012):

- **ARV treatment history:** any changes in VL and CD4+ cell counts over time; results of prior resistance testing (if any)
- **Occurrence of HIV-related clinical events:** thorough interval history and physical exam
- **Medication-taking behavior:** adherence to recommended drug doses, dosing frequency, and food/fasting requirements; if problems are identified, address the underlying cause(s) (e.g., difficulties accessing or tolerating medications, depression, active substance abuse)
- **Tolerability of medications:** severity and duration of side effects; even minor side effects can affect adherence
- **Concomitant medications and supplements:** consider adverse drug-drug interactions
- **Comorbidities:** e.g., substance abuse

With regard to adherence, some patients do not want to disappoint their care providers and will insist that they are adherent even when they are not. Avoid putting such patients on the defensive. Refer to the facts provided by CD4+ cell count and VL load tests and encourage the patient to participate in the process of creating a new regimen or identifying supportive care

or behavioral changes that will ensure treatment success. The following management strategies may be helpful if problems with adherence are suspected or confirmed:

- If possible, simplify the ARV regimen (e.g., decrease pill count or dosing frequency)
- Provide symptomatic treatment of side effects, such as antiemetics or antidiarrheals; some patients may need scheduled antiemetics before each ARV dose until nausea abates
- Exchange one ARV for another within the same drug class (for medication intolerance)
- Exchange ARV from one drug class to another if necessary and if no prior drug resistance is suspected (for medication intolerance)
- Review recent history of gastrointestinal symptoms, such as vomiting or diarrhea, to assess the likelihood of short-term malabsorption
- Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (see Chapter 13, ***Pharmacologic Considerations in HIV Infected Pregnant Patients***; Drug Interactions section, Tables 14–16, *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012) and make appropriate substitutions
- If decreased ARV exposure due to pharmacokinetic drug-drug interactions or impaired drug absorption is suspected, therapeutic drug monitoring (TDM) may be helpful

Resistance Testing

When a regimen is changed for lack of efficacy, information from resistance testing can be of pivotal importance in choosing a new regimen.

Genotypic assays: These assays determine changes in the nucleotide sequences in viral genes. Interpretation of test results requires knowledge of the mutations for which different ARV drugs select and of the potential conferred by certain mutations for cross-resistance to other drugs. The International Antiviral Society-USA maintains an updated list of significant resistance-associated mutations in the RT, PR, integrase, and envelope genes (see https://www.iasusa.org/node/128; accessed 8/25/2012). The Stanford University HIV Drug Resistance Database (see http://hivdb.stanford.edu; accessed 8/25/2012) also provides helpful guidance for interpreting genotypic resistance test results.

Genotypes are reproducible, are less expensive than phenotypes, and provide relatively rapid results (1–2 weeks). Results are reported as a three-piece string of information for each mutation detected: 1) initial associated with the wild-type amino acid (e.g., M for methionine), 2) number of the codon involved (e.g., codon 184 in reverse transcriptase), and 3) initial associated with the

amino acid coded for by the mutated codon (e.g., V for valine). Thus, the common key mutation in the RT gene that confers complete resistance to 3TC and FTC is M184V.

Phenotypic assays: These assays directly determine the amount of a medication that is required to inhibit the patient's virus. The median inhibitory concentration (IC) 50 (the drug concentration that inhibits viral replication by 50%) is calculated and the ratio of the IC50 of test and reference viruses is reported as the *fold increase* in IC50 (i.e., fold resistance). Phenotypic assays are most useful for finding agents with partial activity in patients with multiple drug resistance; this approach is more expensive and time consuming than genotypic assays. In addition, although clinically significant fold-increase cutoffs are now available for some drugs, information is incomplete regarding the specific fold increase in IC50 that is associated with drug failure.

Limitations of resistance testing: Both phenotypic and genotypic assays are typically difficult to perform if the viral copy number is <1000 c/mL, although some specimens with >500 c/mL but <1000 c/mL can be successfully tested. The utility of these assays is also limited by an inability to detect resistant virus that makes up less than 10%–20% of the total viral population in a sample, termed *minority species*.

Furthermore, these assays will only reliably detect mutations that confer resistance to medications the patient is taking at the time the assay is performed; samples from patients who are off therapy are likely to show wild-type (sensitive) virus as the predominant circulating viral strain because it is the strain that replicates most successfully. Thus, resistance testing is insensitive to mutations secondary to selective pressure that is no longer present after a change in regimen. Virus with these mutations likely still exists as a small percentage of the circulating virus and may lead to clinical resistance if drugs that test "sensitive" are used; however, these drugs are inactive against resistant minority species, which can become dominant over time.

If the same ARV agents (or those sharing similar resistance pathways) are reinstated, early drug failure usually occurs; the virus present at failure is derived from previously archived resistant virus (*J Infect Dis* 2006;194(9):1309). Reversion to predominantly wild-type virus can occur in the first 4–6 weeks after drugs are stopped; therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued.

Patients with pansensitive virus in the face of virologic failure should be questioned carefully but nonjudgmentally about their medication-taking behaviors. TDM can also be considered, although no data currently demonstrate that TDM improves clinical outcome.

Treatment Interruptions (Drug Holidays)

Several studies have shown that both HIV-associated and non-HIV-associated outcomes (renal, cardiac, hepatic) are worse when treatment is interrupted (*N Engl J Med* 2006;355(22):2283; *Lancet* 2006;367(9527):1981; *HIV Med* 2007;8(2):96; *AIDS* 2004;18(3):439). Therefore, long-term interruption of HIV therapy should be avoided if at all possible.

Treatment of Acute and Recent HIV Infection

The benefits of treating acute and recent (with the first 6 months) HIV infection are not completely defined. The rationale for early treatment is that it will achieve early suppression of viremia with alteration of the initial viral setpoint. This can slow disease progression rates, reduce the rate of viral mutation by suppressing viral replication, preserve immune function, and reduce the risk of viral transmission. The potential risks of initiating therapy include exposure to ART without a known clinical benefit, drug toxicities, development of drug resistance, creation of an ongoing need for strict adherence to therapy, and adverse effects on quality of life. Unanswered questions about the risks and benefits of early therapy should be addressed with patients and treatment of early HIV infection should be offered. Enrollment in clinical trials and observational studies of acute HIV should be considered.

In treating acute HIV, it is always important to use a three- or four-drug regimen that would be expected to provide complete viral suppression. In addition to considering the source of exposure and local epidemiologic information, genotypic resistance testing should be performed. In acute HIV infection, a patient's predominant virus will be the strain that was transmitted, without reversion to the wild-type (pansensitive) virus that is seen in chronically infected patients who have stopped treatment.

Treatment in Pregnancy

ART is indicated in pregnancy to reduce the risk of perinatal transmission and to treat maternal disease. Specific guidelines for optimal therapy are addressed in Chapter 8, ***HIV and Pregnancy***, and in the DHHS guideline *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*, available at http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0/ (accessed 5/16/2013).

Alternative or Complementary Therapy

Some patients may ask questions about alternative or complementary therapy or may indicate that they are already taking such therapy. All patients should be specifically asked about their use of such therapies because they may not consider these remedies to be medications and may not volunteer the information to a care provider. Specific complementary therapies change rapidly and their use varies widely with geography and patient demographics.

For patients who do choose such therapies, it is important to ensure that they avoid using agents with toxicities or drug interactions that overlap with their prescribed medications and that discussions about complementary or alternative therapies occur in a way that does not alienate patients from their involvement in medical care.

Presentation and Management of Opportunistic Infections and Other Conditions Associated with HIV/AIDS

The risk for various opportunistic processes—so called because they take advantage of a weakened immune system—is defined by the total CD4+ lymphocyte count. Opportunistic processes include OIs and certain malignancies and are similar to the diseases seen in other immunocompromised hosts, such as recipients of solid-organ transplants. AIDS was first recognized as a new entity by the characteristic pattern of opportunistic diseases—especially PCP and Kaposi's sarcoma (KS)—that were being diagnosed in young, previously healthy gay men. The pattern and sequence of OIs that are seen as the total CD4+ cell count decreases, described in Table 4-7, is so reliable that in most cases the total CD4+ cell count limits the differential diagnosis.

Table 4-7

Correlation of Complications with CD4+ Cell Counts

CD4+ Cell Count*	Infectious Complications	Noninfectious† Complications
>500 cells/mm^3	• Acute retroviral syndrome • Candida vaginitis	• PGL • Guillain-Barré syndrome • Myopathy • Aseptic meningitis
200–500 cells/mm^3	• Pneumococcal and other bacterial pneumonia • Pulmonary tuberculosis • Herpes zoster • Oropharyngeal candidiasis (thrush) • Cryptosporidiosis, self-limited • KS • Oral hairy leukoplakia	• CIN • Cervical cancer • B-cell lymphoma • Anemia • Mononeuritis multiplex • ITP • Hodgkin's lymphoma • Lymphocytic interstitial pneumonitis
<200 cells/mm^3	• PCP • Candida esophagitis • Disseminated histoplasmosis and coccidioidomycosis • Miliary/extrapulmonary TB	• Wasting • Peripheral neuropathy • HIV-associated dementia • Cardiomyopathy • Vacuolar myelopathy • Progressive polyradiculopathy • Non-Hodgkin's lymphoma

Table 4-7 *continued*

Correlation of Complications with CD4+ Cell Counts

CD4+ Cell Count*	Infectious Complications	Noninfectious† Complications
<100 cells/mm^3	• Disseminated herpes simplex • Toxoplasmosis • Cryptococcosis • Cryptosporidiosis, chronic • Microsporidiosis • PML	
<50 cells/mm^3	• CMV end-organ disease: primarily retinitis (~80–85%), GI (~15%) • Disseminated MAC	• CNS lymphoma

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* Most complications occur with increasing frequency at lower CD4+ cell counts

† Some conditions listed as "noninfectious" are probably associated with transmissible microbes. Examples include lymphoma (Epstein-Barr virus [EBV]) and cervical cancer (human papillomavirus [HPV]).

Source: © Adapted with permission from *Medical Management of HIV Infection*. Baltimore: Johns Hopkins University School of Medicine; 2009-2010.

At CD4+ cell counts >500 cells/mm^3, illnesses are rarely associated with the patient's HIV serostatus. Non-Hodgkin's lymphoma and, rarely, mucocutaneous KS are occasional exceptions; they can occur at varying CD4+ cell counts but are more frequently diagnosed at lower values. Infections that are virulent among HIV-seronegative women, such as TB, bacterial pneumonia, and invasive cervical cancer, may occur at any CD4+ cell count but are more common and more severe as the CD4+ cell count declines.

Between 200 cells/mm^3 and 500 cells/mm^3, less-serious HIV-associated problems begin to manifest themselves, such as oral hairy leukoplakia, various skin problems, shingles, and oral or recurrent vaginal candidiasis (thrush). According to the 1993 CDC case definition, AIDS may be defined by specified OIs or by a decline in the total CD4+ cell count to below 200 cells/mm^3. This CD4+ cell count criterion acknowledges an important threshold for OI risk. PCP, the most common AIDS-defining OI, is usually diagnosed as patients approach and drift below this critical number. Other OIs, such as toxoplasmosis, cryptococcal meningitis, and disseminated histoplasmosis, tend to occur as the CD4+ cell count declines from <200 cells/mm^3 to <100 cells/mm^3. Typically, end-stage illnesses such as CNS lymphoma, CMV end-organ disease, and disseminated *Mycobacterium avium* complex (MAC), tend to occur at very low CD4+ cell counts, often less than 25–50 cells/mm^3.

Antimicrobial therapy works in concert with a patient's immune system to clear infection. Before the advent of potent combination ART, HIV-associated opportunistic diseases could not be controlled without ongoing suppressive therapy because a patient's immune function was too weak to effect that control. Once an OI was diagnosed and treated acutely (induction therapy, borrowing from the language of oncology), treatment would be continued at a lower maintenance dose or the OI would inevitably recur. "Cure" of OIs was not part of the vocabulary of HIV disease management. With potent combination ART resulting in dramatic improvement in CD4+ cell counts and immune function, however, both prophylactic and chronic suppressive OI therapies are being withdrawn successfully in responders. This has opened an entirely new era in the care of people with advanced HIV (see **Opportunistic Disease in the Era of Antiretroviral Therapy**, p. 132).

Prophylaxis of Opportunistic Infections

One of the early significant advances in the management of HIV/AIDS was the demonstration that chemoprophylaxis could prevent PCP and thereby improve survival. Before the development of potent combination ART, an important focus of the clinical research effort was to identify effective prophylactic agents for other common OIs. The success of this research was in part responsible for the slowdown in the death rate from AIDS that first became apparent near the end of 1995, just before the era of potent combination ART began.

Recommendations for prophylaxis for specific OIs depend on a number of factors (Table 4-8): the CD4+ threshold that defines the greatest risk, overall effectiveness of a given approach, risk of developing resistance, pregnancy, toxicity, and cost. The U.S. Public Health Service (USPHS)/Infectious Diseases Society of America guidelines for OI prophylaxis are updated periodically to reflect the most current understanding of disease risk and prevention. Current recommendations for initiating primary OI prophylaxis can be found on the Clinical Guidelines Portal of the AIDSinfo website (http://www.aidsinfo.nih.gov/guidelines; accessed 5/17/2013).

Table 4-8

Prophylaxis to Prevent a First Episode of Opportunistic Disease in Adults and Adolescents Infected With HIV

Pathogen	Indications	First Choice Regimen	Alternative Regimens
Pneumocystis jirovecii (formerly *carinii*)	Strong recommendation: • CD4+ cell count <200 cells/mm^3 ***or*** • Oropharyngeal candidiasis Moderate recommendation: • CD4+ percentage <14% ***or*** • History of AIDS-defining illness ***or*** • CD4+ cell count >200 but <250 cells/mm^3 and if CD4+ cell count monitoring every 3 mo is not possible	• TMP-SMX 1 DS or 1 SS po qd	• TMP-SMX 1 DS po tiw • Dapsone 100 mg po qd or 50 mg po bid • Dapsone 50 mg po qd + pyrimethamine 50 mg po qw + leucovorin 25 mg po qw • Dapsone 200 mg po qw + pyrimethamine 75 mg po qw + leucovorin 25 mg po qw • Aerosolized pentamidine 300 mg q mo via Respirgard II nebulizer • Atovaquone 1500 mg qd
Tuberculosis	Strong recommendation: • Screen (+) for latent TB infection but no evidence of active TB disease and no history of past treatment for active or latent TB - TST reaction ≥5 mm ***or*** - (+) Interferon gamma release assay • Screen (-) for latent TB infection and no evidence of active TB disease but close contact with case of active TB • *Note:* Patients with negative screening tests for latent TB and with CD4+ cell count <200 cells/mm^3 and no indications for initiating empiric latent TB treatment should be retested for latent TB once they start ART and attain a CD4+ cell count ≥200 cells/mm^3	• Isoniazid 300 mg po qd or isoniazid 900 mg po biw; both with pyridoxine, 25 mg po qd x 9 mo • For exposure to resistant TB, consult expert	• Rifampin 600 mg po qd x 4 mo or • Rifabutin (dose adjusted based on concomitant ART) x 4 mo
Toxoplasma gondii	Strong recommendation: • IgG antibody to toxoplasma and • CD4+ cell count <100 cells/mm^3 ***or*** • If toxoplasma seroconversion occurs	• TMP-SMX 1 DS po qd	• TMP-SMX 1 DS po tiw • TMP-SMX 1 SS po qd • Dapsone 50 mg po qd + pyrimethamine 50 mg po qw + leucovorin 25 mg po qw • Dapsone 200 mg po qw + pyrimethamine 75 mg po qw + leucovorin 25 mg po qw

Table 4-8 *continued*

Prophylaxis to Prevent a First Episode of Opportunistic Disease in Adults and Adolescents Infected With HIV

Pathogen	Indications	First Choice Regimen	Alternative Regimens
Mycobacterium avium complex	Strong recommendation: • CD4+ cell count <50 cells/mm^3 after ruling out active MAC infection (negative clinical assessment +/-negative MAC blood cultures)	• Azithromycin 1200 mg po qw • Clarithromycin 500 mg po bid • Azithromycin 600 mg po twice weekly • Both agents are better tolerated if taken with food	• Rifabutin 300 mg po qd (dosage adjustment based on drug-drug interactions with ART; see Table 13-9, pp. 500–507) • Rule out active TB before starting rifabutin
Malaria	• Travel to disease-endemic area	• Recommendations are the same for patients with and without HIV infection • One of the following three drugs is usually recommended depending on location: atovaquone/proguanil, doxycycline, or mefloquine • Refer to the following website for the most recent recommendations based on region and drug susceptibility: http://www.cdc.gov/malaria/ (accessed 7/31/2012) • Prevent exposure with use of DEET-containing repellants and insecticide-impregnated bed nets, when indicated	
Histoplasma capsulatum	Moderate recommendation: • CD4+ cell count ≤150 cells/μL and at high risk because of occupational exposure or living in area with high rate of histoplasmosis (>10 cases/100 patient-years)	• Itraconazole 200 mg po qd	
Coccidioido-mycosis	Moderate recommendation: • New (+) IgM or IgG in patients living in disease-endemic area and with CD4+ cell count <250 cells/μL	• Fluconazole 400 mg po qd	

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: Adapted from *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*

Regimens, doses, and indications for routine immunizations in HIV infected women are outlined in Table 4-9.

Table 4-9

Routine Immunizations for HIV Infected Women*

Vaccine	Dose and Regimen	Indications and comments
Hepatitis A	• 1 mL IM at 0, 6–12 mo (Havrix) • 1 mL IM at 0, 6–18 mo (Vaqta) • Also available in combination with HBV vaccine (Twinrix) given in 3–4 doses	• IDU, chronic liver disease, HBV or HCV infection, travel to endemic areas • Consider for all HIV infected patients who are hepatitis A antibody negative • IgG antibody response should be assessed 1 mo after vaccination; nonresponders should be revaccinated when CD4+ cell count >200 cells/μL
Hepatitis B	• Engerix B 20 mcg or Recombivax HB 10 mcg IM at 0, 1, and 6 mo • Available in combination with HAV vaccine (Twinrix) given in 3–4 doses	• Administer to patients without evidence of past or current HBV infection • In patients with isolated anti-HBc, consider screening for HBV DNA before vaccination to rule out occult chronic HBV infection • Test for anti-HBs after dose 3; repeat series should be considered for nonresponders (anti-HBs <10 IU/mL 1 mo after dose 3) and higher dose (40 mcg) booster is recommended by some experts • Some experts may delay revaccination until sustained increase in CD4+ cell count with ART if CD4+ cell count is <350 cells/mm^3 when patient is first vaccinated
HPV	• Gardasil 0.5 mL IM at 0, 1–2, and 6 mo or • Cervarix 0.5 mL IM at 0, 1–2, and 6 mo	• Girls and women aged 9–26, ideally before onset of sexual activity; may consider in other groups • Safety and immunogenicity studies in HIV infected patients are ongoing
Influenza	• 0.5 mL IM annually	• All patients • Do not use live attenuated intranasal vaccine (FluMist)
Pneumococcal	• 0.5 mL IM of the polyvalent polysaccharide vaccine 13 followed by 0.5 mL IM of the polyvalent polysaccharide vaccine 23 at least 8 wk later (if CD4+ cell count <200 cells/μL, consider waiting until CD4+ cell count >200 cells/μL)	• All patients, regardless of CD4+ cell count • Moderate recommendation for re-vaccination with 23-valent vaccine ≥5 years after initial vaccination

Table 4-9 *continued*

Routine Immunizations for HIV Infected Women*

Vaccine	Dose and Regimen	Indications and comments
Polio	• 0.5 mL SC; 3 doses over 6–12 mo for primary immunization	• OPV contraindicated; IPV should be given if vaccine is indicated
Tetanus toxoid	• Td 0.5 mL IM; Tdap 0.5–0.75 mL IM as per package insert	• Same as for patients who are not HIV infected • Substitute single dose of Tdap at time of next booster, then Td every 10 y
Varicella	• 0.5 mL IM as two doses given 3 mo apart	• Administer if patient has CD4+ cell count >200 cells/mm^3 and no evidence of immunity to varicella • *Post-exposure prophylaxis:* VZIG, 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 h after exposure to a person with active varicella or herpes zoster for patients with no evidence of immunity to varicella

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* See Chapter 8, ***HIV and Pregnancy***, for recommendations for pregnant women

Source: © Adapted from *Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus*: 2009 Update by the HIV Medicine Association of the Infectious Diseases Society of America (*Clin Infect Dis* 2009;49:651)

Common Opportunistic Infections and Other Conditions Associated with HIV

Summaries with some key points are presented below (adapted from CDC *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents*. 2013). More detailed discussion is beyond the scope of this guide; specific treatment agents and alternatives and dosing regimens for acute conditions and secondary OI prophylaxis, respectively, can be found on the Clinical Guidelines Portal of the AIDSinfo website (http://www.aidsinfo.nih.gov/guidelines).

Initiation of ART as soon as possible during the course of treatment for an acute OI has been associated with longer survival, shorter time to CD4+ cell count >50 cells/mm^3, and no increase in adverse effects (*PLoS One* 2009;4(5):e5575). Rapid initiation of ART will also shorten the duration of chronic maintenance (suppressive) therapy (i.e., secondary prophylaxis) for most patients as they recover immune responsiveness more quickly.

Pneumocystis jirovicii Pneumonia

Diagnosis: Because the presentation of PCP can be subtle and nonspecific, a heightened index of suspicion is warranted in appropriate circumstances. Most commonly, symptoms include the subacute onset of fever, exertional dyspnea, and nonproductive cough and chest discomfort that worsen over days to weeks.

Physical exam findings are also nonspecific. Auscultation may be entirely normal, particularly at rest with mild disease. Fine, dry "cellophane" rales may be heard with exertion. In 2%–6% of patients, PCP may present as spontaneous pneumothorax. The classic CXR findings are diffuse interstitial or perihilar infiltrates, but a wide range of CXR abnormalities is possible and radiography is normal in many cases of early disease. PCP is suggested by oxygen desaturation with exercise, which is easily measured in the office or clinic with a pulse oximeter, with the patient first at rest and then after running up a flight of steps, for example. This is particularly useful when symptoms are minimal, the patient does not appear acutely ill, and the CXR is unimpressive. Severity of illness is indicated by hypoxemia or a widened alveolar-arterial oxygen difference ($AaDO_2$) on blood gas analysis.

Other etiologies of pneumonia may have a similar presentation. The definitive diagnostic test requires histopathologic or cytologic identification of *Pneumocystis* organisms in bronchoalveolar lavage (generally preferred), induced sputum, or transbronchial or open-lung biopsy. Although induced sputum is less invasive and less expensive, it should not be attempted in the absence of expertise in both obtaining and interpreting the smear.

Treatment: The mainstay of treatment for PCP is TMP-SMX, administered intravenously or orally depending on the severity of the episode. PCP should be treated for 21 days. Patients with arterial oxygen pressure <70 mm Hg or with $AaDO_2$ >35 on room air should receive adjunctive steroids, which have been shown to decrease the incidence of ventilatory failure and death. A 21-day course of prednisone (40 mg bid x 5 days, then 20 mg bid x 5 days, followed by 20 mg qd x 11 days) is the most popular and cost-effective approach. No additional taper is required.

After completing acute therapy, the patient should begin routine daily PCP prophylaxis to prevent recurrence. PCP prophylaxis can be discontinued after ART has led to an increase in CD4+ cell count to >200 cells/mm^3 for >3 months. (See **Prophylaxis of Opportunistic Infections**, p. 115.)

Candidiasis

The appearance of mucosal candidiasis is often the first clinical indication of impaired T-cell immunity in HIV infected individuals. Candida esophagitis is the second most common OI after PCP, and other mucosal forms of candidiasis (e.g, oral thrush, vaginal candidiasis) are common. Candidemia and tissue-invasive disease are rare, however.

Candida esophagitis is a serious infection that may result in significant weight loss because of odynophagia and reduced oral intake. Esophagitis should be considered when the patient describes midline substernal chest discomfort with swallowing instead of pain limited to the throat. It may occur in the absence of oropharyngeal thrush and can be diagnosed by endoscopy with visualization of lesions and histopathologic demonstration of characteristic *Candida* yeast forms and/or culture confirmation. Empiric treatment may be considered in many circumstances. If the patient's symptoms do not resolve, endoscopy with biopsy is recommended for a definitive diagnosis, as HSV and CMV infection and giant aphthous ulcers can have the same presentation.

Diagnosis: Oropharyngeal candidiasis is characterized by painless white plaques that can be easily scraped from the pharynx or buccal mucosa; severe cases will involve the tongue, gums, and lips; significant erythema may be present. Less commonly, erythematous patches without white plaques can be seen on the upper palate or tongue. Pharyngitis may be asymptomatic or may cause dysphagia or burning. Vaginal candidiasis presents similarly in HIV infected and uninfected women; however, episodes may be more severe or frequent in women with advanced immunosuppression (see Chapter 6, ***Gynecologic Problems***). For oropharyngeal or vaginal candidiasis, diagnosis usually involves a consistent clinical presentation and demonstration of yeast forms on microscopy from scrapings in potassium hydroxide preparation; culture is rarely needed but can be helpful in some situations.

Treatment: The treatment of choice for esophagitis is oral fluconazole 100–400 mg po or intravenously (IV) qd or itraconazole 200 mg po qd for 14–21 days; topical agents should not be used. Oropharyngeal or vaginal candidiasis may be treated with topical or oral antifungals; topical agents are more cost-effective and avoid the risk of systemic side effects or drug-drug interactions.

Cryptococcal Meningitis

Cryptococcal meningitis may present as nothing more than the worst headache of the patient's life. Fever is common but meningismus may be minimal or absent. Altered mental status is associated with a poorer prognosis. Cranial nerve deficits and seizures are seen only in patients who present very late in the course of their infection.

When cryptococcosis occurs in the setting of HIV infection, disseminated disease is common and virtually any organ can be involved. Skin lesions resembling *Molluscum contagiosum* and isolated pulmonary infection are not infrequent.

Diagnosis: The diagnosis of cryptococcal meningitis is made by detecting cryptococcal capsular antigen in the cerebrospinal fluid (CSF). Relying upon a positive CSF India ink stain that demonstrates the organism's thick capsule is positive in only about 60%–80% of cases. Serum cryptococcal antigen is also almost always positive in cases of CNS disease and in other instances of disseminated infection. *Cryptococcus neoformans* may also be cultured from blood and CSF. When performing a diagnostic lumbar puncture, the opening pressure may be elevated, with pressures $\geq$25 cm H_2O occurring in most patients.

Treatment: The recommended initial standard treatment is IV amphotericin B (liposomal) combined with flucytosine for ≥2 weeks. Renal function should be monitored closely and dose adjustments made if indicated. Intracranial hypertension can be managed with frequent lumbar punctures to remove large volumes of CSF (20–30 mL at a time).

After at least 2 weeks of successful induction therapy (clinical response plus negative CSF culture on repeat lumbar puncture), amphotericin B/flucytosine may be discontinued and therapy with fluconazole 400 mg po or IV qd may be initiated and continued for 8 weeks.

Following the initial 10 weeks of therapy, initiate chronic maintenance therapy with fluconazole 200 mg qd for at least 1 year. Maintenance therapy can be discontinued in patients who have a sustained increase in CD4+ cell count to >100 cells/mm^3 for ≥3 months and suppressed HIV VL in response to ART.

Toxoplasmosis

The most common clinical presentation of *T. gondii* infection among patients with AIDS is focal encephalitis with headache, confusion, or motor weakness and fever. Physical examination may demonstrate focal neurological abnormalities, and in the absence of treatment, disease progression results in seizures, stupor, and coma.

Diagnosis: CT or magnetic resonance imaging (MRI) classically reveals one or more ring-enhancing, space-occupying lesions, although the radiographic appearance of the lesions may mimic other processes, such as primary CNS lymphoma.

Most HIV infected persons are seropositive for anti-toxoplasma IgG; absence of the antibody makes the diagnosis unlikely but not impossible. Definitive diagnosis requires a consistent clinical presentation, compatible radiographic findings, and a brain biopsy demonstrating *T. gondii* organisms. Most clinicians, however, rely initially on empiric treatment for toxoplasmosis in the absence of a likely alternative diagnosis, with confirmation of the diagnosis based on objective response (i.e., clinical and radiographic improvement). Brain biopsy is generally reserved for patients who fail to respond to specific therapy.

Treatment: The initial therapy of choice for toxoplasma encephalitis (TE) is a combination regimen consisting of pyrimethamine, sulfadiazine, and leucovorin. Acute therapy for TE should be continued for at least 6 weeks and longer if clinical or radiologic disease is extensive or if response is incomplete at 6 weeks.

After initial therapy for acute infection, chronic maintenance therapy should be administered, with the preferred regimen also a combination of pyrimethamine, sulfadiazine, and leucovorin (with slightly altered dosing), which also provides protection against PCP. Alternative regimens also provide protection against PCP, with the exception of pyrimethamine plus clindamycin. Secondary prophylaxis can be discontinued after successful initial therapy, when the patient remains without signs or symptoms of TE and her CD4+ cell count increases to >200 cells/mm^3 for >3 months in response to ART.

Tuberculosis

TB is one of the most common HIV-related OIs in the world. Because TB is virulent enough to cause disease in patients with intact immune systems, it may occur in HIV infected individuals who still have high CD4+ cell counts (*MMWR Recomm Rep* 2009;58(RR-4:1). Because rates of progression from latent to active TB are significantly increased in the setting of HIV, annual screening of all HIV infected patients is critical.

TB in HIV infected patients: In HIV infected patients with CD4+ cell counts >350 cells/mm^3, TB clinically resembles TB among HIV uninfected people, with disease generally limited to the lungs. Common CXR findings include upper-lobe infiltrates with or without cavitation. In advanced HIV disease, the CXR findings of pulmonary TB are markedly different: lower-lobe, middle-lobe, interstitial, and miliary infiltrates are common whereas cavitation is less common. Marked mediastinal lymphadenopathy can also be seen.

Extrapulmonary disease is more common in the setting of HIV infection, regardless of CD4+ cell count, and is found in most TB patients with CD4+ cell counts <200 cells/mm^3.

In patients with severe immunodeficiency and a high mycobacterial load, TB disease may have few symptoms. With immune reconstitution after initiation of ART, however, patients may develop acute signs and symptoms of active TB. This type of immune-reconstitution inflammatory syndrome (IRIS) can manifest as early as 7 days after starting ART.

Diagnosis: For both the PPD and interferon-gamma release assays, HIV-related immunosuppression may be associated with false-negative results. Approximately 25% of HIV infected patients with pulmonary TB disease have false-negative results (*Ann Intern Med* 2007;146:340).

If active TB Is suspected, a CXR should be obtained; sputum samples for acid-fast bacilli smear and culture should be obtained from patients with pulmonary symptoms and CXR abnormalities. A normal CXR does not exclude the possibility of active pulmonary TB; sputum samples should still be obtained if suspicion is high. The sputum smear may be negative, particularly with advanced immunosuppression and noncavitary disease, but it is not affected by HIV or immunosuppression. Drug-susceptibility testing and adjustment of the treatment regimen on the basis of the results of such testing are critical to the successful treatment of patients with TB and to preventing transmission of drug-resistant *Mycobacterium tuberculosis*.

Treatment: When active TB is diagnosed or suspected, a multi-drug anti-TB treatment regimen should be started immediately. Directly observed therapy is recommended for all patients. Until susceptibilities are known, all HIV infected patients should be treated initially with at least four drugs expected to be active on the basis of local susceptibility patterns. Treatment of drug-susceptible TB disease should include a 6-month regimen with an initial phase of INH, RIF (or rifabutin), PZA, and EMB administered for 2 months, followed by INH and RIF (or rifabutin) for 4 additional months. More-prolonged therapy is recommended for patients with a delayed response to therapy and for those with CNS disease or bone and joint TB. All patients receiving INH should

also receive pyridoxine supplementation. Expert consultation is recommended when treating TB, including when making decisions about the optimal timing of the initiation of ART. Treatment should be coordinated through the local public health department.

All close contacts of the patient—especially young children—must be evaluated for TB so that they may be treated promptly for active disease or given prophylaxis as indicated.

Herpes Simplex Virus (see Chapter 6, ***Gynecologic Problems***)

Cytomegalovirus

CMV causes retinitis in 80%–85% of AIDS patients with end-organ CMV disease. Gastrointestinal disease, which can occur anywhere from the mouth to the anus, is diagnosed in another 12%–15%. Other diagnoses, such as encephalitis and pneumonitis, are uncommon (1%).

CMV retinitis can cause visual loss and progresses inexorably to blindness in the absence of ART or specific treatment. In two-thirds of patients, CMV retinitis occurs as unilateral disease at presentation; however, most patients develop bilateral disease in the absence of therapy or immune recovery. Patients may be completely asymptomatic or may complain of floaters (due to inflammatory debris), diminished acuity, or visual field defects with peripheral lesions.

Diagnosis: Diagnosis is made by visual inspection of the entire retina by an experienced ophthalmologist using dilated indirect ophthalmoscopy. Extensive disease may lead to retinal detachment, which may require surgical repair. Retinitis near critical structures such as the macula or optic nerve may cause catastrophic visual loss even when the total infected area is small.

Diagnosis of CMV colitis or esophagitis requires the presence of shallow, often large and extensive mucosal ulcerations with histopathologic evidence of characteristic intranuclear and intracytoplasmic inclusions. Culturing CMV from a biopsy or lesion is not sufficient to establish the diagnosis in the absence of histopathologic changes because CMV viremia can be present in the absence of clinical disease in persons with low CD4+ cell counts.

Treatment: The ganciclovir intraocular implant coupled with valganciclovir is the recommended treatment for CMV retinitis for immediate sight-threatening lesions. Systemic therapy has been documented to reduce morbidity in the contralateral eye. Decisions about the choice of treatment should be individualized on the basis of the location and severity of lesions, level of immunosuppression, other medications, and adherence considerations. Generally, CMV colitis or esophagitis is treated with IV ganciclovir or foscarnet or oral valganciclovir in milder disease and if able to tolerate oral therapy.

Secondary prophylaxis is recommended after CMV retinitis. The choice of agent should be made with expert consultation. Prophylaxis can be discontinued after an increase in the CD4+ cell count to >100 cells/mm^3 has been sustained for at least 3–6 months in response to ART, after ophthalmologic consultation.

Disseminated *Mycobacterium avium* Complex

Disseminated MAC presents nonspecifically with fever, weight loss, diarrhea, anemia, elevated alkaline phosphatase, and, in some cases, abdominal distention or discomfort due to organomegaly and massive intra-abdominal lymphadenopathy.

Diagnosis: Mycobacterial culture from blood, lymph-node, bone-marrow, or other normally sterile tissue or body fluid provides a definitive diagnosis; culture of sputum is not helpful.

Treatment: Combination antimycobacterial therapy is required with two or more antimycobacterial drugs to prevent or delay the emergence of resistance. Recommended first-line agents are clarithromycin and ethambutol or azithromycin and ethambutol; some experts recommend adding a third drug for patients with CD4+ cell counts <50 cells/microliter, with high mycobacterial load or in absence of effective ART. Generally, initiation of ART in patients with disseminated MAC disease who are not already on effective ART should be delayed until after the first 2 weeks of antimycobacterial therapy have been completed to reduce the risk for drug-drug interactions, adherence problems due to pill burden, and potential IRIS.

The same drug regimen should be continued for secondary prophylaxis. This regimen can be discontinued after completion of at least a 12-month course of treatment if the CD4+ cell count increases to >100 cells/mm^3 for >6 months in response to ART.

Cryptosporidiosis and Microsporidiosis

These enteric microorganisms can cause debilitating diarrhea and weight loss, often associated with severe dehydration in patients with advanced HIV disease.

Diagnosis: Cryptosporidiosis and microsporidiosis are generally diagnosed with special stool stains.

Treatment: Because no effective specific therapy exists, the mainstay of treatment is ART with immune reconstitution and supportive care (volume repletion and attempts at slowing the diarrhea). Clinical resolution (and even clearing of the organism from stool) have been documented with potent ART.

Attempts at slowing the diarrhea should be made by *adding* (not substituting) additional agents in a stepwise manner as follows:

- Diphenoxylate or loperamide, increased to their maximum dose, followed by
- Tincture of opium or paregoric, with the dose titrated gradually until the desired effect is achieved

HIV-Associated Dementia (HAD) and HIV Encephalopathy

In the pre-ART era, frank dementia was the AIDS-defining illness in up to 10% of patients. HAD is characterized by symptoms of cognitive, motor, and/or behavioral disturbances. The initial manifestations may be subtle and can be uncovered by questioning a patient carefully about short-term memory loss and difficulty concentrating. Useful questions about the latter include the ability to balance a checkbook or make change. In some patients a depressed affect may be a prominent finding, whereas unexplained seizures may bring other patients to medical attention. Psychomotor retardation—slowing of the impulses that match actions to thoughts and intentions—is another hallmark of HAD.

Diagnosis: CT and MRI scans show diffuse cortical loss with prominent sulci ("walnut sign"). A good sense of the patient's level of cognitive functioning can often be obtained at the bedside. In subtle or difficult cases, especially with a history of depression or subnormal intelligence quotient, the patient can be referred for a battery of neuropsychologic tests that demonstrate the losses characteristic of HAD. It is important to rule out other possible causes of changes in mental function (e.g., cerebrovascular disease, CNS neoplasm or other infection, severe depression, substance abuse, or metabolic/systemic disorders).

Treatment: Even patients who present with advanced dementia may demonstrate a remarkable degree of recovery with ART, so it is valuable to attempt treatment of all patients, even those initially referred for hospice or nursing home care. Because of indications that potent ART with poorer CNS penetration may predispose a patient to neurologic problems despite good suppression of HIV VL, it may be particularly useful to include agents that achieve good CSF levels.

Wasting Syndrome (aka "Slim Disease")

Although weight loss is common in HIV disease, especially in its advanced stages, the CDC surveillance definition of wasting syndrome specifically refers to involuntary weight loss that equals or exceeds 10% of the patient's baseline weight plus either diarrhea (≥2 loose stools per day lasting ≥30 days) or chronic weakness with documented fever (intermittent or constant) for ≥30 days that is not attributable to a condition other than HIV itself.

Typically, wasting syndrome is accompanied by loss of muscle mass—for example, in the temporal areas—and complaints of generalized fatigue and weakness. In severe cases, the serum albumin level will be very low.

Wasting can accompany any of the typical end-stage OIs, such as disseminated MAC, or may occur by itself in the absence of any evident concomitant illness. Loss of weight, and especially loss of lean body mass, portends poorer survival.

Treatment: Initiation of effective ART is the best management strategy. Appetite stimulants, such as the progestin megestrol acetate or the marijuana derivative dronabinol, may be used, although weight gain with these agents

typically consists of fat and water rather than an increase in lean body mass. The psychological benefit of an improved appetite and some weight gain cannot be underestimated, however, even if the gain is primarily fat.

Central Nervous System Lymphoma

CNS lymphoma generally occurs at total CD4+ cell counts under 50 cells/mm^3 and is a typical end-stage complication.

Diagnosis: Symptoms include confusion, headache, memory loss, aphasia, and possible seizures without fever. Focal or nonfocal signs may be present. Definitive diagnosis is made by a brain biopsy or by CSF cytology (and possible Epstein-Barr virus [EBV] DNA in CSF) in the presence of one or more space-occupying lesions on CT or MRI scan. A presumptive diagnosis may sometimes be made by nuclear single-photon emission CT scan. Because a brain biopsy may be difficult to obtain, patients who do not respond to a trial of therapy for toxoplasmosis are often assumed to have CNS lymphoma.

Treatment: Standard therapy is radiation plus corticosteroids or methotrexate. Survival after a diagnosis of CNS lymphoma is usually very limited.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is another end-stage complication of HIV disease, usually presenting as cognitive impairment, visual field impairment, or other focal neurologic deficit(s).

Diagnosis: PML is caused by the JC virus, which can be detected by PCR performed on CSF. An MRI scan of the brain demonstrates involvement of the white matter that can be focal or fairly diffuse but is not usually associated with either mass effect or surrounding edema. Most commonly, PML affects areas adjacent to the cortex, but lesions can be located anywhere in the brain. A definitive diagnosis is made by a brain biopsy or positive PCR, which is highly specific in the appropriate clinical context. Where these diagnostic modalities are unavailable, the typical MRI image usually suffices.

Treatment: Although no specific therapy exists for PML, this is another AIDS-associated condition that responds markedly well to potent ART. Patients can recover significant intellectual and physical functioning with ART, although not all deficits may resolve completely.

Systemic Lymphoma

HIV infected patients have an increased frequency of Hodgkin's disease, immunoblastic lymphoma, and Burkitt's lymphoma, as well as less common forms of this disease; however, the most common type of lymphoma in HIV infected patients is an aggressive non-Hodgkin's B cell lymphoma. Although lymphomas may occur at any CD4+ cell count, the prognosis is worse at lower absolute CD4+ cell counts.

A marked tendency for extranodal presentations has been observed and non-Hodgkin's lymphoma has been described over a range of unusual sites in HIV infected patients.

Diagnosis and treatment: AIDS-associated lymphoma is diagnosed and staged in the same manner as in HIV uninfected patients and the same types of combination chemotherapy are used. HIV infected patients may, however, require lower doses of chemotherapy or aggressive support with granulocyte colony-stimulating factor because of their baseline bone-marrow fragility. Advances in bone marrow transplant techniques offer new opportunities for treatment.

Chronic Hepatitis B and Hepatitis C

Many of the same behaviors that put women at risk of acquiring HIV also put them at risk for HBV and/or HCV infection. Up to 90% of HIV infected individuals have evidence of prior exposure to HBV and up to 10% have chronic HBV infection (*J Acquir Immune Defic Syndr* 1991;4(4):416; *J Infect Dis* 1991;163(5):1138). A cross-sectional analysis of a large heterogeneous group of HIV infected individuals found that 16% had HCV coinfection (*Clin Infect Dis* 2002;34(6):831), whereas among HIV infected IDUs in the United States, HCV infection rates range from 70%–95%.

Diagnosis: Both acute and chronic HBV and HCV infections are often asymptomatic or present with minimal or nonspecific symptoms such as fatigue. When present, symptoms of acute infection might include right-upper-quadrant abdominal pain, nausea, vomiting, fever, anorexia, dark urine, and jaundice. All HIV infected women should be serologically screened for HBV and HCV with HBsAg, HBsAb, HBcAb and HCV Ab at entry into care. HBV DNA should be obtained if HBsAg or HBcAb positive. Chronic HBV is defined as HBsAg positive on two occasions at least 6 months apart. Patients with chronic HBV infection should be further tested for HBV e antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA. If there is an isolated HBcAb positive test and HBsAg is negative, HBV DNA testing should be considered. HCV infection is diagnosed if HCV Ab positive with detectable HCV RNA. With abnormal LFTs and negative serology, a qualitative HCV RNA PCR test should also be considered.Women with detectable HCV should be tested for HCV genotype. If acute hepatitis is suspected, screen with HAV IgM Ab, HCV Ab, and HBsAg +/- HBc IgM Ab.

HIV infection is associated with an increased risk of developing chronic HBV infection (*J Infect Dis* 1991;163(5):1138) and more rapid progression of both HBV- and HCV-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC), and fatal hepatic failure (*AIDS* 2008;22(15):1979; *Lancet* 2002;360(9349):1921). Periodic screening for HCC (every 6–12 months) with serum AFP level and ultrasound of the liver is recommended, particularly in patients with documented cirrhosis or other high-risk characteristics (e.g., older age). (*Hepatology* 2002;36(5 Suppl 1):S84). A liver biopsy to evaluate the activity and severity of hepatitis-related disease is useful to monitor progression and guide treatment decisions; decisions to perform liver biopsy should be individualized, with expert consultation.

The goals of therapy are to prevent disease progression, reduce viral hepatitis-related morbidity and mortality and, in the case of HCV infection, eradicate infection. ART may attenuate liver disease progression in persons coinfected with HBV and/or HCV by preserving or restoring immune function and reducing HIV-related immune activation and inflammation (*Hepatology* 2009;50(4):1056; *BMC Res Notes* 2008;1:46; *Haemophilia* 2009;15(2):552).

High HBV DNA levels predict progression of liver disease, development of HCC, and a reduced response to therapy. The decision to treat depends not only on the level of HBV viremia and the degree of biochemical and/or histologic disease but also on whether the patient is initiating ART.

Treatment of HBV: ART is recommended for all HIV/HBV coinfected patients, regardless of CD4+ cell count or HBV treatment status. Regardless of the level of HBV DNA, ART must include two drugs active against HBV, preferably TDF and FTC, to reduce risk for IRIS, reduce the development of HBV drug-resistance mutations, and help to prevent the development of significant liver disease by directly suppressing HBV replication (*Hepatology* 2008;48(4):1062; *Hepatology* 2006;44(5):1110). If HIV/HBV coinfected patients do not want or are unable to take ART, treatment of active HBV (elevated alanine aminotransferase [ALT] and elevated HBV DNA >2000 IU/mL or significant fibrosis) with pegylated interferon (pegIFN) is indicated (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents.* 2013).

Hepatitis C (HCV) becomes a chronic infection in about 85% of cases. Six distinct HCV genotypes have been described, with genotype 1 infection accounting for approximately 75% of all HCV infections in the United States. HCV genotyping should be performed in all HIV infected patients who are considering HCV treatment, both to guide ribavirin (RBV) dosing and because genotyping is the best predictor of response to interferon-based treatment and may therefore influence the decision to treat and/or perform a liver biopsy.

Treatment of HCV: Antiviral treatment for HCV infection should be considered for all HIV infected patients with acute or chronic HCV infection. Treatment of acute infection (<6 months from the time of HCV exposure) may prevent the development of chronic HCV infection. (*N Engl J Med* 2001;345(2):1452; *Gastroenterology* 2006;130:632). In the presence of chronic HCV infection, treatment should be considered in the following situations: HCV genotype 2 or 3 infection, HCV genotype 1 infection with a low HCV RNA level (<800,000 IU/mL), significant hepatic fibrosis (bridging fibrosis or cirrhosis), stable HIV infection not requiring ART, and cryoglobulinemic vasculitis or glomerulonephritis.

PegIFN plus RBV has been the mainstay of treatment for HCV in HIV infected patients. In HCV genotype 1–infected patients without HIV, addition of the recently FDA-approved drugs boceprevir or telaprevir significantly improves the rate of sustained virologic response; clinical trials of these drugs in HIV-infected patients are currently underway. Both boceprevir and telaprevir have significant interactions with certain ARV drugs, which may affect dosing or the ability to use these agents (see Table 13-8, p. 500). For patients with CD4+ counts <200 cells/mm^3, it may be preferable to initiate ART and delay

HCV therapy until CD4+ counts increase because of better response to HCV treatment at higher CD4+ cell counts (*Hepatology* 2009;49:1335; *J Acquir Immune Defic Syndr* 2009;52:452). Taking into account the rapid pace of HCV drug development and evolving information on drug interactions and use in the setting of HIV, treatment decisions should be made with expert consultation (http://www.aidsinfo.nih.gov/guidelines; accessed 5/17/2013).

IRIS with either HBV or HCV may manifest as dramatic increases in serum aminotransferases as CD4+ cell counts rise within the first 6–12 weeks after starting ART, with signs and symptoms of hepatitis flares.

HIV-Associated Nephropathy

In HIV infected patients, HIVAN is the most common cause of chronic kidney disease leading to end-stage kidney disease (*Kidney Int* 2004;66(3):1145). It is seen almost exclusively in Black patients and can occur at any CD4+ cell count. Ongoing viral replication appears to be directly involved in renal injury (*Nat Med* 2002;8(5):522). HIVAN is an uncommon condition in patients with suppressed viral loads (*Clin Infect Dis* 2006;43(3):377).

ART in patients with HIVAN has been associated with preserved renal function and better survival (*Nephrol Dial Transplant* 2006;21(10):2809; *J Am Soc Nephrol* 2005;16(8):2412; *AIDS* 2008;22(4):481) and therefore should be started in these patients.

Cardiovascular Disease

Cardiovascular disease is a major cause of mortality among HIV infected patients, accounting for a third of serious non-AIDS conditions and at least 10% of deaths among HIV infected patients (*AIDS* 2010;24(10):1537; *J Acquir Immune Defic Syndr* 2010;55(2):262).

In some cross-sectional studies, patients with HIV were found to have higher levels of markers of inflammation and endothelial dysfunction than HIV uninfected controls (*J Acquir Immune Defic Syndr* 2008;49(5):499; *J Acquir Immune Defic Syndr* 2009;52(1):25). In addition, several studies have found increased markers of inflammation and coagulation, as well as increased risk of cardiovascular events, following treatment interruption (*AIDS* 2009;23(8):929; *PLoS Med* 2008;5(10):e203; *N Engl J Med* 2006;355(22):2283).

ART has been associated with marked improvements in parameters associated with cardiovascular diseases, including markers of inflammation (e.g., interleukin 6 [IL-6] and high-sensitivity C-reactive protein [hsCRP]) and endothelial dysfunction (*J Am Coll Cardiol* 2008;52(7):569). Early initiation of ART is increasingly being promoted as a strategy to reduce cardiovascular disease risk (*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012).

Malignancies

Several population-based analyses suggest an increased incidence of non-AIDS-associated malignancies during chronic HIV infection compared with that in matched HIV uninfected controls (*J Acquir Immune Defic Syndr* 2009; 52:203). Large cohort studies mostly comprising patients receiving ART have reported a consistent link between low CD4+ cell counts (<350–500 cells/mm^3) and the risk of AIDS and/or non-AIDS-defining malignancy (*J Acquir Immune Defic Syndr* 2009;52(1):203; *AIDS* 2009;23(13):1743; *Lancet Oncol* 2009; 10(12):1152; *AIDS* 2008;22(16):2143; *Clin Infect Dis* 2009;49(7):1109).

One prospective cohort study found a statistically significant relative risk of all cancers evaluated (except for anal carcinoma) in patients with CD4+ cell counts <500 cells/mm^3 compared with patients with current CD4+ cell counts >500 cells/mm^3 and a protective effect of ART for HIV-associated malignancies (*Lancet Oncol* 2009; 10(12):1152). The risk is particularly prominent in cancers associated with chronic viral infections (e.g., HBV, HCV, HPV, EBV, and human herpes virus-8) (*AIDS* 2009;23(17):2337; *Lancet* 2007;370(9581):59).

Anemia

Modest anemia (≥9–10 g/dL) is a hallmark of chronic HIV infection and in women of childbearing age may be complicated by menstrual blood loss. Severe anemia (≤9 g/dL) may occur as part of certain opportunistic diseases, especially MAC, disseminated histoplasmosis, and lymphoma, and may also result from drug toxicity.

Although severe anemia has been shown to be associated with poorer survival in several studies (*J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19(1):29; *Semin Hematol* 2000;37(4 Suppl 6):18), initiation of ART (*J Acquir Immune Defic Syndr* 2002;29(1):54) and diagnosis and treatment of the opportunistic process are often sufficient to improve anemia in these cases.

Patients who are symptomatic with exertional dyspnea and dizziness can be transfused acutely. Most HIV infected patients gradually become anemic and unconsciously limit their activities to control symptoms. These patients can be managed with changes in ART or OI therapies known to have hematologic toxicity (e.g., ZDV, TMP-SMX). In patients whose anemia is refractory to conservative management, red blood cell production can be stimulated by using recombinant erythropoietin along with sufficient iron replacement to stimulate production of new red cells.

Opportunistic Disease in the Era of Antiretroviral Therapy

The impact of ART on the natural history of opportunistic diseases has been profound and the clinician must be familiar with at least the broad outline of these changes. Immune restoration in a patient on ART may be sufficient even for patients with end-stage disease to mount an inflammatory response to opportunistic pathogens. Paradoxically, this can result in worsening of an OI that has been under active treatment or in an atypical presentation of a new acute OI, generally within the first couple of months after initiating potent ART, when CD4+ cell counts have begun to improve. For example, a patient may acutely develop a tender, focal lymphadenitis due to MAC with negative blood cultures, whereas in the pre-ART era MAC would have presented as a disseminated disease with diffuse, nontender adenopathy and high-grade mycobacteremia. This seemingly paradoxical development of an OI in a patient with rising CD4+ cell counts is likely due to an inflammatory response to an OI that was subclinical or recently acquired when ART was initiated. The development of IRIS during treatment for most of the OIs has been well described. Management includes the continuation of ART plus the addition of nonsteroidal anti-inflammatory drugs or corticosteroids (especially in TB) to alleviate the inflammatory reaction.

Patients who recover pathogen-specific immunity in addition to experiencing an overall increase in the CD4+ cell count may be able to discontinue chronic suppressive (maintenance) therapy because their immune systems are now capable of containing the infection. Thus far, this has been best demonstrated for discontinuing chronic suppression of CMV retinitis. Similar phenomena have been described for other OIs, such as disseminated MAC, and there is no reason to think that other OIs will behave differently. Finally, patients with previously untreatable opportunistic processes, such as PML or cryptosporidiosis, have had clinical remissions after initiating ART.

Several studies have shown that patients receiving primary prophylaxis for PCP and MAC are at very low risk for developing these OIs if prophylaxis is withdrawn after total CD4+ cell counts have risen above the threshold risk levels for each specific OI and been sustained for at least 3–6 months. Most of these studies have been performed among patients with reasonably well-controlled HIV VLs, with most having an undetectable VL. At this point, it is clear that specific prophylaxis can be safely stopped for any OI when CD4+ cell counts have increased above the threshold of risk for ≥3 months. The USPHS guidelines on OI prophylaxis describe the data and rationale for discontinuing suppressive therapy and prophylaxis in appropriate patients. These guidelines are revised periodically (www.aidsinfo.nih.gov).

Chapter 5:

Adherence to HIV Treatment and Retention in Care

Laura Armas-Kolostroubis, MD, AAHIVS
Associate Professor, Co-Medical Director, UF CARES
Center for HIV/AIDS Research, Education and Service
University of Florida

Laura Cheever, MD, ScM
Associate Administrator and Chief Medical Officer
HIV/AIDS Bureau
Health Resources and Services Administration

The authors declare no conflicts of interest

Chapter 5: Adherence to HIV Treatment and Retention in Care

Chapter 5 at a Glance

Adherence to HIV Treatment and Retention in Care

With the availability of accurate HIV identification early in the course of infection and the effectiveness of combination antiretroviral (ARV) regimens, HIV infection has evolved from a uniformly progressive and fatal condition into a chronic disease. With effective antiretroviral therapy (ART), people with HIV infection now have the potential to live a near-normal lifespan with a decreased risk of transmitting the infection to others. These advances, however, have ushered in new challenges. Successful treatment requires lifelong ART. Moreover, chronic HIV care and treatment requires a level of adherence that exceeds the requirements of treatment for many other chronic illnesses because the penalties for nonadherence may be severe (e.g., viral resistance, loss of treatment options, potential for transmission of resistant virus strains). Additionally, medical and nonmedical circumstances, such as stigma, comorbidities, and short- or long-term adverse effects, may interfere with optimal adherence and retention in HIV care and treatment. This chapter addresses specific challenges to adherence and retention in comprehensive care in the setting of chronic HIV infection.

Goals of HIV Therapy

The primary goals of HIV therapy are to decrease the morbidity and mortality associated with HIV infection, improve quality of life, restore immune function, maximize suppression of viral load (VL), and reduce the risk of transmission of HIV to others (HHS Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 7/20/2012).

Successful treatment: Successful HIV treatment is generally defined virologically, immunologically, and clinically as follows:

- Consistent virologic suppression below the level of detection by a sensitive assay (e.g., HIV VL <48 copies/mL)
- Increase of CD4+ cell counts to >350 cells/mm^3 or 500 cells/mm^3
- Improved clinical status

Treatment failure: Treatment failure is usually defined virologically as the inability to achieve or maintain suppression of viral replication to a VL <200 copies/mL. Suboptimal adherence is a leading cause of virologic failure (*J Infect Dis* 2010;201(5):662). Immunologic failure is more difficult to define; some patients have a persistently low CD4+ cell count while maintaining maximal VL suppression. Factors associated with poor CD4+ response include later initiation of ART, older age, and co-infection (e.g., with hepatitis C virus). Early in the course of treatment, and particularly if ART is started in advanced immunosuppression, a patient may worsen clinically if she has an underlying opportunistic infection that is "unmasked" or worsened after initiation of ART, a phenomenon known as immune-reconstitution inflammatory syndrome (see Chapter 4, ***Primary Care***). This is ***not*** clinical failure; in general, true clinical failure occurs after both virologic and immunologic failure.

Adherence

Adherence is defined as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider" (World Health Organization (WHO. *Adherence to Long Term Therapies: Evidence for Action.* 2003; http://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed 7/20/2012). The term *adherence* is preferred over *compliance* because adherence implies that the patient is involved in making decisions about her care, whereas compliance suggests that the patient is "bending to the will" of her healthcare provider (WHO. *Adherence to Long Term Therapies: Evidence for Action.* 2003).

Factors That Influence Adherence

Adherence has two components: adherence to medication and adherence to medical care, including medical visits, which is also known as retention or persistence in care. Adherence is a complex behavioral process influenced by several factors that can be categorized across five dimensions, as described in Table 5-1 (WHO. *Adherence to Long Term Therapies: Evidence for Action.* 2003). Given the complexity of adherence, several factors may result in low adherence rates. Likewise, interventions to improve adherence are most successful if they are multifaceted, addressing problems across multiple dimensions, and tailored to overcome individual or clinic-specific barriers.

Table 5-1

Factors That Influence Adherence

Dimension	Factors Affecting Adherence
Healthcare Team and System Factors	• Quality of the patient-provider relationship, including provider attitudes and healthcare-team communication style • Reimbursement and medication distribution systems • Disease management supports, including patient education and community supports • Follow-up and continuity of care • Evaluation of and interventions to improve adherence • Amount of time spent with patient
Social and Economic Factors	• Patients' competing priorities (e.g., Maslow's hierarchy of need [*Perspect Psychol Sci* 2010;5(3):292]) • Socioeconomic status • Availability and quality of social support networks • Transportation • Ability to afford healthcare services and/or medications

Table 5-1 continues on the next page

Table 5-1 *continued*

Factors That Influence Adherence

Dimension	Factors Affecting Adherence
Condition-Related Factors	• Symptom severity (adherence is usually lower when a patient is asymptomatic) • Condition-related disability (physical, psychological, cognitive, vocational) • Rate of progression and prognosis • Disease severity (patients with more advanced HIV are generally more adherent) • Commonly associated comorbidities (e.g., depression, substance abuse, co-infections)
Therapy-Related Factors	• Complexity of regimen (e.g., dosing, pill burden, dosing interval) • Restrictions (e.g., dietary, other drugs, activities) • Duration (i.e., short-term vs. lifetime; "pill fatigue" has been noted in some patients on long-term treatment) • Immediacy of beneficial effects and relief of symptoms • Side effects and availability of interventions to manage them
Patient-Related Factors	• Ability to follow instructions • Knowledge of and skill with self-directed health-related behaviors • Trust in provider and medical system • Degree of family dysfunction and/or chaotic lifestyle • Education and literacy • Age and lifespan factors: - Children's dependency on adult - Adolescents' capacity to understand risks and consequences - Adults' responsibilities for work and care of children, partners, and/or parents • Personal or cultural beliefs regarding health and disease • Motivation and perceived need for treatment • Confidence (self-efficacy) • Acceptance and understanding of disease vs. negative beliefs regarding diagnosis (denial) and treatment efficacy • Ability to engage in illness-management behaviors • Perceptions, attitudes, and expectations (e.g., hopelessness, acceptance, fear of dependence, frustration, anxiety about regimen, disease-associated stigma) • Neurocognitive function and ability (e.g., forgetfulness, prospective memory) • Psychological status (e.g., stress, depression, influence of substance abuse, coping mechanisms)

Source: WHO. *Adherence to Long Term Therapies: Evidence for Action.* 2003

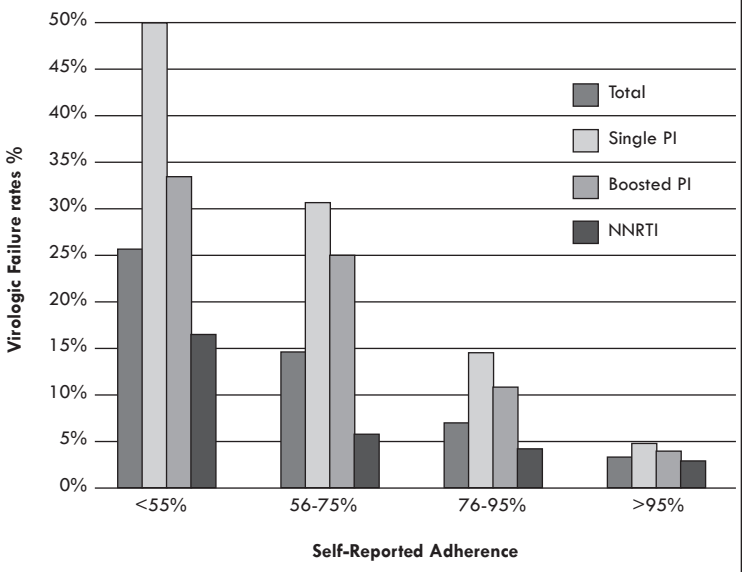
Magnitude of the Adherence Problem

Medication adherence among patients suffering from chronic diseases averages 50% in developed countries (*Adherence to Long Term Therapies: Evidence for Action*. 2003; http://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed 7/20/2012). Among patients with HIV, adherence to both medical visits and medication has been associated with decreased mortality (*Clin Infect Dis* 2007;44:1493). For patients with HIV, the consequences of medication nonadherence are devastating, which is why so much emphasis is placed on adherence to treatment. When medication doses are missed, viral resistance can emerge quickly, particularly with medications that have lower genetic barriers to resistance, such as the NNRTIs (*HIV Clin Trials* 2007;8(5):282). The early literature suggested that >95% adherence was required for success with unboosted protease inhibitors (PIs); more-recent studies of boosted PIs, however, have shown that with these more potent regimens adherence levels of 80% or greater may be sufficient (*Ann Int Med* 2000;133:21; *Ann Pharmacother* 2011;45(3):372).

The level of adherence required for treatment success depends on underlying resistance, the pattern of nonadherence, and the treatment regimen. For example, resistance is less likely to develop in a patient who is 100% adherent to a PI-based regimen, who then stops taking medication altogether for 3 months and then resumes with 100% adherence, and more likely to develop in a patient who regularly takes 60% of her NNRTI-based regimen. NNRTIs have a considerably longer half-life than other ARVs; thus, the patient with intermittent adherence is essentially taking monotherapy for prolonged periods, which increases the likelihood of developing a drug-resistant strain of HIV.

Figure 5-1 illustrates the decrease in virologic failure rates with improved adherence. Conversely, the type of ART regimen has an impact on virologic failure that correlates with intermediate levels of adherence (56%–95%). At high levels of adherence no significant differences are observed in virologic failure rates between regimens (*HIV Clin Trials* 2007;8(5):282).

Figure 5-1
Self-Reported Adherence and Virologic Failure



Source: © *HIV Clin Trials* 2007;8(5):282. Reprinted with permission.

Adherence tends to decrease over time and with the initiation of subsequent ART regimens, such that adherence duration with the first regimen predicts duration with the second and third regimens (*AIDS Patient Care STDS* 2006;20(9):628). Thus, it is critical to focus on adherence to achieve viral suppression; by itself, a change in treatment regimen is not likely to be sufficient. Similarly, many patients who have had long periods of high adherence may struggle with adherence over time owing to a host of factors that may include changes in personal circumstances, such as becoming homeless or relapsing into drug abuse; changes in health insurance that make it more difficult to access medications; or changes in medical condition, such as recurrent hospitalizations, that disrupt medication-taking routines. For all of these reasons, clinicians should ask about adherence at each clinic visit.

Retention in HIV Care

Positive HIV treatment outcomes depend on early diagnosis of HIV infection, linkage to care, and retention (persistence) in care. Gaps in access or retention, such as failure to keep the first or subsequent appointments, are linked with a lack of ART utilization, disease progression, and increased mortality (*Clin Infect Dis* 2007;44:1493; *J Acquir Immune Defic Syndr* 2009;50:100). In many settings, access to HIV care and treatment, defined as no gap between HIV-related medical appointments of > 6 months within the first year, is achieved in only 50% of newly diagnosed patients (*AIDS Care* 2005;17(6):773). Likewise, it is not uncommon for established patients to drop out of HIV care. Fewer data exist regarding the numbers of HIV patients lost to follow-up. Table 5-2 outlines the factors that influence linkage to and retention in care.

Table 5-2

Factors That Influence Linkage to and Retention in Care

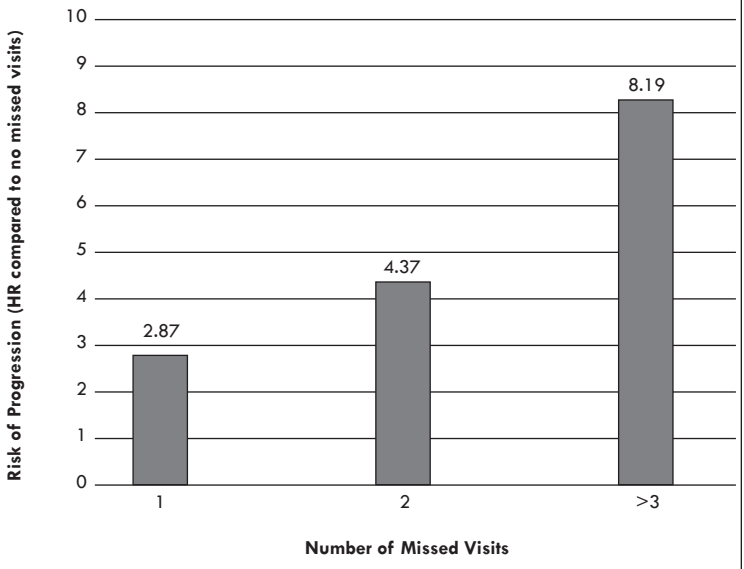
Factors Associated with Successful and/or Sustained Linkage to and Retention in Care	Factors Associated with Unsuccessful and/or Poor Linkage to and Retention in Care
• Co-location of services (e.g., case management, substance abuse, mental health services) • Patient-centered care (e.g., empowered patients, shared decision making) • Transition programs (e.g., from testing sites, jails, hospitalizations, adolescent- to adult-care programs, which may or may not involve the use of patient navigators)	• Untreated substance abuse and/or mental illness • Asymptomatic disease; no ART • Older age (associated with poor linkage to care) or younger age (associated with decreased retention in care) • Lack of health insurance • Longer interval between date of appointment with healthcare provider and patient's initial call to schedule the appointment • African-American race • Privacy concerns • Care-giving responsibilities • Perceived lower social support • Perceived stigma from a health care professional

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Sources: *AIDS Patient Care STDS* 2009;23(1):41; *Top HIV Med* 2008;16(5):156; *AIDS Patient Care STDs.* 2007; 21 Suppl 1:S59; *Am J Public Health.* 2000; 90 (7): 1138; *AIDS Care.* 1999; 11(3):361; *AIDS Patient Care STDs.* 2007; 21(8):584

After adjustment for clinical stage and the number of active drugs in a patient's ART regimen, the hazard ratio for developing an AIDS-defining illness or death increases as patients' number of missed clinic appointments increases, as illustrated in Figure 5-2.

Figure 5-2
Risk of Progression by Missed Visit Status



Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix
Source: *J Intern Med* 2007;261(3):268

Adherence In Women

Gender-specific factors have been noted to influence adherence and retention in care. Some studies have found that women have lower rates of adherence than men. This is not surprising given the association between family and other caretaking responsibilities and lower adherence rates (*Pediatrics* 2008;121(4):e787; *AIDS Patient Care STDS* 2009;23(4):289). Many HIV infected women are diagnosed during pregnancy and are still dealing with the implications of this diagnosis after giving birth, when the new mother becomes responsible for managing the care of a newborn, including administering ARV prophylaxis, while also managing her own health and medications. Mothers are the parents most likely to be responsible for supervising ART for an infected child. Childcare and other responsibilities, as well as postpartum physical and psychological changes, may increase the likelihood that a woman will miss doses of her own medications and may affect the provision of prophylaxis to her infant as well (*Pediatrics* 2002;110(3):e35); *J Acquir Immune Defic Syndr* 2002;30(3):311; *J Acquir Immune Defic Syndr* 2008;48(4):408).

Overview of Study Findings on Adherence in Women

- Women experience higher rates of virologic rebound than men, mostly due to nonadherence (*J Acquir Immune Defic Syndr* 2004;37(4):1470).
- Women are less likely to keep their first HIV healthcare visit appointment and to have remained in care after 2 years (*J Womens Health* 2009;18(10):1627; *J Assoc Nurses AIDS Care* 2007;18(3):33).
- Women have higher rates of mental health problems such as depression, which is associated with decreased adherence (*Psychosom Med* 2008;70(5):531; *J Gen Intern Med* 2003;18(4):248).
- Women often have a history of intimate-partner violence, which is associated with lower adherence (*AIDS Educ Prev* 2010;22(1):61; *J Adolesc Health* 2003;33(2 Suppl):39).
- Women have less knowledge of healthcare system navigation and available ancillary services (*South Med J* 2004;97(4):342).
- Nonadherence is an independent reason for the discontinuation of ART in women (*AIDS Behav* 2009; 13(1):60; *J Acquir Immune Defic Syndr* 2009;52(3):336).
- Women have multiple biological differences that influence drug tolerability and metabolism, including body weight and composition, renal clearance, and protein binding (*Pharmacol Res* 2008;58(3-4):173).
- Pregnancy may have a significant effect on many other factors that influence adherence in women (*Clin Pharmacokinet* 2004;43(15):1071).

With standardized dosing, gender-based biological differences may result in increased side effects; however, more research is needed to better delineate sex differences, particularly hormonal/biological differences that affect drug tolerability and, by extension, adherence (*J Antomicrob Chemother* 2007;60(4):724; *Gend Med* 2007;4(2):106).

Pregnancy and Adherence

Pregnancy may influence adherence to ART, particularly when pharmacokinetic interactions influence drug levels, requiring an increase in pill burden, or when medication side effects such as nausea overlap with symptoms common in pregnancy. Pregnant women, however, may be highly motivated to adhere to therapy and are more likely than nonpregnant women to be adherent to ART regimens: pregnant women report rates of perfect adherence that range from 75% to 91% (*J Acquir Immune Defic Syndr* 2008;48(4):408; *Cell Mol Biol* 2003; 49(8):1187). In the postpartum period, however, rates of adherence significantly decrease (*AIDS Patient Care STDS* 2009;23(2):101). This decrease may be due to a number of factors, including the inherent chaos of life when caring for a newborn, the additional burden of administering ARV prophylaxis during the first 6 weeks of life (which may exacerbate feelings of guilt and concerns about disclosure), and for some women the effects of postpartum depression.

Special Populations

As with men, incarceration and homelessness pose special challenges to adherence for women. Drug interruptions often occur during short jail stays. For example, even in prison systems that have discharge planning, the rate of interruption in medication regimens associated with incarceration has been reported to be 70% (*Public Health Rep* 2010;125(Suppl 1):64).

Homeless patients have inherently chaotic lifestyles. Studies have found, however, that homeless and marginally housed patients can adhere to medication (*AIDS* 2000;14(4):357). Homeless patients need additional supports to ensure access to and adherence with ARVs.

Adherence and Retention Assessment

Accurate assessment of adherence is challenging. Table 5-3 describes the advantages and disadvantages of direct and indirect methods of evaluating adherence. Figure 5-3 is an example of a visual analog scale for assessing adherence.

Table 5-3

Methods of Assessing Adherence

	Method	Advantages	Disadvantages
Behavioral	Self-report	• Easy • Low cost • Accessible	• Subject to recall bias • Often not standardized • Potential for over-reporting to garner provider approval
	Visual analog scale	• Low cost • Accessible • Standardized • Decreases literacy and numeracy barriers	• Subject to recall bias • Potential for over-reporting to garner provider approval

Table 5-3 continues on the next page

Table 5-3 *continued*

Methods of Assessing Adherence

	Method	Advantages	Disadvantages
Measurement of Medication Utilization	Refill history	• Low cost • Easy to implement in closed systems such as onsite pharmacy • May be part of electronic medical record	• Challenging if patients use multiple pharmacies • May not reflect actual behavior, particularly with automatic refills
	Pill counts during healthcare visits	• Low cost • Offers opportunity for education and reassurance	• Time consuming • Depends on patient bringing medications to visits • May be inaccurate (i.e., pills removed before visit)
	Pill counts by phone or in home	• Low cost if by phone • Offers opportunity for education and reassurance	• Costly if in home • May be perceived as invasive • Subject to patient availability • Subject to manipulation if by phone
	Medical Electronic Monitoring System	• More accurate • Easy to use (medication bottle caps)	• Costly • Does not reflect actual ingestion of medications • Depends on use of pills taken directly from container each time
Biologic Measurement	Therapeutic drug levels	• Easy • Minimally invasive if part of routine blood work	• Costly • Not readily available • No standardized values • Does not capture adherence between measurements if patient takes medications only just prior to visits
	Drug-specific surrogate markers: ZDV, AZT: Mean corpuscular volume ATV: Total bilirubin TDF: Alkaline phosphatase	• Part of routine monitoring • Relatively low cost	• May be influenced by effects of other pathologic process(es) • Nonspecific • Nonquantified

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Figure 5-3
Visual Analog Scale for Adherence

Source: © *Health Educ Research* 2005;20(1):24. Reprinted with permission.

Because of cost and convenience, measuring medication adherence by direct report and visual analog scale are most commonly used by healthcare providers in clinical settings. Refill history is also very useful for clinics with onsite pharmacies, as well as for patients who are not responding as expected to HIV treatment and who report 100% adherence. Direct report should be time specific and quantified. For example, care providers should ask, "How many times in the last _____ (week, month, interval since last visit) have you missed a dose of your medicine?" This question should be followed by a nonjudgmental exploration of why the medication was missed, particularly if the patient routinely misses doses, and by brainstorming with the patient to identify ways she might overcome barriers to adherence.

Assessment of Retention in Care

Assessment of retention is important in every clinical setting. Although there is no gold standard for measuring retention in care, potential measures may include the following:

- The number of 6-month blocks during which the patient attended at least one clinic appointment over the 2-year period following an initial visit (*AIDS Patient Care STDS* 2009;23(1):41)
- Number of missed appointments
- Number of kept scheduled appointments per quarter or year
- Percentage of appointments missed

These measures provide different perspectives on appointment adherence (*AIDS Patient Care STDS* 2010;24(10):607). The rate of appointment adherence necessary for good clinical outcomes has not been quantified and may vary on the basis of stage of HIV disease and other comorbidities.

Evidence-Based Interventions to Improve Adherence

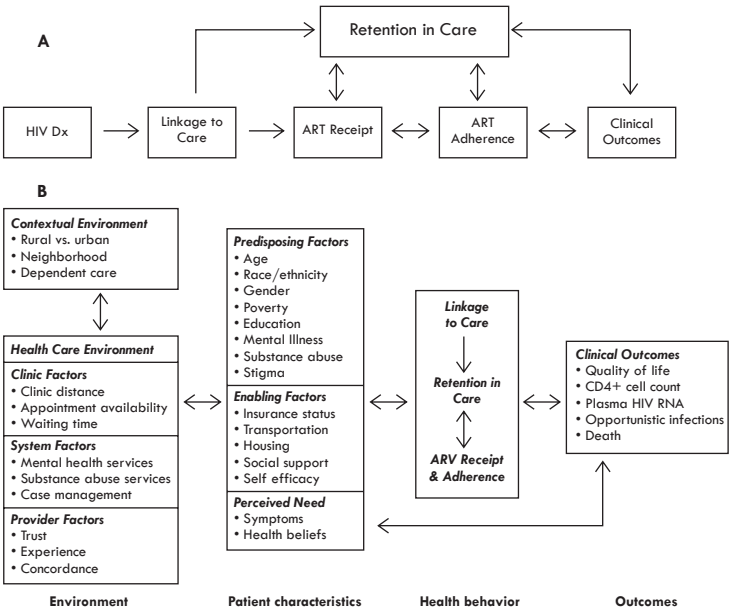
Because the factors associated with adherence are varied, the most effective interventions are multifaceted, individualized, and repeated over time. Asking about adherence at each medical visit and discussing barriers and solutions may be a key component to individualizing interventions in the context of tailoring therapy. Individualized clinic interventions, however, do not address broader provider and healthcare system issues or interventions that may significantly improve adherence across a wide group of patients. HIV treatment response rates have improved significantly in recent years as a result of increasingly potent drugs, significantly simpler drug regimens with fewer side effects, and less significant resistance among patients who are starting second- and third-line therapy (HHS Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 7/20/2012). Combined, these factors result in lower rates of adherence being necessary to achieve viral suppression.

Even in the face of these advances in HIV care and treatment, HIV medical providers must nevertheless maintain a high level of attention to adherence and provide ongoing support to patients. The many evidence-based interventions to improve adherence have been summarized and made available online; see, for example: http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm. These proven interventions can be fairly complex. Many providers practicing routine HIV clinical care take a multifaceted approach that combines evidence-based interventions, clinical experience, and common sense to maximize adherence among their patients.

Clinical Approach

It is critical to consider healthcare system factors that affect a patient's ability to access and stay in HIV care and adhere to an ART regimen. Figure 5-4 illustrates multiple factors that a healthcare provider should consider when determining the right mix of interventions (i.e., clinic/system/care provider-based/patient-based) to improve adherence to HIV care and medications (*AIDS Patient Care STDS* 2009;23(1):41). Table 5-4 describes interventions to support adherence and retention in care.

Figure 5-4
Blueprint for HIV Treatment Success



A: Blueprint for HIV treatment success: requisite processes from initial diagnosis to long-term clinical outcomes. (*Adapted from Curr HIV/AIDS Rep* 2005;2(4):177; *AIDS* 2001;15(1):77.)

B: Adaptation of the behavioral model of health services utilization to provide a conceptual framework for evaluating the relationships between patient characteristics and their contextual and healthcare environmental factors. These relationships contribute to the health behaviors outlined in the "blueprint for HIV treatment success" that ultimately influence clinical outcomes.

Source: © *AIDS Patient Care STDS* 2009;23(1):41. Reprinted with permission.

Table 5-4

Interventions to Support Adherence and Retention in Care

PATIENT

Help the patient become ready for therapy

- Promote the development of adaptive coping skills; identify stressors and use motivational interviewing to elicit positive coping responses
- Improve attitudes toward and perceptions of treatment
- Address patient concerns about treatment, including conspiracy theories, lack of trust in medical system
- Use clear language to discuss short- and long-term goals of therapy, side effects, and known positive outcomes; check to ensure patient understands

Minimize the effects of comorbidities

- Treat substance abuse
- Treat depression
- Consider overlapping symptoms and side effects when choosing a medication regimen

Assist the patient in taking medication as prescribed

- Tailor the regimen to patient preferences and lifestyle
- Use reminders such as telephone calls or texts and alarms
- Provide education about prescribed regimen (e.g., securing refills without gaps in access, developing contingency plans for missed doses or disruptions to daily routine, consequences of nonadherence and drug resistance)

Enhance patient supports

- Encourage the patient to enlist assistance of friends and family in promoting adherence
- Consider use of trained peer outreach workers, pharmacists, nurses, or other healthcare personnel such as health educators
- Have pill boxes, alarms, and other adherence aids available in the clinic

CLINIC/SYSTEM

Improve access to care

- Consider expanding clinic hours to include some evenings and weekends
- Develop a refill policy that minimizes interruptions in therapy; educate patients about the policy
- Use a multidisciplinary team to provide patient education and adherence support (include peers, pharmacists, and system navigators, where appropriate)

Structure clinic systems to promote adherence

- Ask about adherence in a nonjudgmental, quantitative manner at each visit
- Inquire about barriers to adherence and retention and work with patient to overcome them
- Ensure the entire clinic team is aware of and promotes adherence and retention across clinic visits
- Bilingual/bicultural staff on health care team
- Train care providers in motivational interviewing
- Support continuity of care and the building of long-term, trusting relationships between the patient and the entire healthcare team
- Develop a continuum of care that includes such support services as case management, transportation, mental health and substance abuse services, and child care
- Consider developing gender-specific programs that address the special needs of women, particularly pregnant women or those who are caring for small children

Table 5-4 *continued*

Interventions to Support Adherence and Retention in Care

REGIMEN	**Make the patient's drug regimen as simple as possible** • Consider and reduce where possible the number of doses per day and pill burden • Account for food restrictions and requirements • Assess the patient's willingness to take pills in front of others
	Reduce side effects • Evaluate side effects upon initiation of a medication regimen and frequently thereafter • Educate the patient about potential side effects and proactively train her in side-effects management

Sources: *AIDS Behav* 2007;11(6 Suppl):101; *AIDS Behav* 2007;11(6 Suppl):149; *AIDS Care* 2002;14 Suppl 1:S15; *AIDS Care* 2002;14 Suppl 1:S31; *AIDS Care* 2002;14 Suppl 1:S109; *AIDS Care* 2004;16(4):446; *AIDS Care* 2005;17(8):1022; *AIDS Care* 2006;18(4):332; *AIDS Care* 2009;21(4):448; *AIDS Care* 2009;21(7):874; *AIDS Patient Care STDS* 2000;14(4):189; *AIDS Patient Care STDS* 2002;16(6):269; *AIDS Patient Care STDS* 2005;19(5):306; *AIDS Patient Care STDS* 2006;20(4):258; *AIDS Patient Care STDS* 2007;21 Suppl 1:S3; *AIDS Patient Care STDS* 2007;21 Suppl 1:S59; *AIDS Patient Care STDS* 2007;21 Suppl 1:S85; *AIDS Public Policy J* 2005;20(3-4):108; *Health Psychol* 2007;26(4):488; *J Acquir Immune Defic Syndr* 2008;47(1):62; *J Acquir Immune Defic Syndr* 2009;52 Suppl 2:S104; *J Antimicrob Chemother* 2008;62(2):246; *J Gen Intern Med* 1998;13(9):586; *J Gen Intern Med* 2002;17(5):377; *J Gen Intern Med* 2003;18(4):248; *J Urban Health* 2008;85(5):717; *Med Decis Making* 2001;21(1):17; *Qual Health Res* 2008;18(4):458

Conclusion

Treatment success with ART depends on high rates of adherence and retention in HIV care. Assessment of facilitators and barriers to adherence and retention is important for every woman in HIV care. Interventions to address adherence and retention should be tailored to the specific needs and circumstances of each patient. Although system- and policy-related interventions are important and necessary long-term goals, patient-specific and healthcare-related interventions are suitable for everyday clinical practice.

Chapter 15:
Resources

Lori DeLorenzo, RN, MSN
Executive Director, Organizational Ideas

with Skyler Tyne Sharp, RN, BSN

The authors declare no conflicts of interest

Chapter 15: Resources

Chapter 15 at a Glance

How to Use this Chapter

A chapter devoted to additional resources is an essential part of this guide. First, HIV clinical care evolves so rapidly that some information in the guide will soon be out of date. Second, a wealth of information that supplements these chapters in specialized areas of care is available. We have included some of the most important resources for clinical care of women with HIV, but the list is by no means exhaustive. Readers can explore the websites for which we have provided URLs to find many other informative sites.

In this electronic information age, the term *resources* includes Internet sites and electronic documents as well as organizations and published documents, so the chapter includes a range of mechanisms for obtaining more information. We consider the Web-based resources to be primary because they are available from anywhere in the world and are usually updated on a periodic basis. Phone contact information is provided where available, so that readers without access to the Internet can still obtain information.

The resources are listed alphabetically in a grid that identifies major topics addressed by each resource as well as the type of information available. There is a brief description of the resource and website and phone contact information. The phone numbers with 800, 888, 877, and 866 prefixes are only toll-free in the United States.

Regarding special populations, many of the resources contain some information (e.g., fact sheets) about or for groups of people with special needs, such as people who are homeless, incarcerated, or transgender. Information for special populations is usually just one component of a resource, which makes the search function on most websites a useful tool for locating information on specific topics or special populations. In addition, providers caring for lesbians with HIV can find relevant information by searching The Body (www.thebody.com) and the website of the American Psychological Association Office on AIDS (www.apa.org/pi/aids/index.aspx).

Table 15-1

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
AIDS Clinical Trials Group (ACTG)*	https://actgnetwork.org/	NIH-funded AIDS Clinical Trial Groups	• Website • Print materials • Tel/e-mail/Web consultation	• Research and clinical trials
AIDS Alliance for Children, Youth & Families (*formerly the AIDS Policy Center for Children, Youth and Families*)	www.aids-alliance.org Tel: 202-785-3564 888-917-2437	Policy center that promotes advocacy, education, and support for children and families affected by HIV/AIDS	• Website • Print materials • Tel/e-mail/Web consultation • Meetings and conferences • Patient education	• Treatment • Peds/adolescents • Psychosocial support and quality of life • Research and clinical trials
AIDS Education Global Information System (AEGIS)	www.aegis.com Tel: 949-495-1952	Nonprofit group that assembles and archives information and resources from the mainstream press, professional journals, and legal and legislative sources	• Website • Tel/e-mail/Web consultation • Meetings and conferences • Patient education	• Prevention • Occupational exposure
AIDS Education and Training Centers (AETCs)	www.aidsetc.org	Network of regional centers that provide HIV training and education for healthcare providers	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Prevention • Peds/adolescents • OB-GYN • Adherence • Psychosocial support and quality of life • Substance abuse • Research and clinical trials • Occupational exposure • Quality improvement • Palliative care

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
AIDSInfo* (*AIDS Clinical Trials Information Services and AIDS Treatment Information Services have been integrated into AIDSInfo*)	www.aidsinfo.nih.gov Tel: 301-519-0459 800-HIV-0440 TTY: 888-480-3739 Spanish speakers available M–F, 12 pm–5 pm, EST	HHS project that offers the latest federally approved information on HIV/AIDS clinical research, treatment, prevention, and medical practice guidelines	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Treatment • Prevention • Peds/ adolescents • OB-GYN • Nutrition • Occupational exposure
American Academy of HIV Medicine (AAHIVM)*	www.aahivm.org Tel: 202-659-0699	Professional association for HIV specialists; promotes excellence in HIV/AIDS care and offers HIV credentialing for physicians, nurse practitioners, and physician assistants	• Website • Meetings and conferences	• Treatment
American Congress of Obstetricians and Gynecologists (ACOG)*	www.acog.org Tel: 202-638-5577	Professional association for specialists in OB-GYN; provides guidelines and information on reproductive care of women	• Website • Meetings and conferences	• OB-GYN
Association of Nurses in AIDS Care (ANAC)*	www.anacnet.org Tel: 800-260-6780	Professional association for nurses; provides information and advises members about clinical and policy issues related to nursing and HIV care; offers the ACRN credential	• Website • Print materials • Meetings and conferences	• Epidemiology • Nursing standards of practice • Nutrition • Adherence • Treatment • Psychosocial support

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
AIDSVU	www.aidsvu.org	Interactive online map of HIV prevalence in U.S. with national, state, and local map views	• Website	• Epidemiology • HIV testing center locations • HIV treatment locations • NIH-funded HIV Prevention and Vaccine Trials Sites
The Body Pro*	www.thebodypro.com	HIV resource for healthcare professionals; goal is to use the Internet to "lower barriers between healthcare professionals and their HIV-infected patients"	• Website • Guidelines • Tel/e-mail/Web consultation • Meetings and conferences	• Epidemiology • Prevention • OB-GYN • Psychosocial support and quality of life • Research and clinical trials • Palliative care
CDC Division of HIV/AIDS Prevention (DHAP)	www.cdc.gov/hiv/resources/guidelines/index.htm Tel: 800-232-4636 TTY: 800-232-6348	Government site that details clinical guidelines and information on prevention of HIV and hepatitis	• Website • Guidelines	• Epidemiology • Prevention • Occupational Exposure • Research and clinical trials
CDC National Prevention Information Network (CDC NPIN)	www.cdcnpin.org Tel: 404-679-3860, 800-458-5231 M–F, 9 am–6 pm, EST	Government site that provides comprehensive reference, referral, and distribution service for information on HIV/AIDS, STIs, and TB; information specialists can assist in identifying appropriate resource materials	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation • Patient education	• Prevention • STIs and TB • Patient education

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
CDC Prevention with Positives (PWP)	www.cdc.gov/hiv/pwp/index.htm	Government site that provides basic information about scope of PWP and PWP recommendations	• Website • Guidelines • Implementation resources	• Prevention with positives • Reproductive and pregnancy issues
Community Programs for Clinical Research on AIDS (CPCRA)*	http://cpcra.s-3.com	Network of research sites comprising community-based healthcare providers who offer their patients the opportunity to participate in research where they receive their health care	• Website	• Research and clinical trials
HIV and Hepatitis	www.hivandhepatitis.com	Nonprofit agency that provides clinical information and resources on hepatitis and HIV	• Website • Tel/e-mail/Web consultation • Meetings and conferences • Patient education	• Treatment
HIVdent	www.hivdent.org	Nonprofit coalition focused on providing information on dental manifestations of HIV/AIDS	• Website • Guidelines • Meetings and conferences • Articles • Patient education	• Oral health • Treatment • Research and clinical trials
HIV InSite	hivinsite.ucsf.edu	Information on medical treatment, prevention, and policy from the University of California at San Francisco (UCSF)	• Website • Patient education	• Epidemiology • Treatment • Prevention • Peds/adolescents • Psychosocial support and quality of life • Nutrition • Palliative care

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
HIV Medication Guide	www.hivmedicationguide.com	Pharma-sponsored website that provides drug information and software to assess for potential drug interactions	• Website • Patient education	• Treatment
HIV Medicine Association (HIVMA)*	www.hivma.org	Professional association within the IDSA; guidelines and information on HIV treatment and care	• Website • Guidelines • Print • Meetings and conferences	• Treatment • Quality improvement • Care in resource-poor settings
HRSA HIV/AIDS Bureau (HAB)	hab.hrsa.gov	Federal agency that administers Ryan White HIV/AIDS Program; provides information supporting care of people with HIV; HRSA/HAB's Special Projects of National Significance grant program tests innovative approaches to the care of people with HIV/AIDS	• Website • Print • Meetings and conferences	• Epidemiology • Treatment • Prevention • Peds/adolescents • OB-GYN • Adherence • Nutrition • Quality improvement • Palliative care • Care in resource-poor settings
Institute of Medicine (IOM)	www.iom.edu	Nonprofit independent organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public	• Reports	• Broad range of topics related to health and health care

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
International HIV/AIDS Alliance	www.aidsalliance.org	Nonprofit organization that helps communities in developing countries play an effective role in the global response to AIDS	• Website • Print materials	• Prevention • Care in resource-poor settings • Youth • Stigma
Johns Hopkins University AIDS Service	www.hopkins-aids.edu http://www.hopkinsmedicine.org/gim/fellowship/moore_clinic.html	Detailed information on medical treatment and prevention from Johns Hopkins University AIDS Service	• Website • Print • Tel/e-mail/Web consultation • Meetings and conferences	• Treatment • Adherence • Research and clinical trials
National Alliance of State and Territorial AIDS Directors (NASTAD)	www.nastad.org/default.aspx	Represents chief state health agency staff who have programmatic responsibility for administering HIV/AIDS and viral hepatitis healthcare, prevention, education, and supportive service programs funded by state and federal governments	• Website • Policies • Technical assistance • Print	• Policy and advocacy • Health care access • Prevention • Viral hepatitis • HIV counseling and testing
National HIV/AIDS Clinicians' Consultation Center	www.nccc.ucsf.edu/home/ Warmline: 800-933-3413 M–F, 6 am–5 pm, PST PEPline: 888-448-4911 (24/7) Perinatal HIV Hotline: 888-448-8765	National toll-free hotline to counsel healthcare workers with job-related exposure to HIV, hepatitis, and other bloodborne pathogens; offers treating clinicians up-to-the-minute advice on managing occupational exposures and answers other questions on topics related to HIV care	• Website • Guidelines • Tel/e-mail/Web consultation • Meetings and conferences	• Treatment • Peds/adolescents • Occupational exposure

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
NIAID Database for Anti-HIV Compounds	www.niaid.nih.gov/daids/dtpdb Tel: 301-496-5717 866-284-4107 TDD: 800-877-8339 M–F, 8:30 am–5 pm, EST	Government site housing computerized databases of chemical structures and biologic data on ARVs	• Website • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Prevention • Research and clinical trials
Caring Connections	www.caringinfo.org/ Tel: 800-658-8898 Multilingual Line: 877-658-8896	Program of the National Hospice and Palliative Care Organization that provides resources, education, advocacy, and a hotline on palliative care and end-of-life issues such as living wills	• Website • Print materials • Tel/e-mail/Web consultation • Patient education	• Peds/adolescents • Psychosocial support and quality of life • Palliative care
PEPFAR	www.pepfar.gov	Government site for the U.S. President's Emergency Plan for AIDS Relief which provides global support to limited-resource countries for HIV prevention, care, and treatment	• Website • Guidance	• Country operational plans • PEPFAR reports
Population Council	www.popcouncil.org Tel: 212-339-0500 877-339-0500	International organization; research and policy on reproductive health and family planning	• Website • Guidelines • Print materials	• Treatment • Peds/adolescents • Research and clinical trials • Care in resource-poor settings

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
Reproductive Health Online (Reproline)	www.reproline.jhu.edu	Information and training tools on reproductive health in resource-poor settings provided by Johns Hopkins Program for International Education in Gynecology and Obstretrics; information available in Spanish, French, Portuguese, and Russian	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Prevention • OB-GYN • Psychosocial support and quality of life
Resource Center for Prevention with Persons Living with HIV	http://hivpwp.org/	Government initiative focused on persons living with HIV/AIDS to improve their individual health and reduce risk of transmission to others	• Website • Podcasts • Slides • Online training • Webinars	• Linkage to care • Retention • Risk screening and reduction • Partner services • ART as prevention • Adherence • STDs • Reproductive health care • PMTCT
UNAIDS: Joint United Nations Programme on HIV/AIDS	www.unaids.org Tel:+41 22 791 36 66 (Switzerland)	International program; provides technical assistance and HIV/AIDS information to countries and communities	• Website • Guidelines • Print • Patient education	• Epidemiology • Treatment • Psychosocial support and quality of life • Substance abuse • Nutrition • TB

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
The Well Project	www.thewellproject.com Tel: 888-616-9355	Nonprofit organization developed and administered by HIV-positive women; Web portal for women living with HIV; treatment information, groups, organizational tools, slide sets, searchable clinical trials listings, and resource information	• Website • Guidelines • Print • Tel/e-mail/Web consultation • Meetings and conferences • Patient education	• Treatment • Prevention • Peds/adolescents • OB-GYN • Adherence • Substance abuse • Nutrition • Care in resource-poor settings
Women, Children, and HIV	www.womenchildrenhiv.org	Project of UCSF Center for HIV Infection; Information on HIV and pregnancy, prevention of perinatal HIV transmission, and pediatric care; global focus	• Website • Guidelines • Print materials	• Treatment • Prevention • Peds/adolescents • OB-GYN • Psychosocial support and quality of life • Nutrition • Palliative care
WHO HIV/AIDS Department	www.who.int/hiv/en	Technical support for HIV/AIDS treatment and prevention	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Peds/adolescents • OB-GYN • Nutrition

Notes: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix. All URLs were active as of September 2012.

*Must be member to access select information

Table 15-2

Resources for Patients

Name	URL and/or Telephone Number	Brief Description	Resources	Topics Covered
American Social Health Association	www.ashastd.org/ Tel: 919-361-8400 STI Resource Center Hotline: 919-361-8488, M–F, 8 am–6 pm EST	Answers to confidential inquiries about HIV/AIDS prevention, risks, testing, treatment, and other concerns; referrals provided	• Website • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Prevention • General HIV information • Common illnesses associated with HIV • Risk reduction
AVERTing HIV and AIDS	www.avert.org/women-hiv-aids.htm	An international HIV and AIDS charity based in the United Kingdom that works to avert HIV/AIDS through education, treatment, and care	• Website • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Prevention • Peds/adolescents • OB-GYN • Adherence • Psychosocial support and quality of life • Nutrition • Occupational exposure • Palliative care
The Body	www.thebody.com	Comprehensive HIV information and resources	• Website • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Prevention • Psychosocial support and quality of life • Nutrition • Palliative care

Table 15-2 *continued*

Resources for Patients

Name	URL and/or Telephone Number	Brief Description	Resources	Topics Covered
Canadian AIDS Treatment Information Exchange (CATIE)	www.catie.ca Tel: 416-203-7122 800-263-1638	Comprehensive HIV information and resources on drugs, other medical treatments, and complementary therapies, among other topics; available in English and French.	• Website • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Epidemiology • Treatment • Prevention • Adherence
Gay Men's Health Crisis Women and Family Services (New York, NY)	www.gmhc.org Tel: 800-243-7692	Information and services for people with HIV/AIDS, including the Lesbian AIDS Project	• Website • Print materials	• Psychosocial support and quality of life • Nutrition
Healthy Women	www.healthywomen.org/condition/hivaids Tel: 877-986-9472	Health information to educate, inform, and empower women to make smart health choices	• Website • Tel/e-mail/Web consultation	• Treatment • Prevention
National Association of People With AIDS (NAPWA)	www.napwa.org Tel: 240-247-0880 866-846-9366	Advocacy, information, and support for people living with HIV/AIDS	• Website • Print materials • Meetings and conferences	• Treatment • Prevention
New Mexico AIDS Infonet	www.aidsinfonet.org	Nontechnical fact sheets on treatment	• Website • Print materials	• Treatment • Prevention • Peds/adolescents • OB-GYN • Nutrition

Table 15-2 *continued*

Resources for Patients

Name	URL and/or Telephone Number	Brief Description	Resources	Topics Covered
The Office on Women's Health	http://womenshealth.gov/hiv-aids/ Tel: 202-690-7650	Aims to improve the health and sense of well-being of all U.S. women and girls through innovative programs that focus on health and education	• Website • Tel/e-mail/Web consultation	• Treatment • Prevention • Adherence • Psychosocial support and quality of life • Care in resource-poor settings
Project Inform	www.projectinform.org Treatment hotline: 415-558-9051 800-822-7422 M–F, 9 am–5 pm; Sat 10 am–4 pm, PST	Treatment Information and tools for living with HIV, including confidential treatment information by phone and Project Wise, a program focused on HIV/AIDS treatment information and advocacy for women	• Website • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Treatment • Prevention • OB-GYN • Adherence • Nutrition • Care in resource-poor settings
San Francisco AIDS Foundation	www.sfaf.org Tel: 415-487-3000 866-245-3424	Information about prevention, care, and experimental treatments	• Website • Print materials	• Epidemiology • Treatment • Prevention • Psychosocial support and quality of life
Women Alive	www.women-alive.org Tel: 323-965-1564	Organization by and for women living with HIV that offers local services in Los Angeles as well as Internet services	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation • Meetings	• Peds/adolescents • Psychosocial support and quality of life • Research and clinical trials • Care in resource-poor settings

Table 15-2

Resources for Patients

Name	URL and/or Telephone Number	Brief Description	Resources	Topics Covered
Women Organized to Respond to Life-threatening Disease (WORLD)	www.womenhiv.org Tel: 510-986-0340 M–F, 10 am–6 pm, PST	Organization in Oakland, CA, for women with HIV that provides peer advocacy, treatment education training, and retreats	• Website • Tel/e-mail/Web consultation • Meetings	• Adherence • Care in resource-poor settings

Notes: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix. All URLs were active as of September 2012.

Chapter 16:
International Perspectives

Stacie C. Stender, MSN, MSc ID, FNP-BC
Africa Region Technical Advisor, TB/HIV/ID, Jhpiego
Associate, Department of International Health
Johns Hopkins Bloomberg School of Public Health

Kelly Curran
Director, HIV and Infectious Diseases, Jhpiego
Associate, Department of International Health
Johns Hopkins Bloomberg School of Public Health

The authors declare no conflicts of interest

Chapter 16 International Perspectives

Chapter 16 at a Glance

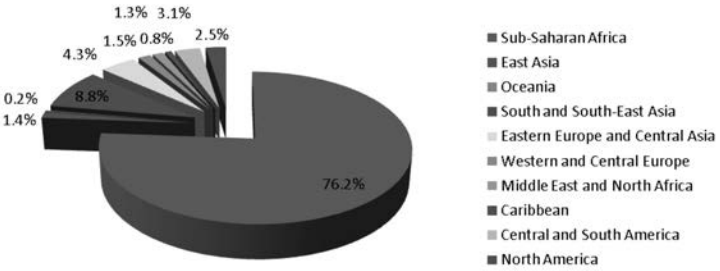
International Perspectives

The primary focus of this guide is to provide a resource for HIV providers in the United States and other high-resource settings. At the same time, though, the global perspective should be considered, because the overwhelming majority of women with HIV live in low- and middle-income countries (LMICs). *LMIC* is a World Bank classification for countries with gross national income (GNI) less than $12,196 per capita in 2009; it excludes the 69 high-income countries with per capita GNI above this level.

Three-quarters of women and girls living with HIV are in sub-Saharan Africa, and half of them live in countries of southern Africa specifically. HIV prevalence among young women aged 15–24 years in sub-Saharan Africa (3.4%) is more than 5 times higher than the global average (0.6%) and more than 30 times higher than that of Western Europe (0.1%) (UNAIDS, *Report on the Global AIDS Epidemic* 2010, *CDC, HIV/AIDS Surveillance Report* 2009;19). Figure 16-1 illustrates the proportion of people living with HIV who are female and aged >15 years.

This chapter explores some of the factors unique to lower-resource settings and the consequent differences in the approach to HIV prevention, care, and treatment, many of which are driven by access or lack of access to human and financial resources.

Figure 16-1
Estimated Proportion of Women and Girls (>15 Years of Age) Living with HIV by Region



Source: Data from UNAIDS, *Report on the Global AIDS Epidemic* 2010. Available at http://www.unaids.org/globalreport/global_report.htm. Accessed 9/9/2012.

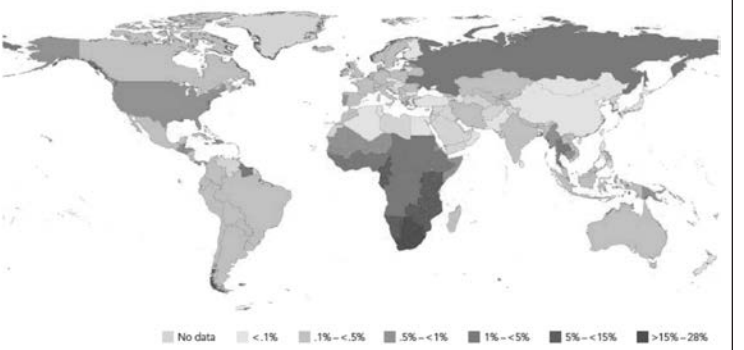
Factors That Influence Approaches to HIV Care in Low- to Middle-Income Countries

Factors that affect HIV care in a given country include the burden of disease, barriers to care, and prevalence and type of comorbidities.

Burden of Disease

HIV is a leading cause of death worldwide and the number one cause of death in Africa. The highest adult HIV prevalence worldwide is in Swaziland, where 1 in 4 people between ages 15 and 49—and 42% of pregnant women—are living with HIV (UNAIDS, *Report on the Global AIDS Epidemic* 2010, p. 28). This extent of infection is in stark contrast to the United States, which has an estimated 0.6% adult prevalence. The global average prevalence is 0.8%, and many LMICs, including Indonesia, India, and Ecuador, have prevalence less than 0.5%. Even in sub-Saharan Africa, where the regional adult prevalence averages 5.0%, there is great variability among countries: Madagascar, Niger, and Senegal have rates similar to that of the United States, whereas Angola, Ghana, and Ethiopia have rates below 5%. Southern Africa is hardest hit by the epidemic: National adult prevalence rates there range from 12% to 26% (UNAIDS, *Report on the Global AIDS Epidemic* 2010).

Figure 16-2
Global Prevalence of HIV, 2009



Source: Data from UNAIDS, *Report on the Global AIDS Epidemic* 2010

Although most countries are on track to meet the 2015 UN Millennium Development Goal 5 target of reducing the maternal mortality ratio, defined as maternal death (the death of a woman while pregnant within 42 days of termination of pregnancy) per 100,000 live births, by 75% , five countries in southern Africa—where HIV prevalence is highest—have had increases in maternal deaths since 1990, largely attributable to HIV: Botswana (133%), Zimbabwe (102%), South Africa (80%), Swaziland (62%), and Lesotho (44%) (World Health Organization [WHO], *Trends in Maternal Mortality* 2010; *Lancet*

2007;370:1311). Two countries, Botswana and South Africa, are upper/middle income countries, which mean they are in the same economic category as Brazil and the Russian Federation.

Epidemiology of transmission: The differences in HIV prevalence among countries and regions of the world reflect the differences in epidemiology of HIV transmission in those areas and the degree to which the epidemic is generalized or concentrated. In *generalized epidemics*, transmission is widespread in the heterosexual population, whereas in *concentrated epidemics*, transmission is confined mainly to people who engage in high-risk behaviors and general population prevalence is less than 1%. These differences in epidemiology have implications for prevention, care, and treatment interventions. Table 16-1 characterizes regional epidemics worldwide.

Table 16-1

Characteristics of Regional Epidemics

Region	Description of Epidemic	% of People With HIV >15 Years of Age Who Are Women
Asia	• No country has a generalized epidemic. • HIV is concentrated among IDUs (16% are living with HIV), sex workers and their partners, and MSM.	34
Caribbean	• Unprotected sex, especially paid sex, between men and women is driving transmission.	55
Central and South America	• Main routes of transmission in this region are concentrated among MSM and IDUs. • Brazil accounts for one-third of those infected.	35
Eastern Europe and Central Asia	• Epidemics continue to rise in this region, concentrated mainly among IDUs (25% are living with HIV) and sex workers and their partners.	49
Oceania	• Papua New Guinea has the only generalized epidemic in the region. • Unprotected sex is driving transmission.	46
Sub-Saharan Africa	• The epidemic is stable or decreasing in most countries. • The majority of transmission is due to unprotected heterosexual intercourse. • Mother-to-child transmission during pregnancy, labor, or breastfeeding is also a major source of transmission.	60
Western and Central Europe and North America	• Unprotected sex between men and IDUs continues to dominate patterns of HIV transmission. • Discrete geographic areas are affected, particularly urban coastal settings.	27

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Sources: Adapted from UNAIDS, *Report on the Global AIDS Epidemic* 2010; CDC, *HIV/AIDS Surveillance Report* 2009;19; and *UN Millennium Development Goals Report* 2010

Barriers to Care

System factors: In many countries of the world, particularly LMICs, healthcare services are provided primarily by Ministries of Health or faith-based (mission) hospitals rather than by private-sector hospitals and clinicians (as in the United States). In those countries, various health system factors contribute to patients' inability to access care:

- *Political factors*, which may include lack of government financial commitment to health, inadequate health facility coverage for the population, competing health priorities, and lack of universal health coverage or individual or group insurance schemes.
- *Economic factors*, such as poor or absent facility and transportation infrastructure, inadequate human resources, and poor pay for healthcare providers. In sub-Saharan Africa, healthcare workers must care for 2 of every 3 people living with HIV globally, yet they represent only 3% of the world's human resources for health (WHO, *Global Tuberculosis Control* 2010). Many healthcare workers in this region are themselves living with HIV, and most are in some way affected by the virus and have responsibilities to orphaned or ill family members.
- *Geographic factors*, such as physical barriers (e.g., impassable roads during rainy season).
- *Organizational factors*, such as lack of interpreters, negative attitudes among staff, inadequate staffing, and vertical and nonintegrated programs.

Patient factors: In countries that have functioning healthcare systems, access to services may be limited by patient factors that serve as barriers to care:

- *Socioeconomic factors*, such as extreme poverty with inability to pay for diagnostic tests, therapeutic interventions, or travel to clinic or hospital; and poor education and health literacy.
- *Cultural factors*, such as traditional practices, cultural and religious beliefs that influence health-seeking behavior, gender disparities, gender-based violence, and stigma related to HIV.

In adopting the 2001 *Declaration of Commitment on HIV/AIDS* (UN General Assembly Resolution S-26/2, 27 June 2001), UN member states agreed to systematically review and regularly report on their progress in realizing universal access to HIV prevention, treatment, care, and support by 2010. When widespread access to antiretroviral therapy (ART) began in 2004 (UNAIDS, *Report on the Global AIDS Epidemic* 2010), it was considered a significant achievement given the health system challenges known to exist in most LMICs.

Comorbidities

Comorbidities commonly associated with or affected by HIV in lower resource countries are often not the same as those seen in the United States, or they may have more significant implications for health because of inadequate resources for screening and treatment. In low-resource settings, common HIV co-infections include infections of significant public health consequence in the general population. This overlap may create competing health priorities and insufficiently coordinated resources where programs are not integrated. In the setting of HIV, increased rates of TB can result in greater risk of TB transmission to people who are not HIV infected. Where HPV infection is endemic, a lack of effective cervical cancer screening programs leads to increased risk of cervical cancer that may not be offset by adequate ART. Malaria and HIV have important interactions in both pregnant and nonpregnant women. All of these co-infections have significant implications for HIV prevention and care needs.

Tuberculosis: An estimated 380,000 HIV infected people died from TB in 2009. Among people living with HIV globally, TB is the leading cause of death. It is the third leading cause of death for HIV infected women of reproductive age. TB is the most common presenting opportunistic infection in the world, and it is the point of entry into HIV care for many patients, particularly in sub-Saharan Africa. South Africa alone accounts for 25% of all HIV-related TB infections globally (UNAIDS, *Report on the Global AIDS Epidemic* 2010; WHO/UNAIDS/UNICEF, *Towards Universal Access Progress Report* 2010).

HIV infection is the single greatest risk factor for the reactivation of latent mycobacterial infection (*Tubercle Lung Dis* 1992;73:311, *Int J Tuberc Lung Dis* 2000;4(2):9). Because of this relationship, there has been a dramatic increase in the incidence of TB in countries with a high prevalence of both TB and HIV (*AIDS* 1995;9:665). In the setting of HIV, TB is more likely to be smear negative or extrapulmonary, making diagnosis more challenging. HIV progression also appears to be increased in the setting of TB (*J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19:361, AIDS 2001;15:143).

The rate of TB is approximately 10-fold higher in HIV infected pregnant women than in pregnant women who are not HIV infected, and TB–HIV co-infection increases maternal mortality. In some tertiary hospitals in South Africa, HIV–TB coinfection accounts for approximately 14% of all maternal mortality (*AIDS* 2001;15:1857). Results of a study from India indicate that HIV–TB coinfection in the mother was associated with a 3.4 increased probability of infant death with maternal HIV infection alone (*Clin Infect Dis* 2007;45:241).

Malaria: Malaria is a leading global cause of death and disability. Eighty-five percent of the 250 million cases and 91% of the 800,000 annual malaria deaths occur in Africa in areas where HIV prevalence is also elevated (Roll Back Malaria, *Key facts*, http://www.rollbackmalaria.org/keyfacts.html; Wellcome Trust, *Illustrated History of Tropical Diseases* 1996;231). Moreover, the interaction of the two diseases may affect transmission, clinical manifestations, and treatment outcomes of both diseases. HIV impairs acquired immunity to malaria, and like other concomitant infections, malaria

can cause a transient increase in HIV viral load (*Lancet* 2000;356:1051, *J Infect Dis* 2005;192:984, *Lancet* 2005;365:233). In pregnancy, HIV infection increases malaria susceptibility and adverse outcomes; placental malaria is associated with increased risk of mother-to-child transmission of HIV (*AIDS* 2003;17:2539).

Human papillomavirus: HPV is the most common sexually transmitted pathogen worldwide and is the major etiologic agent of cervical cancer. In women in most developing countries, cervical cancer is the most common cancer and the most common cause of cancer death (Cervical Cancer Action, *Progress in Cervical Cancer Prevention: The CCA Report Card* 2011); it kills nearly 250,000 women per year. HIV is associated with higher incidence and prevalence and longer persistence of HPV; with a greater likelihood of oncogenic HPV subtypes; and with increased frequency and severity of cervical dysplasia, a precancerous condition. Invasive cervical cancer is an AIDS-defining illness, and rates of cervical cancer may be increased in the setting of HIV, especially if screening is not adequate.

Different Interventions for Different Settings

Public Health Approach

A public health approach to HIV prevention, care, and treatment is essential in LMICs, where financial constraints, competing health priorities, and shortages of healthcare providers are common. This requirement is particularly true for areas with generalized epidemics. In countries with concentrated epidemics, targeted approaches are essential for efficient use of scarce resources.

Decentralized services for universal access: The Declaration of Alma-Ata, accepted by WHO member countries, emphasizes the importance of primary healthcare for equitable access to health (*Declaration of Alma-Ata* 1978). Universal access to HIV services requires decentralized services at the primary care and community levels. Essential to expansion of services for HIV prevention, care, and treatment in many LMICs is the allocation of clinical tasks to cadres of healthcare workers, who may include the following:

- Lay workers who are trained to provide HIV counseling and testing
- HIV infected women who have gone through prevention of mother-to-child transmission (PMTCT) programs themselves and are then trained to provide peer counseling to other HIV infected pregnant women
- Nurses and clinical officers who are trained to initiate and manage ART
- Nurses who perform voluntary medical male circumcision
- High school graduates who are trained to perform smear microscopy to diagnose TB.

In LMICs, nongovernmental organizations (NGOs) are intimately involved in the provision of HIV prevention, care, and treatment services. By contrast, in well-resourced countries, HIV infected women receive care in a formal public or private healthcare system.

The United States is the largest donor to global AIDS response efforts. Through the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (in partnership with other high-income countries), the United States provides national governments and NGOs in LMICs with support to expand access to services, without which HIV incidence and mortality would continue to increase in many regions.

Different Prevention Interventions

For every two people who start ART each year, five are newly infected with HIV. In 2008, 72% of all new HIV infections occurred in sub-Saharan Africa (WHO, *Guidance on provider-initiated HIV testing and counselling in health facilities* 2007). Of the 1.4 million pregnant women in need of HIV care, treatment, and support, including options for PMTCT, 91% are in sub-Saharan Africa (WHO/UNAIDS/UNICEF, *Towards Universal Access Progress Report* 2010).

Targeted prevention: HIV prevention efforts should be evidence based and target the common drivers of transmission in different epidemic settings. In the words of UNAIDS, "know your epidemic and respond accordingly." Knowing one's epidemic often means knowing where the last 1,000 new HIV infections occurred, because the next 1,000 infections are likely to occur in similar populations. In concentrated epidemic settings, new HIV infections disproportionately affect "most-at-risk" populations, including sex workers, MSM, and IDUs. In hyperendemic settings such as southern Africa, the majority of new infections occur within the general population, often within stable partnerships (UNAIDS, *HIV Prevention Toolkit*, http://hivpreventiontoolkit.unaids.org/Knowledge_Epidemic.aspx). In several African countries, 50% or more of HIV infected people may be in serodiscordant relationships (*Reprod Health Matters* 2008;16:151, *Lancet Infect Dis* 2010;10:770).

Combination prevention: Combination prevention uses a mixture of behavioral, biomedical, and structural interventions and targets the prevention needs of different populations on the basis of epidemiologic and demographic data (*MMWR* 2006;*55* RR14:1). Successful prevention efforts effect change on multiple levels—individual, organizational, and societal—and provide mutually reinforcing messages and interventions (USAID/AIDSTAR-One, *Combination Approaches: An Overview of Combination Prevention*, http://www.aidstar-one.com/focus_areas/prevention/pkb/combination_approaches/overview_combination_prevention).

Behavioral prevention: Behavioral prevention includes the ABC approach—**A**bstinence, **B**e faithful (partner reduction), and **C**ondom use (and promotion). One challenge with behavioral approaches is that many women in LMICs find these prevention strategies difficult to use. For instance, in settings where a woman's status in the family and the community is determined by the number

of children she bears, condom use may be prohibited because it prevents pregnancy. And in many cases, women have little or no control over the conduct of sexual relationships, particularly in the context of stable partnerships.

Biomedical prevention: Biomedical prevention includes medical approaches to block infection, decrease infectiousness, or reduce risk of infection. One such approach is voluntary male circumcision. Following issuance of WHO and UNAIDS recommendations, this approach is now being scaled up widely in Southern and Eastern Africa , where it has the potential to avert 4.1 million new HIV infections by 2025 if coverage rapidly reaches 80% (USAID Health Policy Initiative, *Potential Cost and Impact of Expanding Male Circumcision in 14 African Countries* 2009). As described in Chapter 3, ***Prevention***, ARV-based vaginal microbicides are showing promise as a woman-directed method of prevention (*Science* 2010; 329 :1168). Data from HPTN 052, a randomized clinical trial designed to evaluate ART for prevention of sexual transmission among serodiscordant couples, indicates that earlier initiation of ART (at CD4+ cell counts of 350–550/mm^3) reduced HIV transmission to the uninfected partner by 96% as compared with people who initiated ART at lower CD4+ cell counts (*N Engl J Med* 2011; 365:493).

Results of several PrEP clinical trials using either daily TDF or TDF/FTC in at risk HIV-uninfected individuals are now available and show mixed results (see Chapter 3: ***Prevention of HIV Infection***). It is likely that adherence was a key factor in the discrepant results of these studies (*AIDS* 2012;26(7):F13). In July 2012 the FDA approved a label indication for TDF/FTC for reduction of risk for sexual acquisition of HIV infection among adults, including heterosexual women. In August 2012 the CDC issued interim guidance for clinicians considering the use of PrEP for HIV prevention in heterosexually active adults, particularly those with known HIV-infected partners (*MMWR* 2012; 61(31):586):1).

These studies and the HPTN 052 results have major implications for the use of antiretroviral agents for prevention, particularly among serodiscordant couples, and especially for those who wish to conceive or are unable or unwilling to use safer sexual practices. These results may also have implications for prevention in the setting of generalized epidemics or among high-risk groups in concentrated epidemic settings.

Structural prevention: Structural prevention takes into account social, political, and economic factors that contribute to individual risk and vulnerability. A recent study from Malawi found that paying school fees for adolescent girls and providing the girls and their families with a small amount of discretionary income (as little as $4 USD per month) reduced HIV acquisition by 50% and herpes simplex virus-2 (HSV-2) acquisition by 75% among schoolgoing adolescent girls, who were less likely to engage in transactional sex (World Bank, *A cash transfer program reduces HIV infections among adolescent girls*, http://siteresources.worldbank.org/DEC/Resources/HIVExeSummary(Malawi).pdf).

Testing and HIV Diagnosis

Provider-initiated testing and counseling for HIV, also known as *opt-out screening*, in which a patient is notified that testing will be performed unless he or she declines, has been recommended by WHO since 2007 for countries with generalized epidemics (WHO, *Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities* 2007). However, implementation has been less than ideal in most settings. For example, in 2008, only 22% of TB patients globally knew their HIV status, despite the clear indication for HIV testing that TB provides in most settings, given high co-infection rates (WHO, *Towards Universal Access Progress Report* 2010).

Rapid tests: The use of rapid diagnostic tests for HIV, through either parallel or serial testing, is the mainstay of laboratory diagnosis of HIV in most resource-limited settings, given limited laboratory capacity. Selection of tests in any setting depends on available resources and prevalence of HIV types 1 and 2, which will have an effect on negative and positive predictive values. In addition to the FDA-approved rapid tests described in Chapter 3, several other rapid tests are available internationally.

Diagnosis in infants: With regard to diagnosis of HIV in infants, DNA PCR is used in resource-limited settings if laboratory capacity is sufficient. Where climate, transport of specimens, and laboratory capacity are especially challenging, dry blood spot samples are collected. Because breastfeeding is the primary infant feeding choice of women in most LMICs, HIV testing is conducted again 6 weeks after cessation of breastfeeding to avoid the risk of breast milk transmission.

HIV Care and Treatment in Lower-Resource Settings

The approach to HIV care and treatment in resource-limited settings is substantially different from the approach in the United States, which emphasizes use of state-of-the-art medications and laboratory testing. Care and treatment in lower resource settings, however, emphasize PMTCT and treatment of co-occurring infections such as malaria, TB, and cervical cancer (HPV). Availability of other types of care, including ART, varies from country to country. Laboratory tests for CD4+, viral load, and viral resistance often are not an option.

Prevention of Mother-to-Child Transmission

The international community has set a goal of virtual elimination of mother-to-child transmission of HIV by 2015. However, in 2009, only half of HIV infected pregnant women in LMICs received any antiretrovirals (ARVs) for PMTCT (53%). One country, Nigeria, accounts for one-third of this gap between women in need of ARVs for PMTCT and those who actually receive any intervention, whether single-dose nevirapine, AZT + single dose nevirapine, or HAART. (UNAIDS, *Report on the Global AIDS Epidemic* 2010; WHO, *Towards Universal Access Progress Report* 2010; UN, *Millennium Development Goals Report* 2010).

It is estimated that half of HIV infected pregnant women have CD4+ cell counts <350/mm^3 and require ARVs for their own health. Yet, in 59 LMICs that reported in 2009, only 15% of women who received any ARVs received highly active antiretroviral therapy (HAART) as treatment (UNAIDS, *Report on the Global AIDS Epidemic* 2010; WHO, *Towards Universal Access Progress Report* 2010, *AIDS* 2010;24: 1374; *J Acquir Immune Defic Syndr* 2010;55:404; *WHO Guidelines on HIV and Infant Feeding* 2010).

Care and treatment of HIV infected women, irrespective of pregnancy status, must take priority if universal access to care and treatment is to be achieved. Although 80% of UN member states reported the percentage of adults and children receiving ART and 70% reported on percentage of HIV infected pregnant women who received ARVs to reduce the risk of mother-to-child transmission in 2009, few were able to report on whether pregnant women were receiving ARVs for treatment rather than prevention. Even fewer were able to report on the impact of PMTCT interventions.

In April 2012, WHO endorsed a new option for PMTCT known as Option B+. This involves use of a single universal regimen to both treat HIV-infected pregnant women and for PMTCT and to continue this therapy for life, regardless of CD4+ cell count. The strategic advantages of this approach include further simplification of regimen and service delivery and harmonization with ART programs; protection against MTCT in future pregnancies; prevention against sexual transmission to HIV serodiscordant partners; and avoidance of treatment interruption between pregnancies. Numerous countries are now adopting this approach, although systems and support requirements need careful assessment and outcomes after program implementation need evaluation. (WHO, Programmatic Update-Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. April 2012 (http://www.who.int/hiv/PMTCT_update.pdf)

With regard to choices for infant feeding, although replacement feeding undoubtedly prevents postnatal transmission, in LMICs it has been associated with increased risk of death from other causes. Therefore, in 2010, WHO infant feeding recommendations changed to include the key principle that infant feeding choices for HIV prevention must be balanced with protection from other causes of child mortality (*WHO, Guidelines on HIV and Infant Feeding* 2010). In most low-resource settings, breastfeeding has significant benefits that outweigh risk of HIV transmission: It provides ideal infant nutrition in the first 6 months of life; reduces infant morbidity and mortality; delays return of fertility with exclusive breastfeeding, promoting child spacing and maternal recovery from blood loss; and is low cost and culturally acceptable (*Lancet* 2000;355:451).

Comprehensive Care

Care and treatment of people living with HIV should address the needs of the patient as an individual and as a member of a family; however, the approach to care and treatment in resource-limited settings is substantially different from the approach in the U.S. Comprehensive packages of HIV care vary across countries and depend on resources available and prevalent diseases.

For example, in Africa, the package of care may include insecticide-treated nets for the prevention of transmission of malaria by mosquito vectors and safe water vessels and chlorine for the prevention of water-borne diseases, in addition to condoms and cotrimoxazole.

Tuberculosis: The dual epidemics of TB and HIV require specific interventions to reduce transmission of the bacilli and prevent progression from TB infection to disease. This approach is particularly the case in sub-Saharan Africa, where up to 80% of patients diagnosed with TB are co-infected with HIV. Essential components of care for people living with HIV in such areas include a high index of suspicion combined with isoniazid preventive therapy, respiratory infection prevention and control, and prompt diagnosis and treatment of TB (intensified case finding). TB symptom screening at each patient visit is becoming common in settings of co-epidemics, a situation not applicable to the United States, where incidence of TB is significantly lower.

Malaria: HIV infected people are at increased risk of severe or complicated malaria, depending on the malaria transmission setting, and therefore have an even greater need for malaria prevention and control measures. Insecticide-treated bed nets, confirmed diagnosis (particularly as rapid diagnostic tests are more readily available), and appropriate treatment should be afforded to everyone, regardless of HIV status, but are particularly important for those who are HIV infected. The recommended intermittent preventive therapy for malaria (i.e., 2 to 3 doses of sulfadoxine–pyrimethamine during pregnancy for women in malaria-endemic areas) is not given to HIV infected women taking cotrimoxazole, given the similar effects of the two sulfa drugs (WHO, *Malaria and HIV Interactions and Their Implications for Public Health Policy* 2004).

Cervical cancer: The most effective approach for cervical cancer control is cervical screening. Pap smear with adjunctive high-risk HPV testing is the standard of care in the United States and other high-income countries, but in LMICs, lack of adequate financing, healthcare infrastructure, human resources, and capacity to follow up often make such screening unavailable. Visual inspection with acetic acid (VIA) is considered safe and acceptable, is inexpensive, and provides results immediately, thereby allowing for prompt treatment with cryotherapy or loop electrosurgical excisional procedure (LEEP) or referral for more suspicious lesions. Implementation of this low-tech screening procedure is expanding across many LMICs in HIV care settings. Compared with Pap smear, VIA generally has higher sensitivity but lower specificity, and it has high negative predictive value but low positive predictive value (*Gynecol Oncol* 2010;1793, *J Obstet Gynaecol* 2008;28:638). Results of a cluster randomized trial in India comprising approximately 31,000 women receiving VIA and a similar number of controls indicated the following: VIA+ women received cryotherapy at the same visit, and VIA was associated with a 24% reduction in Stage 2 or higher invasive cervical cancer and a 35% reduction in cervical cancer mortality (*Lancet* 2007;370:398).

In general, HPV DNA testing appears to be more objective and reproducible and has higher sensitivity than VIA. In another cluster randomized trial in India, HPV testing was compared with VIA, cytology, and standard of care (no screening) in >31,000 women in each arm and with 8 years follow-up. HPV testing was associated with 50% reduction in detection of advanced cervical

cancer and cervical cancer deaths compared with women with no screening. No significant differences were found between women screened with VIA or cytology and standard-of-care participants (*New Engl J Med* 2009;360:1385).

More recently, an HPV DNA test has been adapted for low-resource settings and is being field tested; it can detect 14 high-risk HPV types, and results are available within 2 hours using basic laboratory facilities. However, cost may be a significant barrier. It is likely that more effective screening strategies will utilize both HPV testing and VIA, possibly using one technique as an initial screen with triage of positive results to the second technique. PEPFAR is providing funding to implement use of non-cytology-based screening techniques in HIV programs.

Antiretroviral Treatment

Unmet goals: The international community target of achieving at least 80% ART coverage for treatment-eligible patients by 2010 has not been met, and it is not likely to be met by the renewed goal of 2015. By 2009, of the people who needed HIV treatment, only 19% in Eastern Asia , 25% in Western and Central Africa, 41% in Eastern and Southern Africa, and 57% in Southeast Asia and Oceania had access to ART. However, these percentages represent significant progress, because only 2% of all eligible people were receiving therapy in 2002. Eight LMICs—Botswana, Cambodia, Croatia, Cuba, Guyana, Oman, Romania, and Rwanda—achieved universal access by December 2009, and currently, more than 5 million people are receiving these life-saving drugs (*UNAIDS Global Report* 2010, *WHO Towards Universal Access Progress Report* 2010, *UN Millennium Development Goals Report* 2010).

Eligibility: In 2010, the WHO HIV treatment guidelines were changed to recommend earlier initiation of ART (from CD4+ cell count $<200/mm^3$ to CD4+ cell count $<350/mm^3$) irrespective of clinical symptoms and WHO Clinical Stage 3 and 4, including TB, irrespective of CD4+ cell count. This change increases the estimated number of patients eligible for ART from 10 million to 15 million (UNAIDS, *Report on the Global AIDS Epidemic* 2010; WHO, *Towards Universal Access Progress Report* 2010).

Challenges: Although six classes of drugs and more than 20 FDA-approved ARVs are available for use in the United States, only three classes of drugs are widely available for use in the developing world, and choices within those classes are limited, largely related to cost. Standardized first-line and second-line treatment regimens are generally recommended. Common challenges of ARV provision in many countries include the following:

- Limited availability or accessibility of drug alternatives when drug toxicity or failure occurs
- Refrigeration requirement for some formulations where electricity and refrigeration are not widely available
- Co-treatment with TB and the challenge of drug interactions between rifampicin and nevirapine and protease inhibitors

- Limited ability to evaluate and manage adverse effects related to treatment (e.g., hyperlactatemia, lactic acidosis related to d4T)
- Stock-outs: More than one-third (38%) of countries reported at least one stock-out of ARVs (i.e., drug not available at the service delivery point) procured centrally in health facilities in 2009 (WHO, *Towards Universal Access Progress Report* 2010)
- Adherence concerns related to several factors:
  - Stigma of HIV diagnosis, which is often greater in these settings and may affect willingness to take drugs on a regular schedule
  - Sharing of drugs with other infected family members
  - Improvement in symptoms, weight gain, etc., which may be interpreted as a signal that treatment is no longer needed
- Limited number of healthcare providers in general and, in particular, few who are able to prescribe ART
- Inadequate training and mentorship in prescribing ART
- Inadequate availability of referral and consultative services.

Cost: The cost of ART has dropped substantially in the past 10 years, in large part because of pressure from international groups and greater availability of generic formulations, including fixed-dose combinations.

WHO guidelines reserve protease inhibitors for second-line treatment, because of cost as well as other considerations (e.g., storage requirements, more extensive drug interactions). The weighted median costs of second-line regimens that include protease inhibitors are 10- to 40-fold greater than the least expensive first-line regimen, d4T/3TC/NVP (WHO/UNAIDS/UNICEF, *Towards Universal Access Progress Report* 2010).

In 2004, d4T was changed from a preferred to an alternative drug for treatment of HIV-1 by the U.S. Department of Health and Human Services (HHS) because of increasing reports of associated toxicities (HHS, *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, 2004), yet in LMICs, it has been the backbone of ART in combination with 3TC since the introduction of ARVs. The most common first-line regimen in the 59 LMIC countries evaluated in 2009 (excluding the Americas region) were d4T/3TC/NVP (38.1%), d4T/3TC/EFV (21.5%), AZT/3TC/NVP (18.9%) and AZT/3TC/EFV (12.6%). However, as of 2010, WHO no longer recommends d4T in the first-line regimen as a result of drug toxicity (hyperlactatemia affects up to 5% of those taking d4T), and many governments are currently phasing out the use of the drug entirely (WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* 2010). Table 2 presents a comparison of HIV prevention, care, and treatment in the United States and LMICs.

Table 16-2

Comparison of Recommended HIV Prevention, Care, and Treatment in the United States and in Low- and Middle-Income Countries

Intervention	United States	International (LMICs)
Primary HIV prevention	• Condoms (male and female) • Reduced number of partners • STI prevention/screening/ treatment • Harm reduction for IDUs • Drug abuse treatment • PEP • ART as prevention	• Condoms (male and female) • Voluntary male medical circumcision • Reduced number of partners • STI prevention/screening/ treatment • PEP • ART as prevention
HIV testing	• Opt-out testing recommended • Reactive rapid or conventional screening test, with confirmation by supplemental antibody test (e.g., Western blot)	• Opt-out testing recommended in regions with generalized epidemics • Serial or parallel rapid tests for screening and confirmation
STI screening in pregnancy	• HIV, syphilis, HbsAg, *C. trachomatis*, *N. gonorrhoea,* and trichomoniasis • HCV in high-risk women	• HIV and syphilis
Cervical cancer screening and prevention	• Year 1, cytology x2; annually thereafter if normal • Colposcopy if any abnormal Pap smear • Excisional treatment with LEEP or cervical conization for high-grade lesions • HPV vaccine recommended for primary prevention	• Pap smear where available, but access is extremely limited Alternatives include VIA; cryotherapy or LEEP can be performed at same visit if VIA is abnormal • HPV testing an option if rapid test available and affordable • HPV vaccine largely unavailable due to cost
Vaccinations for primary prevention	• HPV recommended for children and adolescents irrespective of HIV status • HBV, HAV, pneumococcal, and influenza vaccines recommended	• HBV recommended if serological testing is available • Influenza vaccination where available and feasible
Other prevention	• Primary prevention of several opportunistic infections, on the basis of CD4+ cell count: - PCP (CD4+ cell count <200/mm^3): TMP–SMX - Toxoplasmosis (CD4+ cell count <100/mm^3):TMP–SMX - Disseminated MAC disease (CD4+ cell count<50/mm^3): azithromycin - TB (test for (+) latent TB and/or close contact with active TB, if active TB ruled out): isoniazid + pyridoxine	• TMP–SMX decreases clinical malaria in areas of stable malaria transmission • Isoniazid for HIV-infected persons with unknown or (+) TB skin test, once active TB excluded • Sulfadoxine–pyrimethamine during pregnancy for women in malaria-endemic areas (this is not needed of woman already on cotrimoxazole)

Table 16-2 *continued*

Comparison of Recommended HIV Prevention, Care, and Treatment in the United States and in Low- and Middle-Income Countries

Intervention	United States	International (LMICs)
STI screening and treatment	• Annual screening for HIV, syphilis, chlamydia, gonorrhea, and trichomoniasis • Treatment widely available and based on etiologic diagnosis	• Passive case finding, with syndromic management. • Antivirals for HSV not widely available
HIV assessment at diagnosis	• CDC clinical staging • CD4+ cell count • HIV viral load • HIV drug-resistance testing	• WHO clinical staging • CD4+ cell count if available
Initiation of ART	• ART recommended for all with HIV - Strong recommendation: CD4+ cell count <200–500 cells/μl - Moderate recommendation: CD4+ cell count >500 cells/μl • ARV resistance testing prior to initiation • Screen for HLA-B5701 before starting ABC • Co-receptor tropism assay before starting CCR5 inhibitor	• CD4+ cell count <350/mm^3 • WHO Clinical Stage 3 or 4 irrespective of CD4+ cell count
PMTCT: maternal interventions	• HAART for all, irrespective of CD4+ cell count or signs/symptoms • Cesarean delivery if viral load >1,000 c/mL at 36 weeks • Monitor viral load and CD4+ cell count in pregnancy	• HAART if CD4+ cell count ≤350/mm^3 or WHO Clinical Stage 3 or 4 • If CD4+ cell count >350/mm^3, then choose option A or B: - **Option A:** AZT beginning at 14 weeks + single dose NVP at onset of labor + AZT/3TC in labor and for 7 days postpartum **or** - **Option B:** triple ARV prophylaxis with AZT/3TC/LPV/r or AZT/3TC/ABC or AZT/3TC/EFV or TDF/3TC(FTC)/EFV beginning at 14 weeks and continuing until delivery or, if breastfeeding, until 1 week after complete cessation - **Option B+:** triple ARVs with TDF/3TC/FTC/EFV, starting as soon as diagnosed and continued for life
PMTCT: ART preferred/ alternative drugs/ regimen	• **NRTIs:** AZT, 3TC, ABC, FTC, TDF • **NNRTIs:** NVP; EFV • **PIs:** LPV/r, ATV, SQV/r; DRV/r • **INSTI:** RAL	• AZT/3TC/NVP or AZT/3TC/EFV or TDF/3TC(FTC)/NVP or TDF/3TC(FTC)/EFV

Table 16-2 *continued*

Comparison of Recommended HIV Prevention, Care, and Treatment in the United States and in Low- and Middle-Income Countries

Intervention	United States	International (LMICs)
PMTCT: infant interventions	• Avoid breastfeeding • Infant prophylaxis with AZT for 6 weeks • When the mother has not received antepartum ARV drugs: add 3 doses of NVP in the first week of life • DNA–PCR or RNA assay at 14–21 days, 2–3 months and 4–6 months; confirm positive test on separate sample to diagnose HIV	• Exclusive breastfeeding for 6 months • Infant prophylaxis if mother is on HAART: AZT or NVP for 4-6 weeks • If mother is on ARV prophylaxis only: *Option A:* - **Breastfeeding:** daily NVP until 1 week after all exposure to breast milk (minimum 4–6 weeks if breastfeeding stops before 6 weeks) - **Nonbreastfeeding:** daily NVP or sd-NVP at birth and twice daily AZT for 4–6 weeks • Mother on ARV prophylaxis only: *Maternal Option B:* breastfeeding or replacement feeding: - Daily NVP or twice-daily AZT for 4–6 weeks • DNA–PCR at 6 weeks (if available); otherwise, antibody testing at 18 months
Preferred first-line ART regimens	• EFV/TDF/FTC *or* ATV/r/TDF/FTC *or* DRV/r/TDF/FTC *or* RAL/TDF/FTC	• AZT or TDF +3TC (or FTC) + EFV or NVP • Move toward AZT or TDF-based regimens from d4T, when d4T regimens have been used as principal option
TB/HIV co-infection	• Preferred: rifampin plus EFV-based ART • Rifabutin is preferred rifamycin in PI-based regimen needed, dose reduction of rifabutin indicated	• EFV-based regimen (alternatives if EFV not tolerated: NVP or triple NRTI) • Rifampicin is in first-line TB regimen: co-administration with PI-based regimen not recommended because of drug interactions

Notes: If an intervention is included in the U.S. column but not in the international guidelines column, then that intervention is not recommended by WHO. All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix.

Sources: WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* 2010; ACOG, *Practice Bulletin: Clinical Management Guidelines for Obstetrician–Gynecologists* 2010;117; *MMWR* 2010;59 RR12 ;1; WHO, *Guidelines for the Management of Sexually Transmitted Infections* 2003; WHO, *Essential Prevention and Care Interventions for Adults and Adolescents Living With HIV in Resource-Limited Settings* 2008; WHO, *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants* 2010; WHO, *Cervical Cancer Screening in Developing Countries* 2002

Targeted Laboratory Testing

Country-level guidelines: In most LMICs, the WHO guidelines are adapted at the country level to guide provision of HIV services; in the United States and other high-resource countries, guidelines for care are developed nationally and updated regularly. Guidelines vary from country to country, largely as a result of differential resources. Access to resistance testing in LMICs is virtually nonexistent, in stark contrast to the United States, where HIV resistance testing is widely available and implemented at patient entry into care and with treatment failure. Even viral load testing is not widely available in LMICs, where one test may cost more than the country's per capita health expenditure (WHO, *Patterns of Global Health Expenditures: Results for 191 Countries* 2002).

Efficient use of resources: In the United States, laboratory tests are considered essential elements of HIV care because they assist clinicians in determining the optimal treatment regimen. However, in LMICs, considerations of cost, efficient use of resources, and inadequate laboratory infrastructure have precluded their widespread use. In addition to a country-level HIV drug resistance and assessment strategy, WHO recommends targeted use of viral load testing to reduce the risk of resistance (WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* 2010)

It has been established that routine laboratory monitoring for toxic effects, such as hematology and liver function tests, are not necessary for safe delivery of ART; however, CD4+ cell count monitoring is important in determining eligibility for treatment and deciding when a switch to second-line treatment might be necessary (*Lancet* 2010; 375: 123). Now that eligibility includes anyone with CD4+ cell count $<350/mm^3$, a lack of access to CD4+ testing will exclude many patients who may need HAART but do not have WHO Clinical Stage 3 or 4 disease.

Managing ART: The WHO guiding principles for ART management include the following:

- Laboratory monitoring is not a prerequisite for initiation of ART.
- CD4+ cell count and viral load testing are not essential for monitoring.
- Laboratory monitoring should be symptom directed.
- If resources allow, viral load should be used to confirm treatment failure suspected on the basis of immunological or clinical criteria.
- If resources allow, viral load should be measured every 6 months to detect failure earlier (WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* 2010).

Table 16-3 shows the divergence between U.S. and WHO recommendations for laboratory monitoring. In many LMICs, even CD4+ cell count, the only recommended test (all others are considered desirable), is not widely available.

Table 16-3

Minimum Recommended Laboratory Monitoring Schedules

Time	U.S. Guidelines: HHS 2011	International Guidelines: WHO 2010
At diagnosis or entry into care	• CD4+ cell count • HIV viral load • Resistance testing • HBV and HCV serology • Basic chemistry • ALT, AST, total and direct bilirubin • CBC with differential • Fasting lipid profile • Fasting glucose or hemoglobin A1C • Urinalysis	• CD4+ cell count • *HBsAg*
Routine care when not on ART	• CD4+ cell count every 3–6 mo. • HIV viral load every 3–6 mo. • Basic chemistry every 6–12 mo. • ALT, AST, total and total bilirubin every 6–12 mo. • CBC with differential every 3–6 mo. • Fasting lipid profile v 12 mo. • Fasting glucose or hemoglobin A1C every 12 mo.	• CD4+ cell count every 6 months
At initiation of ART or switch	• CD4+ cell count • HIV viral load • Resistance testing • HLA–B*5701 testing if considering ABC • Tropism testing if considering CCR5 antagonist • HBV serology repeated if not immune at baseline • Basic chemistry • ALT, AST, total and total bilirubin • CBC with differential • Fasting lipid profile • Fasting glucose or hemoglobin A1C • Urinalysis • Pregnancy test if starting EFV	• CD4+ cell count • *Creatinine clearance if starting TDF and high risk*[1] • *ALT if starting NVP and high risk*[2] • *Hb if starting AZT and low CD4+ cell count or BMI*
2-8 weeks after ART initiation or switch	• HIV viral load • Basic chemistry • ALT, AST, total and direct bilirubin • CBC with differential if on AZT • Fasting lipid profile	• *ALT and AST at 2 and 4 weeks for women with CD4+ cell count >250/mm³ and NVP* • *ALT and AST at 4 weeks if HCV or HBV co-infection* • *Hb if on AZT at 4 weeks and low CD4+ cell count or BMI*

Table 16-3 *continued*

Minimum Recommended Laboratory Monitoring Schedules

Time	U.S. Guidelines: DHHS 2	International Guidelines: WHO 2010
Every 3-6 months after ART initiation or switch	• CD4+ cell count • HIV viral load • Basic chemistry • ALT, AST, total and direct bilirubin • CBC with differential • Fasting glucose or hemoglobin A1C, if abnormal at last measurement	• *ALT and AST at 12 weeks for women with CD4+ cell count >250/mm³ and NVP* • *Hb if on AZT and low CD4+ or BMI*
Every 6 months after ART initiation or switch	• Fasting glucose • Urinalysis if on TDF • Fasting lipid profile if abnormal at last measurement	• CD4+ cell count • *Creatinine clearance if on TDF*
At 12 months after ART initiation or switch	• Fasting lipid profile • Urinalysis • CD4+ cell count (in clinically stable patients with suppressed viral load, monitor every 6–12 mo.)	
Treatment failure[3]	• CD4+ cell count • HIV viral load • Resistance testing • Tropism testing if considering a CCR5 antagonist	• CD4+ cell count • *HIV viral load to confirm treatment failure* • HIV viral load if immunological failure

Notes: "Desirable" tests are in *italics*. All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix.

[1] Defined as underlying renal disease, older age group, low BMI, diabetes, hypertension, and concomitant use of boosted PI or nephrotoxic drugs.

[2] Defined as ART-naïve HIV infected women with CD4+ cell count >250/mm³ or HCV coinfection.

[3] Treatment failure in resource-limited settings is diagnosed differently from in the United States, because viral load monitoring is not readily available. If it is available, virological failure is only diagnosed when the viral load remains >5,000 copies/mL. Alternatively, clinical failure is the diagnosis of new or recurrent WHO Stage 4 condition on HAART (not immune reconstitution and inflammatory syndrome), and immunological failure is a fall of CD4+ cell count to below baseline, 50% from peak value, or failure to rise above 100/mm³.

Conclusion

Scientific knowledge and advances, translated into effective clinical interventions, are the fundamental underpinnings of HIV prevention, care, and treatment; however, for most of the world, social and economic factors are the prime determinants of the approach to HIV/AIDS care. Healthcare structure and social support systems must be strengthened if global HIV control is to be achieved. Gender equity in society, including reproductive choice, economic independence, and freedom from gender-based violence, is essential for optimal HIV prevention and care in women.