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

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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/mm^3, 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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