Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Considerations for Antiretroviral Use in Special Patient Populations

Acute and Recent (Early*) HIV Infection (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all persons with HIV infection and should be offered to those with early* HIV infection **(BII)**, although definitive data are lacking as to whether this approach will result in long-term virologic, immunologic, or clinical benefits.
• All pregnant women with early HIV infection should start ART as soon as possible to prevent perinatal transmission of HIV **(AI)**.
• If treatment is initiated in a patient with early HIV infection, the goal is to suppress plasma HIV RNA to below detectable levels **(AIII)**.
• For patients with early HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels, CD4 count, and toxicity monitoring should be performed as described for patients with chronic HIV infection **(AII)**.
• Genotypic drug-resistance testing should be performed before initiation of ART to guide the selection of the regimen **(AII)**. If therapy is deferred, genotypic resistance testing should still be performed because the results will be useful in selecting a regimen with the greatest potential for achieving optimal virologic response when therapy is ultimately initiated **(AII)**.
• For patients without transmitted drug resistant virus, therapy should be initiated with a regimen that is recommended for patients with chronic HIV infection (see What to Start) **(AIII)**.
• ART can be initiated before drug resistance test results are available. Since resistance to ritonavir (RTV)-boosted protease inhibitors (PIs) emerges slowly and since clinically significant transmitted resistance to PIs is uncommon, these drugs combined with nucleoside reverse transcriptase inhibitors (NRTIs) should be used in this setting **(AIII)**.
• Patients starting ART should be willing and able to commit to treatment and should understand the possible benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy because of clinical and/or psychosocial factors.
* Early infection represents either acute or recent infection as defined in the first paragraph below.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Definitions: Acute HIV infection is the phase of HIV disease immediately after infection during which the initial burst of viremia in newly infected patients occurs; anti-HIV antibodies are undetectable at this time while HIV RNA or p24 antigen are present. Recent infection generally is considered the phase up to 6 months after infection during which anti-HIV antibodies are detectable. Throughout this section, the term "early HIV infection" is used to refer to either acute or recent HIV infection.

An estimated 40% to 90% of patients with acute HIV infection will experience symptoms of acute retroviral syndrome, characterized by fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias, and other symptoms.[1-6] Primary care clinicians, however, often do not recognize acute HIV infection because the self-limiting symptoms are similar to those of many other viral infections, such as influenza and infectious mononucleosis. Acute infection can also be asymptomatic. Table 10 provides practitioners with guidance to recognize, diagnose, and manage acute HIV infection.

Diagnosis of Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV infection in patients who have a compatible clinical syndrome—especially in those who report recent high-risk behavior (Table 10).[7] Patients may not always disclose or admit to high-risk behaviors or they may not perceive that their behaviors put them at risk for HIV acquisition. Thus, signs and symptoms consistent with acute retroviral syndrome should motivate consideration of a diagnosis of acute HIV infection even in the absence of reported high-risk behaviors.

Acute HIV infection is usually defined as detectable HIV RNA or p24 antigen, the latter often used in currently available HIV antigen/antibody (Ag/Ab) combination assays, in serum or plasma in the setting of a negative or indeterminate HIV antibody test.[7, 8] When the acute retroviral syndrome is suspected in a patient with a negative or indeterminate HIV antibody test result, a test for HIV RNA should be performed to diagnose acute infection **(AII)**. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test result because values in acute infection are generally very high (>100,000 copies/mL).[5, 6] A presumptive diagnosis of acute HIV infection can be made on the basis of a negative or indeterminate HIV antibody test result and a positive HIV RNA test result. However, if the results of an HIV RNA test are low-positive, the test should be repeated using a different specimen from the same patient. It is highly unlikely that a second test will reproduce a false-positive result.[6] Interest in routine screening for acute infection has led select centers to use the HIV Ag/Ab test as the primary HIV screening assay or to test all HIV antibody negative samples for HIV RNA.[9] Combination HIV Ag/Ab tests (ARCHITECT HIV Ag/Ab Combo and GS HIV Combo Ag/Ab) now are approved by the Food and Drug Administration; however, the currently available tests do not differentiate between a positive antibody test result and a positive antigen result. Thus HIV Ag/Ab-reactive specimens should be tested with an antibody assay, and if the test results are negative or indeterminate and if acute HIV infection is suspected, be further tested for HIV RNA.[10, 11] Because HIV RNA or Ag/Ab combination assays are not yet used routinely for HIV screening in all settings, clinicians should not assume that a laboratory report of a negative HIV test result indicates that screening for acute HIV infection has been conducted. Patients also should know that home HIV testing only detects HIV antibodies and therefore will not detect very early acute HIV infection. Persons diagnosed presumptively with acute HIV infection should have serologic testing repeated over the next 3 to 6 months to document seroconversion **(AI)** (see Table 10).

Treatment for Early HIV Infection

Clinical trial data regarding the treatment of early HIV infection is limited. Many patients who enrolled in studies to assess the role of antiretroviral therapy (ART) in early HIV infection, as outlined below, were identified as trial participants because they presented with signs or symptoms of acute infection. With the introduction of HIV screening tests that include assays for HIV RNA or p24 antigen and wider HIV screening in healthcare systems, the number of asymptomatic patients identified with early infection may be increasing. The natural history of HIV disease in these patients may differ from that in persons with symptomatic infections, thus further studies on the impact of ART on the natural history of asymptomatic acute HIV infection are needed. The initial burst of high level viremia in infected adults usually declines shortly after acute infection (e.g., within 2 months); however, a rationale for treatment during recent infection (e.g., 2–6 months after infection) remains because the immune system may not yet have maximally contained viral replication in the lymphoid tissue during this time.[12] Several trials have addressed the question of the long-term benefit of potent treatment regimens initiated during early HIV infection. The potential benefits and risks of treating HIV during this stage of disease are discussed below:

- **Potential Benefits of Treatment During Early HIV Infection.** Preliminary data indicate that treatment of early HIV infection with combination ART improves laboratory markers of disease progression.[13-17] The data, though limited, indicate that treatment of early HIV infection may also decrease the severity of acute disease; lower the viral set point,[18-20] which can affect disease progression rates in the event therapy

is stopped; reduce the size of the viral reservoir;[21] and decrease the rate of viral mutation by suppressing viral replication and preserving immune function.[22] Because early HIV infection often is associated with high viral loads and increased infectiousness,[23] and ART use by HIV-infected individuals reduces transmission to serodiscordant sexual partners,[24] treatment during this stage of infection is expected to substantially reduce the risk of HIV transmission. In addition, although data are limited and the clinical relevance unclear, the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection may be mitigated by initiating ART during early HIV infection.[25, 26] Many of the potential benefits described above may be more likely to occur with treatment of acute infection, but they also may occur if treatment is initiated during recent HIV infection.

- **Potential Risks of Treatment During Early HIV Infection.** The potential disadvantages of initiating therapy during early HIV infection include more prolonged exposure to ART without a known long-term clinical benefit. This could result in drug toxicities, development of drug resistance, and adverse effects on an individual's quality of life due to earlier initiation of lifelong therapy that requires strict adherence.

Several randomized controlled trials have studied the effect of ART during acute and recent infection to assess whether initiating early therapy would allow patients to stop treatment and maintain lower viral loads and higher CD4 counts while off ART for prolonged periods of time. This objective was of interest when these studies were initiated but is less relevant in an era in which treatment is recommended for virtually all HIV-infected patients and treatment interruptions are not recommended (see Initiating Antiretroviral Therapy in Treatment-Naive Patients).

The Setpoint Study (ACTG A5217 Study) randomized patients with recent but not acute HIV infection to either defer therapy or immediately initiate ART for 36 weeks and then stop.[18] The primary study end point was a composite of meeting criteria for ART or re-initiation of ART and viral load results at week 72 in both groups and at week 36 in the deferred treatment group. The study was stopped prematurely by the Data and Safety Monitoring Board because of an apparent benefit associated with early therapy that was driven mostly by greater proportion of participants meeting criteria for ART initiation in the deferred treatment group (50%) than in the immediate treatment group (10%). Nearly half of the patients in the deferred treatment group needed to start therapy during the first year of study enrollment.

The Randomized Primo-SHM Trial randomized patients with acute (~70%) or recent (~30%) infection to either defer ART or to undergo treatment for 24 or 60 weeks and then stop.[19] Significantly lower viral loads were observed 36 weeks after treatment interruption in the patients who had been treated early. These patients also experienced a longer time before the need to initiate therapy, primarily on the basis of reaching a CD4 count of <350 cells/mm^3. The median time to starting treatment was 0.7 years for the deferred therapy group and 3.0 and 1.8 years for the 24- and 60-week treatment arms, respectively. The time to reaching a CD4 count of <500 cells/mm^3 was only 0.5 years in the deferred group.

Finally, the SPARTAC Trial included patients with acute and recent infection randomized to either defer therapy or to undergo treatment for 12 or 48 weeks and then stop.[20] In this case, the time to CD4 <350 cells/mm^3 or initiation of therapy was significantly longer in the group treated for 48 weeks than in the deferred treatment group or the group treated for 12 weeks. However, no difference was observed comparing persons who received 12 weeks of ART with those who deferred treatment during early infection.

The strategies tested in these studies are of limited relevance in the current treatment era in which treatment interruption is not recommended. The study results may not fully reflect the natural history of HIV disease in persons with asymptomatic acute infection because most patients in these trials were enrolled on the basis of identified early symptomatic HIV infections. Nevertheless, the results do demonstrate that some immunologic and virologic benefits may be associated with the treatment of early HIV infection. Moreover, all the findings suggest, at least in the population recruited for these studies, that the time to initiating ART after identification

of early infection is quite short when the threshold for ART initiation is 350 CD4 cells/mm³, and nonexistent when therapy is advised for all individuals regardless of CD4 cell count as currently recommended in these guidelines. These observations must be balanced with the risks of early treatment, risks that are largely the same as those of therapy initiated in chronically infected asymptomatic patients with high CD4 counts. Consequently, the health care provider and the patient should be fully aware that the rationale for initiating therapy during early HIV infection is based on theoretical benefits and the extrapolation of data from the strategy trials outlined above. These potential benefits must be weighed against the risks. For these reasons, and because ART is currently recommended for all HIV-infected patients (see Initiating Antiretroviral Therapy in Treatment-Naive Patients), ART should be offered to all patients with early HIV infection **(BII).** However, patients must be willing and able to commit to treatment and providers, on a case-by-case basis, may elect to defer therapy for clinical and/or psychosocial reasons. Providers also should consider enrolling patients with early HIV infection in clinical studies to further evaluate the natural history of this stage of HIV infection and to further define the role of ART in this setting. Providers can obtain information regarding such trials at www.clinicaltrials.gov or from local HIV treatment experts.

Treatment for Early HIV Infection During Pregnancy

Because early HIV infection is associated with a high risk of perinatal transmission, all HIV-infected pregnant women should start combination ART as soon as possible to prevent perinatal transmission of HIV **(AI)**.[27]

Treatment Regimen for Early HIV Infection

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least 1 antiretroviral in 6% to 16% of patients.[28-30] Up to 21% of isolates from contemporary patients with acute HIV infection demonstrated resistance to at least 1 drug.[31] Therefore, before initiation of ART in a person with early HIV infection, genotypic antiretroviral drug-resistance testing should be performed to guide the selection of a regimen **(AII)**. If the decision to initiate therapy during early infection is made, especially in the setting of acute infection, treatment initiation should not be delayed pending resistance testing results. Once results are available, the treatment regimen can be modified if warranted. If therapy is deferred, resistance testing still should be performed because the results will help guide selection of a regimen to optimize virologic response once therapy is initiated **(AII)**.

The goal of therapy during early HIV infection is to suppress plasma HIV RNA to undetectable levels **(AIII)**. Because data to draw firm conclusions regarding specific drug combinations to use in this stage of HIV infection are insufficient, ART should be initiated with one of the combination regimens recommended for patients with chronic infection **(AIII)** (see What to Start). If therapy is started before the results of drug-resistance testing are available, because resistance to RTV-boosted protease inhibitors (PIs) emerge slowly and clinically significant transmitted resistance to PIs is uncommon **(AIII)**. If available, the results of ARV drug-resistance testing or the ARV resistance pattern of the source person's virus should be used to guide the selection of the ARV regimen. Given the recent approval of daily tenofovir DF/emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP),[32-34] early infection may be diagnosed in some patients while they are taking TDF/FTC as PrEP. In this setting, resistance testing should be performed; however, because PI resistance is unlikely, use of a RTV-boosted PI with TDF/FTC remains a reasonable option pending resistance testing results (see What to Start).

Patient Follow-up

Testing for plasma HIV RNA levels, CD4 cell counts, and toxicity monitoring should be performed as described in Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy (i.e., HIV RNA at initiation of therapy, after 2 to 8 weeks, then every 4 to 8 weeks until viral suppression, and thereafter, every 3 to 4 months) **(AII)**.

Duration of Therapy for Early HIV Infection

The optimal duration of therapy for patients with early HIV infection is unknown. Recent studies of early HIV infection have evaluated the potential for starting and then stopping treatment.[18-20] Although these studies showed some benefits associated with this strategy, a large randomized controlled trial of patients with chronic HIV infection found that treatment interruption was harmful in terms of increased risk of AIDS and non-AIDS events,[35] and that the strategy was associated with increased markers of inflammation, immune activation and coagulation.[36] For these reasons and because of the potential benefit of ART in reducing the risk of HIV transmission, the Panel recommends against discontinuation of ART in patients treated for early HIV infection **(AIII)**.

Table 10. Identifying, Diagnosing, and Managing Acute and Recent HIV-1 Infection

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2 to 6 weeks) high risk of exposure to HIV[a]
  - Signs/symptoms/laboratory findings may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.
  - High-risk exposures include sexual contact with an HIV-infected person or a person at risk of HIV infection, sharing injection drug use paraphernalia, or contact of mucous membranes or breaks in skin with potentially infectious fluids.
- **Differential diagnosis:** Includes but is not limited to viral illnesses such as Epstein-Barr virus (EBV)- and non-EBV (e.g., cytomegalovirus) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis.
- **Evaluation/diagnosis of acute HIV infection:**
  - Acute infection is defined as detectable HIV RNA or p24 antigen (the antigen used in currently available HIV antigen/antibody [Ag/Ab] combination assays), in serum or plasma in the setting of a negative or indeterminate HIV antibody test result
    - A reactive HIV antibody test or Ag/Ab test must be followed by supplemental confirmatory testing.
    - A negative or indeterminate HIV antibody test in a person with a positive Ag/Ab test or in whom acute HIV infection is suspected requires assessment of plasma HIV RNA[b] to assess for acute HIV infection.
    - A positive plasma HIV RNA test in the setting of a negative or indeterminate antibody result is consistent with acute HIV infection.
  - Patients presumptively diagnosed with acute HIV infection should have serologic testing repeated over the next 3 to 6 months to document seroconversion.
- **Considerations for antiretroviral therapy (ART) during early HIV infection:**
  - All pregnant women with early HIV infection should begin taking combination ART as soon as possible because of the high risk of perinatal HIV transmission **(AI)**.
  - Treatment for early HIV infection should be offered to all non-pregnant persons **(BII)**.
  - The risks of ART during early HIV infection are largely the same as those for ART initiated in chronically infected asymptomatic patients with high CD4 counts.
  - If therapy is initiated, the goal should be sustained plasma virologic suppression **(AIII)**.
  - Providers should consider enrolling patients with early HIV infection in clinical studies.

[a] In some settings, behaviors conducive to acquisition of HIV infection might not be ascertained or might not be perceived as high risk by the health care provider or the patient or both. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high-risk behaviors.

[b] Plasma HIV RNA can be measured by a variety of quantitative assays, including branched DNA (bDNA) and reverse transcriptase-polymerase chain reaction (RT-PCR)-based assays as well as by a qualitative transcription-mediated amplification assay (APTIMA, GenProbe).

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HIV-Infected Adolescents and Young Adults (Last updated January 10, 2011; last reviewed January 10, 2011)

Older children and adolescents now make up the largest percentage of HIV-infected children cared for at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 15% of the 35,314 new HIV diagnoses reported among the 33 states that participated in confidential, name-based HIV infection reporting in 2006 were among youth 13–24 years of age.[1] Recent trends in HIV prevalence reveal that the disproportionate burden of HIV/AIDS among racial minorities is even greater among youth 13–19 years of age than among young adults 20–24 years of age.[2] Furthermore, trends for all HIV/AIDS diagnoses in 33 states from 2001 to 2006 decreased for all transmission categories except among men who have sex with men (MSM). Notably, among all black MSM, the largest increase in HIV/AIDS diagnoses occurred among youth 13–24 years of age.[3] HIV-infected adolescents represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start antiretroviral therapy (ART) and what antiretroviral (ARV) medications should be used.

Most adolescents who acquire HIV are infected through high-risk behaviors. Many of them are recently infected and unaware of their HIV infection status. Thus, many are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage, and engagement to care. A recent study among HIV-infected adolescents and young adults presenting for care identified primary genotypic resistance mutations to ARV medications in up to 18% of the evaluable sample of recently infected youth, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing.[4] This transmission dynamic reflects that a substantial proportion of youth's sexual partners are likely older and may be more ART experienced; thus, awareness of the importance of baseline resistance testing among recently infected youth naive to ART is imperative.

A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or in infancy through blood products. Such adolescents are usually heavily ART experienced and may have a unique clinical course that differs from that of adolescents infected later in life.[5] If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be based on the same guiding principles as for heavily ART-experienced adults. (See Virologic and Immunogic Failure.)

Adolescents are developmentally at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity intersect and compete with concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and the need to "fit in" with their peers. This makes it challenging to attract and sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage them in care so they can improve and maintain their health for the long term.

Antiretroviral Therapy Considerations in Adolescents

Adult guidelines for ART are usually appropriate for postpubertal adolescents, because the clinical course of HIV-infected adolescents who were infected sexually or through injection drug use during adolescence is more similar to that of adults than to that of children. Adult guidelines can also be useful for postpubertal youth who were perinatally infected because these patients often have treatment challenges associated with the use of long-term ART that mirror those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects.

Dosage of medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not solely on the basis of age.[6-7] Adolescents in early puberty (i.e., Tanner

Stages I and II) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. However, Tanner stage and age are not necessarily directly predictive of drug pharmacokinetics. Because puberty may be delayed in children who were infected with HIV perinatally,[8] continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each ARV medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt period (i.e., Tanner Stage III in females and Tanner Stage IV in males) and following adult or pediatric dosing guidelines and adolescents who have transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in selected circumstances to help guide therapy decisions in this context. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.[9]

Adherence Concerns in Adolescents

HIV-infected adolescents are especially vulnerable to specific adherence problems based on their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health care systems and who lack health insurance. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include:

- denial and fear of their HIV infection;
- misinformation;
- distrust of the medical establishment;
- fear and lack of belief in the effectiveness of medications;
- low self-esteem;
- unstructured and chaotic lifestyles;
- mood disorders and other mental illness;
- lack of familial and social support;
- absence of or inconsistent access to care or health insurance; and
- incumbent risk of inadvertent parental disclosure of the youth's HIV infection status if parental health insurance is used.

In selecting treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ART regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., beepers, timers, and pill boxes) that are stylish and inconspicuous.[10] It is important to make medication adherence as user friendly and as little stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers.[11-13] Directly observed therapy might be considered for selected HIV-infected adolescents such as those with mental illness.[14-18]

Difficult Adherence Problems

Because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and life style, predicting long-term adherence in an adolescent can be very challenging. The ability of youth to adhere

to therapy needs to be included as part of therapeutic decision making concerning the risks and benefits of starting treatment. Erratic adherence may result in the loss of future regimens because of the development of resistance mutations. Clinicians who care for HIV-infected adolescents frequently manage youth who, while needing therapy, pose significant concerns regarding their ability to adhere to therapy. In these cases, alternative considerations to initiation of therapy can be the following: (1) a short-term deferral of treatment until adherence is more likely or while adherence-related problems are aggressively addressed; (2) an adherence testing period in which a placebo (e.g., vitamin pill) is administered; and (3) the avoidance of any regimens with low genetic resistance barriers. Such decisions are ideally individualized to each patient and should be made carefully in context with the individual's clinical status. For a more detailed discussion on specific therapy and adherence issues for HIV-infected adolescents, see Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection.[9]

Special Considerations in Adolescents

Sexually transmitted infections (STIs), in particular human papilloma virus (HPV), should also be addressed in all adolescents. For a more detailed discussion on STIs, see the most recent CDC guidelines[19] and the pediatric opportunistic infection treatment guidelines on HPV among HIV-infected adolescents.[20] Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce risks, should be provided to all youth. Providing gynecologic care for the HIV-infected female adolescent is especially important. Contraception, including the interaction of specific ARV drugs on hormonal contraceptives, and the potential for pregnancy also may alter choices of ART. As an example, efavirenz (EFV) should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring—including periodic pregnancy testing—and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see HIV-Infected Women and the Perinatal Guidelines.[21]

Transitioning Care

Given lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for HIV-infected children, adolescents, and young adults. A successful transition requires an awareness of some fundamental differences between many adolescent and adult HIV care models. In most adolescent HIV clinics, care is more "teen-centered" and multidisciplinary, with primary care being highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some adult HIV clinics may rely more on referral of the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considerations of areas such as medical insurance, independence, autonomy, decisional capacity, confidentiality, and consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less motivated patients. As an additional complication to this transition, HIV-infected adolescents belong to two epidemiologically distinct subgroups: (1) those perinatally infected—who would likely have more disease burden history, complications, and chronicity; less functional autonomy; greater need for ART; and higher mortality risk; and (2) those more recently infected due to high-risk behaviors. Thus, these subgroups have unique biomedical and psychosocial considerations and needs.

To maximize the likelihood of a successful transition, facilitators to successful transitioning are best implemented early on. These include the following: (1) optimizing provider communication between adolescent and adult clinics; (2) addressing patient/family resistance caused by lack of information, stigma or disclosure concerns, and differences in practice styles; (3) preparing youth for life skills development, including counseling them on the appropriate use of a primary care provider and appointment management,

the importance of prompt symptom recognition and reporting, and the importance of self-efficacy with medication management, insurance, and entitlements; (4) identifying an optimal clinic model for a given setting (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in); (5) implementing ongoing evaluation to measure the success of a selected model; (6) engaging in regular multidisciplinary case conferences between adult and adolescent care providers; (7) implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation; and (8) incorporating a family planning component into clinical care. Attention to these key areas will likely improve adherence to appointments and avert the potential for a youth to "fall through the cracks," as it is commonly referred to in adolescent medicine.

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HIV and Illicit Drug Users (Last updated March 27, 2012; last reviewed March 27, 2012)

Treatment Challenges of HIV-Infected Illicit Drug Users

Injection drug use is the second most common mode of HIV transmission in the United States. In addition, noninjection illicit drug use may facilitate sexual transmission of HIV. Injection and noninjection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate [i.e., poppers]). The most commonly used illicit drugs associated with HIV infection are heroin and stimulants (e.g., cocaine and amphetamines); however, the use of club drugs has increased substantially in the past several years and is common among individuals who have HIV infection or who are at risk of HIV infection. The association between club drugs and high-risk sexual behavior in men who have sex with men (MSM) is strongest for methamphetamine and amyl nitrate; this association is less consistent with the other club drugs.[1]

Illicit drug use has been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection because depression is one of the strongest predictors of poor adherence and poor treatment outcomes.[2] Treatment of HIV disease in illicit drug users can be successful but HIV-infected illicit drug users present special treatment challenges. These challenges may include the following: (1) an array of complicating comorbid medical and mental health conditions; (2) limited access to HIV care; (3) inadequate adherence to therapy; (4) medication side effects and toxicities; (5) the need for substance abuse treatment; and (6) drug interactions that can complicate HIV treatment.[3]

Underlying health problems in injection and noninjection drug users result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis (TB), skin and soft tissue infections, recurrent bacterial pneumonia, and endocarditis. Other morbidities such as alteration in levels of consciousness and neurologic and renal disease are not uncommon. Furthermore, these comorbidities are associated with a higher risk of drug overdoses in illicit drug users with HIV disease than in HIV-uninfected illicit drug users, due in part to respiratory, hepatic, and neurological impairments associated with HIV infection.[4] Successful HIV therapy for illicit drug users often depends on clinicians becoming familiar with and managing these comorbid conditions and providing overdose prevention support.

Illicit drug users have less access to HIV care and are less likely to receive antiretroviral therapy (ART) than other populations.[5-6] Factors associated with low rates of ART use among illicit drug users include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and health care providers' lack of expertise in HIV treatment.[5-6] The typically unstable, chaotic life patterns of many illicit drug users; the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of ART all contribute to decreased adherence.[7] The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness that antedates and/or is exacerbated by illicit substance use, additionally complicate the relationship between health care workers and illicit drug users.[8-9] The first step in provision of care and treatment for these individuals is to recognize the existence of a substance abuse problem. It is often obvious that the problem exists, but some patients may hide these problem behaviors from clinicians. Assessment of a patient for substance abuse should be part of routine medical history taking and should be done in a professional, straightforward, and nonjudgmental manner.

Treatment Efficacy in HIV-Infected Illicit Drug Use Populations

Although illicit drug users are underrepresented in HIV therapy clinical trials, available data indicate that efficacy of ART in illicit drug users—when they are not actively using drugs—is similar to that seen in other

populations.[10] Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use per se.[11] Providers need to remain attentive to the possible impact of disruptions caused by drug use on the patient both before and while receiving ART. Although many illicit drug users can sufficiently control their drug use for long enough time to benefit from care, substance abuse treatment is often necessary for successful HIV management.

Close collaboration with substance abuse treatment programs and proper support and attention to this population's special multidisciplinary needs are critical components of successful HIV treatment. Essential to this end are accommodating, flexible, community-based HIV care sites that are characterized by familiarity with and nonjudgmental expertise in management of drug users' wide array of needs and in development of effective strategies to promote medication adherence.[9] These strategies should include, if available, the use of adherence support mechanisms such as modified directly observed therapy (mDOT), which has shown promise in this population.[12]

Antiretroviral Agents and Opioid Substitution Therapy

Compared with noninjection drug users receiving ART, injection drug users (IDUs) receiving ART are more likely to experience an increased frequency of side effects and toxicities of ART. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal (GI), and hematologic disorders are highly prevalent among IDUs. These comorbid conditions should be considered when selecting antiretroviral (ARV) agents in this population. Opioid substitution therapies such as methadone and buprenorphine/naloxone and extended-release naltrexone are commonly used for management of opioid dependence in HIV-infected patients.

Methadone and Antiretroviral Therapy. Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur.[13] These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. Patients and substance abuse treatment facilities should be informed of the likelihood of this interaction. The clinical effect is usually seen after 7 days of co-administration and may be managed by increasing the methadone dosage, usually in 5-mg to 10-mg increments daily until the desired effect is achieved.

Buprenorphine and Antiretroviral Therapy. Buprenorphine, a partial μ-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is increasingly used for opioid dependence treatment. Compared with methadone, buprenorphine has a lower risk of respiratory depression and overdose. This allows physicians in primary care to prescribe buprenorphine for the treatment of opioid dependency. The flexibility of the primary care setting can be of significant value to opioid-addicted HIV-infected patients who require ART because it enables one physician or program to provide both medical and substance abuse services. Limited information is currently available about interactions between buprenorphine and ARV agents.[13-14] Findings from available studies show that the drug interaction profile of buprenorphine is more favorable than that of methadone.

Naltrexone and Antiretroviral Therapy. A once-monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP450 enzyme system and is not expected to interact with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).[15]

Table 11 provides the currently available pharmacokinetic (PK) interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine. Particular attention is needed concerning communication between HIV care providers and drug treatment programs regarding additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolized, at least in part, by the CYP450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported.[16]

Summary

It is usually possible over time to support most active drug users such that acceptable adherence levels with ARV agents can be achieved.[17-18] Providers must work to combine all available resources to stabilize an active drug user in preparation for ART. This should include identification of concurrent medical and psychiatric illnesses, drug treatment and needle and syringe exchange programs, strategies to reduce high-risk sexual behavior, and harm-reduction strategies. A history of drug use alone is insufficient reason to withhold ART because individuals with a history of prior drug use have adherence rates similar to those who do not abuse drugs.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include need for supportive clinical sites; linkage to substance abuse treatment; and awareness of the interactions between illicit drugs and ARV agents, including the increased risk of side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to ARV agents that have a lower risk of hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

Concomitant Drug	Antiretroviral Drug	Pharmacokinetic Interactions Clinical Comments/Recommendations
Buprenorphine	EFV	buprenorphine AUC ↓ 50%; norbuprenorphine[a] AUC ↓ 71% No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
	ETR	buprenorphine AUC ↓ 25% No dosage adjustment necessary.
	ATV	buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%; ↓ ATV levels possible Do not co-administer buprenorphine with unboosted ATV.
	ATV/r	buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105% Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect; norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71% No dose adjustment necessary.
	FPV/r	buprenorphine: no significant effect; norbuprenorphine AUC ↓ 15% No dosage adjustment necessary.
	TPV/r	buprenorphine: no significant effect; norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80%; TPV C_{min} ↓ 19%–40% Consider monitoring TPV level.
	3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV	No significant effect No dosage adjustment necessary.
	ABC, d4T, FTC, ETR, IDV +/- RTV, SQV/r, RAL, MVC, T20	No data
Methadone	ABC	methadone clearance ↑ 22% No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44% No dosage adjustment necessary.
	ZDV	ZDV AUC ↑ 29%–43% Monitor for ZDV-related adverse effects.
	EFV	methadone AUC ↓ 52% Opioid withdrawal common; increased methadone dose often necessary.

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (page 2 of 2)

Methadone, cont'd	NVP	methadone AUC ↓ 41% NVP: no significant effect Opioid withdrawal common; increased methadone dose often necessary.
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	With ATV/r, DRV/r, FPV/r: R-methadone[b] AUC ↓ 16%–18%; With LPV/r: methadone AUC ↓ 26%–53%; With SQV/r 1000/100 mg BID: R-methadone AUC ↓ 19%; With TPV/r: R-methadone AUC ↓ 48% Opioid withdrawal unlikely but may occur. Adjustment of methadone dose usually not required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	FPV	No data with FPV (unboosted) With APV: R-methadone C_{min} ↓ 21%, no significant change in AUC Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	methadone AUC ↓ 40% Opioid withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require increased methadone dose.
	ddI (EC capsule), 3TC, TDF, ETR, RTV, ATV, IDV, RAL	No significant effect No dosage adjustment necessary.
	FTC, MVC, T20	No data

[a] Norbuprenorphine is an active metabolite of buprenorphine.
[b] R-methadone is the active form of methadone.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir/ ritonavair, AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, EC = enteric coated, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, IDV = indinavir, IDV/r = indinavir/ritonavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, RAL = raltegravir, RTV = ritonavir, SQV/r = sacquinavir/ritonavir, T20 = enfuvirtide, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

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Panel's Recommendations
• The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents **(AI)**.
• Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method to prevent unintended pregnancy **(AIII)**.
• In pregnant women, an additional goal of therapy is prevention of perinatal transmission of HIV, with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn **(AI)**.
• When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data on use during pregnancy for each agent **(AIII)**.
• Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz (EFV) and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on EFV-based regimens **(AIII)**.
• Alternative regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health **(BIII)**.
• Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, EFV can be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression **(CIII)**.
• When designing a regimen for a pregnant woman, clinicians should consult the most current Health and Human Services (HHS) Perinatal Guidelines **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

This section provides discussion of some basic principles and unique considerations to follow when caring for HIV-infected women, including during pregnancy. Clinicians who provide care for pregnant women should consult the current *Perinatal Guidelines*[1] for more in-depth discussion and management assistance. <mark>Additional guidance on the management of HIV-infected women can be found at http://hab.hrsa.gov/deliverhivaidscare/clinicalguide11.</mark>

Gender Considerations in Antiretroviral Therapy

In general, studies to date have not shown gender differences in virologic responses to antiretroviral therapy (ART),[2-4] but a number of studies have suggested that gender may influence the frequency, presentation, and severity of selected antiretroviral (ARV)-related adverse events.[5] Although data are limited, evidence also exists that pharmacokinetics for some ARV drugs may differ between men and women, possibly because of variations between men and women in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, cytochrome P (CYP) 450 activity, drug transporter function, and excretion activity.[6-8]

Adverse Effects:

• *Nevirapine (NVP)-associated hepatotoxicity:* NVP has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity in ARV-naive individuals; women with higher CD4 counts (>250 cells/mm^3) or elevated baseline transaminase levels appear to be at

greatest risk.[9-12] It is generally recommended that NVP not be prescribed to ARV-naive women who have CD4 counts >250 cells/mm³ unless there is no other alternative and the benefit from NVP outweighs the risk of hepatotoxicity **(AI)**.

- *Lactic acidosis:* There is a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to nucleoside reverse transcriptase inhibitors (NRTIs). Lactic acidosis is most common with stavudine (d4T), didanosine (ddI), and zidovudine (ZDV) but it can occur with other NRTIs.[13]

- *Metabolic complications:* A few studies have compared women and men in terms of metabolic complications associated with ARV use. Compared with HIV-infected men, HIV-infected women are more likely to experience increases in central fat with ART and are less likely to have triglyceride elevations on treatment.[14, 15] Women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk is exacerbated by HIV and ART.[16, 17] At the present time, none of these differences requires women-specific recommendations regarding treatment or monitoring.

Women of Childbearing Potential

All women of childbearing potential should be offered pre-conception counseling and care as a component of routine primary medical care. Counseling should include discussion of special considerations pertaining to ARV use when trying to conceive and during pregnancy (see *Perinatal Guidelines*[1]). Safe sexual practices, reproductive desires and options for conception, HIV status of sexual partner(s), and use of effective contraception to prevent unintended pregnancy should be discussed. An HIV-infected woman who wishes to conceive with an HIV-uninfected male partner should be informed of options to prevent sexual transmission of HIV while attempting conception. Interventions include initiation of maximally suppressive ART, which significantly decreases the risk of sexual transmission (see Preventing Secondary Transmission of HIV), and artificial insemination, including the option to self-inseminate with the partner's sperm during the periovulatory period[18] (for more extensive discussion on this topic, see the Reproductive Options for HIV-Concordant and Serodiscordant Couples section of the *Perinatal Guidelines*.[1]

Efavirenz (EFV) is teratogenic in non-human primates. Women of childbearing potential should undergo pregnancy testing before initiation of EFV and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on EFV-based regimens **(AIII)**. Alternative regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health **(BIII)**. The most vulnerable period in fetal organogenesis is early in gestation, before pregnancy is recognized.

Hormonal Contraception

Safe and effective reproductive health and family planning services to reduce unintended pregnancy and perinatal transmission of HIV are an essential component of care for HIV-infected women of childbearing age. Counseling about reproductive issues should be provided on an ongoing basis.

Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives that could lower contraceptive efficacy. Several protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have drug interactions with combined oral contraceptives (COCs). Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see Tables 15a and 15b), which potentially decreases contraceptive efficacy or increases estrogen- or progestin-related adverse effects (e.g., thromboembolism). Small studies of HIV-infected women receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART showed no significant interactions between DMPA and EFV, NVP, nelfinavir (NFV), or NRTI drugs.[19-21] Contraceptive failure of the etonogestrel

implant in two patients on EFV-based therapy has been reported and a study has shown EFV may decrease plasma progestin concentrations of COCs containing ethinyl estradiol and norgestimate.[22, 23] Several RTV-boosted PIs decrease oral contraceptive estradiol levels.[24, 25] A small study from Malawi showed that NVP use did not significantly affect estradiol or progestin levels in HIV-infected women.[26] Overall, data are relatively limited and the clinical implications of these findings are unclear. The magnitudes of change in drug levels that may reduce contraceptive efficacy or increase adverse effects are unknown. Concerns about pharmacokinetic interactions between oral and implant hormonal contraceptives and ARVs should not prevent clinicians from prescribing hormonal contraceptives for women on ART if that is their preferred contraceptive method. However, when women wish to use hormonal contraceptives and drug interactions with ARVs are known, additional or alternative contraceptive methods may be recommended (see drug interaction Tables 15a, 15b, and 15d and *Perinatal Guidelines*[1]). Consistent use of male or female condoms to prevent transmission of HIV and protect against other sexually transmitted diseases (STDs) is recommended for all HIV-infected women and their partners, regardless of contraceptive use.

The data on the association between hormonal contraception and the risk of acquisition of HIV are conflicting.[27] A retrospective secondary analysis of two studies of serodiscordant couples in Africa in which the HIV-infected partner was not receiving ART found that women using hormonal contraception (the vast majority using injectable DMPA) had a twofold increased risk of acquiring HIV (for HIV-infected male/HIV-uninfected female couples) or transmitting HIV (HIV-infected female/HIV-uninfected male couples). HIV-infected women using hormonal contraception had higher genital HIV RNA concentrations than did women not using hormonal contraceptives.[28] Oral contraceptive use was not significantly associated with transmission of HIV; however, the number of women using oral contraceptives in this study was insufficient to adequately assess risk. It is important to note that not all studies have supported a link between hormonal contraception and transmission or acquisition of HIV and that the individuals in this study were not receiving ART. Further research is needed to definitively determine if hormonal contraceptive use is an independent risk factor for acquisition and transmission of HIV, particularly in the setting of ART.[27, 29]

Intrauterine devices (IUDs) appear to be a safe and effective contraceptive option for HIV-infected women.[30-33] Although studies have focused primarily on non-hormone-containing IUDs (e.g., copper IUD), several small studies have also found levonorgestrel-releasing IUDs to be safe and not associated with increased genital tract shedding of HIV.[31, 34, 35]

Pregnant Women

Clinicians should review the *Perinatal Guidelines*[1] for a detailed discussion of the management of HIV-infected pregnant women. The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic, or clinical parameters **(AI)**. Pregnant HIV-infected women should be counseled regarding the known benefits and risks of ARV use during pregnancy to the woman, fetus, and newborn. A woman's decision regarding ARV use should be respected. Coercive and punitive approaches undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize maternal, fetal, and neonatal well-being.

Prevention of Perinatal Transmission of HIV. The use of ARVs and the resultant reduction of HIV RNA levels decrease perinatal transmission of HIV.[36-38] The goal of ARV use is to achieve maximal and sustained suppression of HIV RNA levels during pregnancy.

As in non-pregnant individuals, genotypic resistance testing is recommended for all pregnant women before ARV initiation **(AIII)** and for pregnant women with detectable HIV RNA levels while on therapy **(AI)**. Optimal prevention of perinatal transmission may require initiation of ARV drugs before results of resistance testing are available. If results demonstrate the presence of significant mutation(s) that may confer resistance to the prescribed ARV regimen, the regimen should be modified.

Long-term follow-up is recommended for all infants born to women who have received ARVs during pregnancy, regardless of the infant's HIV status (see the *Perinatal Guidelines*[1]).

Regimen Considerations. Pregnancy should not preclude the use of optimal drug regimens. Because recommendations on ARVs to use for treatment of HIV-infected pregnant women are subject to unique considerations, recommendations specific to the timing of therapy initiation and the choice of ARVs for pregnant women may differ from those for non-pregnant individuals. These considerations include the following:

- Potential changes in pharmacokinetics and, thus, dosing requirements, which result from physiologic changes associated with pregnancy;
- potential ARV-associated adverse effects in pregnant women and the woman's ability to adhere to a particular regimen during pregnancy; and
- potential short- and long-term effects of the ARV on the fetus and newborn, which are unknown for many drugs.

Combination drug regimens are considered the standard of care in pregnancy, both for the treatment of HIV infection and for the prevention of perinatal transmission of HIV. Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, EFV can be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression **(CIII)**. Detailed recommendations on ARV choice in pregnancy are discussed in detail in the Perinatal Guidelines (see *Perinatal Guidelines*[1]).

Intravenous (IV) zidovudine (ZDV) infusion to the mother during labor is recommended if maternal HIV RNA is ≥400 copies/mL (or with unknown HIV RNA levels) near delivery, regardless of antepartum regimen or mode of delivery **(AI)**. Consideration can be given to omitting IV ZDV infusion during labor for HIV-infected women receiving combination ART regimens who have HIV RNA <400 copies/mL near delivery **(BII)**; however, the combination ART should continue to be administered during labor.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to ARVs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (http://www.apregistry.com). The registry collects observational data regarding exposure to Food and Drug Administration-approved ARV drugs during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of ART during pregnancy, refer to the *Perinatal Guidelines*.[1]

Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for non-pregnant adults and adolescents. Because maternal ART reduces but does not eliminate the risk of transmission of HIV in breast milk and postnatal transmission can occur despite maternal ART, women should also be counseled to avoid breastfeeding.[1] HIV-infected women should avoid pre-mastication of food fed to their infants because the practice has been associated with transmission of HIV from mother to child.[39] Considerations regarding continuation of ART for maternal therapeutic indications are the same as those for ART use in other non-pregnant individuals. For more information regarding postpartum discontinuation of ART, refer to the *Perinatal Guidelines*.[1]

Several studies have demonstrated that adherence to ART may worsen in the postpartum period.[40-44] Clinicians caring for women postpartum who are receiving ART should specifically address adherence, including an evaluation of specific facilitators and barriers to adherence. Clinicians may consider an intervention to improve adherence (see Adherence to Antiretroviral Therapy).

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HIV-2 Infection (Last updated January 10, 2011; last reviewed January 10, 2011)

HIV-2 infection is endemic in West Africa. Although HIV-2 has had only limited spread outside this area, it should be considered in persons of West African origin or those who have had sexual contact or shared needles with persons of West African origin. The prevalence of HIV-2 infection is also disproportionately high in countries with strong socioeconomic ties to West Africa (e.g., France; Spain; Portugal; and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India near Goa).

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rates compared with HIV-1 infection.[1-2] However, HIV-2 infection can progress to AIDS, and thus antiretroviral therapy (ART) may become necessary during the course of infection. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from an area with high prevalence of HIV-2. In the appropriate epidemiologic setting, HIV-2 infection should be suspected in patients with clinical conditions suggestive of HIV infection but with atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot).[3] The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in patients with serologically confirmed HIV infection but low or undetectable viral loads or in those with declining CD4 counts despite apparent virologic suppression on ART.

The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is Food and Drug Administration (FDA) approved for differentiating HIV-1 from HIV-2 infection. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2, and no HIV-2 commercial viral load assays are currently available.[4-5] Most studies reporting HIV-2 viral loads use "in-house" assays that are not widely available, making it difficult to monitor virologic response in the clinical setting. In addition, no validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are available.

To date, there have been no randomized trials addressing the question of when to start ART or the choice of initial or second-line therapy for HIV-2 infection;[6] thus, the optimal treatment strategy has not been defined. HIV-2 appears intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs)[7] and to enfuvirtide.[8] *In vitro* data suggest HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs), although with a lower barrier to resistance than HIV-1.[9-10] Variable sensitivity among protease inhibitors (PIs) has been reported; lopinavir (LPV), saquinavir (SQV), and darunavir (DRV) are more active against HIV-2 than other approved PIs.[11-14] The integrase inhibitor, raltegravir (RAL),[15] and the CCR5 antagonist, maraviroc (MVC), appear active against some HIV-2 isolates, although no approved assays to determine HIV-2 coreceptor tropism exist and HIV-2 is known to utilize multiple minor coreceptors in addition to CCR5 and CXCR4.[16] Several small studies suggest poor responses among HIV-2 infected individuals treated with some ARV regimens, including dual-NRTI regimens, regimens containing two NRTIs + NNRTI, and some unboosted PI-based regimens including nelfinavir (NFV) or indinavir (IDV) plus zidovudine (ZDV) and lamivudine (3TC).[6, 17-19] Clinical data on the utility of triple-NRTI regimens are conflicting.[20-21] In general, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses.[21] One small study suggested satisfactory responses to lopinavir/ritonavir (LPV/r)-containing regimens in 17 of 29 (59%) of ARV-naive subjects.[22]

Resistance-associated mutations develop commonly in HIV-2 patients on therapy.[17, 21, 23] Genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because pathways and mutational patterns leading to resistance may differ.[10, 21, 24] CD4 cell recovery on therapy may be poor,[25] suggesting that more reliable methods for monitoring disease progression and treatment efficacy in HIV-2 infection are needed.

Some groups have recommended specific preferred and alternative regimens for initial therapy of HIV-2 infection,[24] though as yet there are no controlled trial data to reliably predict their success. Until more definitive data are available in an ART-naive patient with HIV-2 mono-infection or with HIV-1/HIV-2 dual

infection who requires treatment, clinicians should initiate a regimen containing two NRTIs and a boosted PI. Monitoring of virologic response in such patients is problematic because of the lack of a commercially available HIV-2 viral load assay; however, clinical and CD4 count improvement can be used to assess treatment response.

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HIV and the Older Patient (Last updated March 27, 2012; last reviewed March 27, 2012)

Key Considerations When Caring for Older HIV-Infected Patients
• Antiretroviral therapy (ART) is recommended in patients >50 years of age, regardless of CD4 cell count **(BIII)**, because the risk of non-AIDS related complications may increase and the immunologic response to ART may be reduced in older HIV-infected patients.
• ART-associated adverse events may occur more frequently in older HIV-infected adults than in younger HIV-infected individuals. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health of older HIV-infected adults should be monitored closely.
• The increased risk of drug-drug interactions between antiretroviral (ARV) drugs and other medications commonly used in older HIV-infected patients should be assessed regularly, especially when starting or switching ART and concomitant medications.
• HIV experts and primary care providers should work together to optimize the medical care of older HIV-infected patients with complex comorbidities.
• Counseling to prevent secondary transmission of HIV remains an important aspect of the care of the older HIV-infected patient.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional *Rating of Evidence:* I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Effective antiretroviral therapy (ART) has increased survival in HIV-infected individuals, resulting in an increasing number of older individuals living with HIV infection. In the United States, approximately 30% of people currently living with HIV/AIDS are age 50 years or older and trends suggest that the proportion of older persons living with HIV/AIDS will increase steadily.[1] Care of HIV-infected patients increasingly will involve adults 60 to 80 years of age, a population for which data from clinical trials or pharmacokinetic studies are very limited.

There are several distinct areas of concern regarding the association between age and HIV disease.[2] First, older HIV-infected patients may suffer from aging-related comorbid illnesses that can complicate the management of HIV infection, as outlined in detail below. Second, HIV disease may affect the biology of aging, possibly resulting in early manifestations of many clinical syndromes generally associated with advanced age. Third, reduced mucosal and immunologic defenses (such as post-menopausal atrophic vaginitis) and changes in risk behaviors (for example, decrease in condom use because of less concern about pregnancy and increased use of erectile dysfunction drugs) in older adults could lead to increased risk of acquisition and transmission of HIV.[3-4] Finally, because older adults generally are perceived to be at low risk of HIV infection, screening for HIV in this population remains low. For these reasons, HIV infection in many older adults may not be diagnosed until late in the disease process. This section focuses on HIV diagnosis and treatment considerations in the older HIV-infected patient.

HIV Diagnosis and Prevention

Even though many older individuals are engaged in risk behaviors associated with acquisition of HIV, they may be perceived to be at low risk of infection and, as a result, they are less likely to be tested for HIV than younger persons.[5] According to one U.S. survey, 71% of men and 51% of women age 60 years and older continue to be sexually active,[6] with less concern about the possibility of pregnancy contributing to less condom use. Another national survey reported that among individuals age 50 years or older, condoms were not used during most recent intercourse with 91% of casual partners or 70% of new partners.[7] In addition,

results from a CDC survey[8] show that in 2008 only 35% of adults age 45 to 64 years had ever been tested for HIV infection despite the 2006 CDC recommendation that individuals age 13 to 64 years be tested at least once and more often if sexually active.[9] Clinicians must be attuned to the possibility of HIV infection in older patients, including those older than 64 years of age who, based on CDC recommendations, would not be screened for HIV. Furthermore, sexual history taking, risk-reduction counseling, and screening for sexually transmitted diseases (STDs) (if indicated), are important components of general health care for HIV-infected and -uninfected older patients.

Failure to consider a diagnosis of HIV in older persons likely contributes to later disease presentation and initiation of ART.[10] One surveillance report showed that the proportion of patients who progressed to AIDS within 1 year of diagnosis was greater among patients >60 years of age (52%) than among patients younger than 25 years (16%).[1] When individuals >50 years of age present with severe illnesses, AIDS-related opportunistic infections (OIs) need to be considered in the differential diagnosis of the illness.

Initiating Antiretroviral Therapy

Concerns about decreased immune recovery and increased risk of serious non-AIDS events are factors that favor initiating ART in patients >50 years of age regardless of CD4 cell count **(BIII)**. (See Initiating Antiretroviral Therapy in Treatment-Naive Patients.) Data that would favor use of any one of the Panel's recommended initial ART regimens (see What to Start) on the basis of age are not available. The choice of regimen should be informed by a comprehensive review of the patient's other medical conditions and medications. A noteworthy limitation of currently available information is lack of data on the long-term safety of specific antiretroviral (ARV) drugs in older patients, such as use of tenofovir disoproxil fumarate (TDF) in older patients with declining renal function. The recommendations on how frequently to monitor parameters of ART effectiveness and safety for adults age >50 years are similar to those for the general HIV-infected population; however, the recommendations for older adults focus particularly on the adverse events of ART pertaining to renal, liver, cardiovascular, metabolic, and bone health (see Table 13).

HIV, Aging, and Antiretroviral Therapy

The efficacy, pharmacokinetics, adverse effects, and drug interaction potentials of ART in the older adult have not been studied systematically. There is no evidence that the virologic response to ART is different in older patients than in younger patients. However, CD4 T-cell recovery after starting ART generally is less robust in older patients than in younger patients.[11-14] This observation suggests that starting ART at a younger age will result in better immunologic and possibly clinical outcomes.

Hepatic metabolism and renal elimination are the major routes of drug clearance, including the clearance of ARV drugs. Both liver and kidney function may decrease with age, which may result in impaired drug elimination and drug accumulation.[15] Current ARV drug doses are based on pharmacokinetic and pharmacodynamic data derived from studies conducted in subjects with normal organ function. Most clinical trials include only a small proportion of study participants >50 years of age. Whether drug accumulation in the older patient may lead to greater incidence and severity of adverse effects than seen in younger patients is unknown.

HIV-infected patients with aging-associated comorbidities may require additional pharmacologic intervention, making therapeutic management increasingly complex. In addition to taking medications to manage HIV infection and comorbid conditions, many older HIV-infected patients also are taking medications to ameliorate discomfort (e.g., pain medications, sedatives) or to manage adverse effects of medications (e.g., anti-emetics). They also may self-medicate with over-the-counter medicines or supplements. In the HIV-negative population, polypharmacy is a major cause of iatrogenic problems in

geriatric patients.[16] This may be the result of medication errors (by prescribers or patients), nonadherence, additive drug toxicities, and drug-drug interactions. Older HIV-infected patients probably are at an even greater risk of polypharmacy and its attendant adverse consequences than younger HIV-infected or similarly aged HIV-uninfected patients.

Drug-drug interactions are common with ART and easily can be overlooked by prescribers.[17] The available drug interaction information on ARV agents is derived primarily from pharmacokinetic studies performed in a small number of relatively young, HIV-uninfected subjects with normal organ function (see Tables 14-16b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of the interaction may be different in older HIV-infected patients than in younger HIV-infected patients.

Nonadherence is the most common cause of treatment failure. Complex dosing requirements, high pill burden, inability to access medications because of cost or availability, limited health literacy including lack of numeracy skills, misunderstanding of instructions, depression, and neurocognitive impairment are among the key reasons for nonadherence.[18] Although many of these factors likely will be more prevalent in an aging HIV-infected population, some data suggest that older HIV-infected patients may be more adherent to ART than younger HIV-infected patients.[19-21] Clinicians should assess adherence regularly to identify any factors, such as neurocognitive deficits, that may make adherence a challenge. One or more interventions such as discontinuation of unnecessary medications; regimen simplification; or use of adherence tools, including pillboxes, daily calendars, and evidence-based behavioral approaches may be necessary to facilitate medication adherence (see Adherence to Antiretroviral Therapy).

Non-AIDS HIV-Related Complications and other Comorbidities

With the reduction in AIDS-related morbidity and mortality observed with effective use of ART, non-AIDS conditions constitute an increasing proportion of serious illnesses in ART-treated HIV-infected populations.[22-24] Heart disease and cancer are the leading causes of death in older Americans.[25] Similarly, for HIV-infected patients on ART, non-AIDS events such as heart disease, liver disease, and cancer have emerged as major causes of morbidity and mortality. Neurocognitive impairment, already a major health problem in aging patients, may be exacerbated by the effect of HIV infection on the brain.[26] That the presence of multiple non-AIDS comorbidities coupled with the immunologic effects of HIV infection could add to the disease burden of an aging HIV-infected person is a concern.[27-29] At present, primary care recommendations are the same for HIV-infected and HIV-uninfected adults and focus on identifying and managing risks of conditions such as heart, liver, and renal disease; cancer; and bone demineralization.[30-32]

Discontinuing Antiretroviral Therapy in Older Patients

Important issues to discuss with aging HIV-infected patients are living wills, advance directives, and long-term care planning including financial concerns. Health care cost sharing (e.g., co-pays, out-of-pocket costs), loss of employment, and other financial-related factors can cause interruptions in treatment. Clinic systems can minimize loss of treatment by helping patients maintain access to insurance.

For the severely debilitated or terminally ill HIV-infected patient, adding palliative care medications, while perhaps beneficial, further increases the complexity and risk of negative drug interactions. For such patients, a balanced consideration of both the expected benefits of ART and the toxicities and negative quality-of-life effects of ART is needed.

Few data exist on the use of ART in severely debilitated patients with chronic, severe, or non-AIDS terminal conditions.[33-34] Withdrawal of ART usually results in rebound viremia and a decline in CD4 cell count. Acute

retroviral syndrome after abrupt discontinuation of ART has been reported. In very debilitated patients, if there are no significant adverse reactions to ART, most clinicians would continue therapy. In cases where ART negatively affects quality of life, the decision to continue therapy should be made together with the patient and/or family members after a discussion on the risks and benefits of continuing or withdrawing ART.

Conclusion

HIV infection may increase the risk of many major health conditions experienced by aging adults and possibly accelerate the aging process.[35] As HIV-infected adults age, their health problems become increasingly complex, placing additional demands on the health care system. This adds to the concern that outpatient clinics providing HIV care in the United States share the same financial problems as other chronic disease and primary care clinics and that reimbursement for care is not sufficient to maintain care at a sustainable level.[36] Continued involvement of HIV experts in the care of older HIV-infected patients is warranted. However, given that the current shortage of primary care providers and geriatricians is projected to continue, current HIV providers will need to adapt to the shifting need for expertise in geriatrics through continuing education and ongoing assessment of the evolving health needs of aging HIV-infected patients.[37] The aging of the HIV-infected population also signals a need for more information on long-term safety and efficacy of ARV drugs in older patients.

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