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\textsuperscript{a}) HIV Infection  (Last updated January 28, 2016; last reviewed January 28, 2016)

### Panel’s Recommendations

- Antiretroviral therapy (ART) is recommended for all individuals with HIV-1 infection (AI) including those with early\textsuperscript{a} HIV-1 infection.
- Once initiated, the goal of ART is to suppress plasma HIV-1 RNA to undetectable levels (AIII). Testing for plasma HIV-1 RNA levels, CD4 T lymphocyte counts, and toxicity monitoring should be performed as recommended for patients with chronic HIV-1 infection (AII).
- Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen (AII).
- ART can be initiated before drug resistance test results are available. Because resistance to pharmacokinetically enhanced protease inhibitors (PIs) emerges slowly and clinically significant transmitted resistance to PIs is uncommon, ritonavir-boosted darunavir (DRV/r) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is a recommended regimen in this setting (AII). For similar reasons, dolutegravir (DTG) plus TDF/FTC is also a reasonable option although data regarding transmission of integrase strand transfer inhibitor (INSTI)-resistant HIV and the efficacy of this regimen in early HIV infection is limited (AIII).
- When results of drug resistance testing are available, the treatment regimen can be modified if warranted (AII). In patients without transmitted drug resistant virus, therapy should be initiated with one of the combination regimens that is recommended for patients with chronic HIV-1 infection (see What to Start) (AII).
- Patients starting ART should be willing and able to commit to treatment and should understand the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may recommend that patients defer therapy because of clinical and/or psychosocial factors.

**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

\textsuperscript{a} Early infection represents either acute or recent infection.

### Definitions

Acute HIV-1 infection is the phase of HIV-1 disease immediately after infection that is characterized by an initial burst of viremia; although anti-HIV-1 antibodies are undetectable, HIV-1 RNA or p24 antigen are present. Recent infection generally is considered the phase up to 6 months after infection during which anti-HIV-1 antibodies are detectable. Throughout this section, the term “early HIV-1 infection” is used to refer to either acute or recent HIV-1 infection.

An estimated 40% to 90% of patients with acute HIV-1 infection will experience symptoms of acute retroviral syndrome, such as fever, lymphadenopathy, pharyngitis, skin rash, myalgia, arthralgia, and other symptoms.\textsuperscript{1-6} However, because the self-limiting symptoms are similar to those of many other viral infections, such as influenza and infectious mononucleosis, primary care clinicians often do not recognize acute HIV-1 infection. Acute infection can also be asymptomatic. Table 11 provides practitioners with guidance to recognize, diagnose, and manage acute HIV-1 infection.

### Diagnosing Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV-1 infection in patients who have a compatible clinical syndrome—especially in those who report recent high-risk behavior (see Table 11).\textsuperscript{7} Patients may not always disclose or admit to high-risk behaviors or perceive that their behaviors put them at risk for HIV-1 acquisition. Thus, even in the absence of reported high-risk behaviors, signs and symptoms consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV-1 infection.

Acute HIV-1 infection is usually defined as detectable HIV-1 RNA or p24 antigen in serum or plasma in the setting of a negative or indeterminate HIV-1 antibody test result.\textsuperscript{7,8} Combination immunoassays that detect
HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen are now approved by the Food and Drug Administration, and the most recent Centers for Disease Control and Prevention testing algorithm recommends them as the preferred assays to use for HIV screening, including for possible acute HIV-1 infection. Specimens that are reactive on an initial antigen/antibody (Ag/Ab) assay should be tested with an immunoassay that differentiates HIV-1 from HIV-2 antibodies. Specimens that are reactive on the initial assay and have either negative or indeterminate antibody differentiation test results should be tested for quantitative or qualitative HIV-1 RNA; a negative HIV-1 RNA test result indicates that the original Ag/Ab test result was a false positive. Detection of HIV-1 RNA in this setting indicates that acute HIV-1 infection is highly likely (see Treatment for Early HIV-1 Infection). HIV-1 infection should be confirmed by subsequent testing to document HIV antibody seroconversion.

Some health care facilities may still be following HIV testing algorithms that recommend initial testing with an assay that only tests for anti-HIV antibodies. In such settings, when acute HIV-1 infection is suspected in a patient with a negative or indeterminate HIV antibody test result, a quantitative or qualitative HIV-1 RNA test should be performed. A negative or indeterminate HIV antibody test result and a positive HIV-1 RNA test result indicate that acute HIV-1 infection is highly likely. Providers should be aware that a low-positive quantitative HIV-1 RNA level (e.g., <10,000 copies/mL) may represent a false-positive result because HIV-1 RNA levels in acute infection are generally very high (e.g., >100,000 copies/mL). Therefore, when a low-positive quantitative HIV-1 RNA test result is obtained, the HIV-1 RNA test should be repeated using a different specimen from the same patient. The diagnosis of HIV-1 infection should be confirmed by subsequent documentation of HIV antibody seroconversion (see Table 11).

**Treating Early HIV-1 Infection**

Clinical trial data regarding the treatment of early HIV-1 infection are limited. Many individuals who enrolled in studies to assess the role of ART in early HIV-1 infection 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-1 RNA or p24 antigen and wider HIV screening in health care settings—particularly HIV testing associated with broader use of pre-exposure prophylaxis (PrEP) by individuals at higher risk for HIV—the number of asymptomatic patients identified with early infection may increase. The initial burst of high level viremia in infected individuals usually declines shortly after acute infection (e.g., within 2 months). However, there is a rationale for treatment during recent infection (e.g., 2–6 months after infection) because during the transition to chronic infection, the immune system may not yet have maximally contained viral replication in the lymphoid tissue. Several trials have addressed the question of the long-term benefit of potent treatment regimens initiated during early HIV-1 infection. The potential benefits and risks of treating early HIV-1 infection are discussed below.

**Potential Benefits of Treatment During Early HIV-1 Infection**

Preliminary data indicate that treatment of early HIV-1 infection with ART improves laboratory markers of disease progression. The data, though limited, indicate that treatment of early HIV-1 infection may also reduce the severity of acute disease, lower the viral set point, reduce the size of the viral reservoir, delay disease progression, enhance CD4 T lymphocyte (CD4) cell recovery, and decrease the rate of viral mutation by suppressing viral replication and preserving immune function. Because early HIV-1 infection is often associated with high viral loads and increased infectiousness, and ART use by HIV-1-infected individuals reduces transmission to uninfected sexual partners, treatment during early HIV-1 infection is expected to substantially reduce the risk of HIV-1 transmission. In addition, although data are limited and the clinical relevance unclear, initiating ART during early HIV-1 infection may preserve mucosal Th17 cell function and mitigate the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection. 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-1 infection.

The START Trial enrolled HIV-infected patients with CD4 counts >500 cells/mm³ and randomized them to...
either start ART immediately or defer ART until their CD4 counts fell below 350 cells/mm³ or an AIDS event occurred. The study demonstrated that immediate treatment resulted in a decrease in the combined endpoint of AIDS-defining illnesses, serious non-AIDS events, or death.27 Similarly, TEMPRANO demonstrated decreased risk of death or severe HIV-related illness among HIV-infected patients who initiated ART with baseline CD4 counts >500 cells/mm³.28 The results from these studies strengthen the evidence for the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)’s recommendation for ART initiation in all patients regardless of CD4 cell count (AI) (see Initiation of Antiretroviral Therapy section). Although neither trial collected specific information on patients with early infection, the strength of the overall results of the two studies and the evidence from other studies described above strongly suggest that, whenever possible, patients should begin ART upon diagnosis of early infection.

Considerations When Treating Early HIV-1 Infection
As with chronic infection, patients with early HIV-1 infection must be willing and able to commit to treatment. On a case-by-case basis, providers may recommend that patients defer therapy for clinical and/or psychosocial reasons. If treatment during early infection is deferred, patients should be maintained in care and every effort should be made to initiate therapy as soon as they are ready.

Treating Early HIV-1 Infection During Pregnancy
Because early HIV-1 infection, especially in the setting of high level viremia, is associated with a high risk of perinatal transmission, all HIV-1-infected pregnant women should start ART as soon as possible to prevent perinatal transmission of HIV-1.29

Treatment Regimen for Early HIV-1 Infection
Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one antiretroviral drug in up to 16% of patients.30,31 In one study, 21% of isolates from patients with acute HIV-1 infection demonstrated resistance to at least 1 drug.32 Therefore, before initiating ART in a person with early HIV-1 infection, genotypic antiretroviral (ARV) drug resistance testing should be performed to guide selection of an ARV regimen (AII). However, treatment initiation should not be delayed pending resistance testing results. Once results are available, the treatment regimen can be modified if warranted (AII).

As during chronic infection, the goal of therapy during early HIV-1 infection is to suppress plasma HIV-1 RNA to undetectable levels (AIII). ART should be initiated with one of the combination regimens recommended for patients with chronic infection (AIII) (see What to Start). 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 selection of the ARV regimen. If therapy is started before the results of drug resistance testing are available, a pharmacologically boosted protease inhibitor (PI)-based regimen should be used (darunavir/ritonavir [DRV/r] is recommended) because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon (AIII). For similar reasons, dolutegravir (DTG) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is a reasonable treatment option, although data regarding transmission of INSTI-resistant HIV and the efficacy of DTG plus TDF/FTC in patients with acute/early infection are limited (AIII). DTG/abacavir (ABC)/lamivudine (3TC) is not recommended for empiric treatment of acute infection unless the patient is known to be HLA-B*5701 negative, information that is seldom available when patients with acute infection present for care.

Given the increasing use of daily TDF/FTC for PrEP in HIV-negative individuals,33-35 early infection may be diagnosed in some patients taking TDF/FTC for PrEP. In this setting, resistance testing should be performed; however, as described above, use of a pharmacologically boosted PI (DRV/r) and TDF/FTC or DTG and TDF/FTC remain reasonable treatment options pending resistance testing results (see What to Start).

Patient Follow-Up
Testing for plasma HIV-1 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 (e.g., HIV-1 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-1 Infection

Once ART is initiated in patients with early HIV infection, therapy should be continued indefinitely as in guidelines for patients with chronic infection. Recent studies of early HIV-1 infection have shown some benefits of starting and then stopping treatment as a potential therapeutic strategy. However, a large randomized controlled trial of patients with chronic HIV-1 infection found that treatment interruption was harmful in terms of increased risk of AIDS and non-AIDS events, and that the strategy was associated with increased markers of inflammation, immune activation, and coagulation. For these reasons and the potential benefit of ART in reducing the risk of HIV-1 transmission, the Panel recommends indefinite continuation of ART in patients treated for early HIV-1 infection (AIII).

Table 11. Identifying, Diagnosing, and Managing Acute and Recent HIV-1 Infection

<table>
<thead>
<tr>
<th><strong>Suspicion of Acute HIV-1 Infection:</strong></th>
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</thead>
<tbody>
<tr>
<td>• Acute HIV-1 infection should be considered in individuals with signs or symptoms described below and recent (within 2 to 6 weeks) high risk of exposure to HIV-1.</td>
</tr>
<tr>
<td>• Signs, symptoms, or laboratory findings of acute HIV-1 infection 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.</td>
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<tr>
<td>• High-risk exposures include sexual contact with an HIV-1-infected person or a person at risk of HIV-1 infection, sharing of injection drug use paraphernalia, or any exposure in which an individual’s mucous membranes or breaks in the skin come in contact with bodily fluid potentially infected with HIV.</td>
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<tr>
<td>• <strong>Differential diagnosis:</strong> The differential diagnosis of patients presenting with HIV-1 infection may include 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.</td>
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**Evaluation/Diagnosis of Acute HIV-1 Infection:**

- Acute HIV-1 infection is defined as detectable HIV-1 RNA or p24 antigen (the antigen used in currently available HIV antigen/antibody [Ag/Ab] combination assays) in the setting of a negative or indeterminate HIV-1 antibody test result.
- A reactive HIV antibody test result or Ag/Ab combination test result must be followed by supplemental confirmatory testing.
- A negative or indeterminate HIV-1 antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV-1 infection is suspected requires plasma HIV-1 RNA testing to diagnose acute HIV-1 infection.
- A positive result on a quantitative or qualitative plasma HIV-1 RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV-1 infection is highly likely.

**ART After Diagnosis of Early HIV-1 Infection:**

- ART is recommended for all HIV-infected individuals (AI), and should be offered to all patients with early HIV-1 infection.
- All pregnant women with early HIV-1 infection should begin ART as soon as possible for their health and to prevent perinatal transmission of HIV-1.
- Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen (AII).
- If ART is initiated before drug resistance test results are available, a pharmacologically boosted PI-based regimen is recommended because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. DRV/r plus TDF/FTC is a recommended regimen in this setting (AII). For similar reasons, DTG plus TDF/FTC is a reasonable option although the data regarding transmission of INSTI-resistant HIV and the efficacy of this regimen in early HIV infection are limited (AIII).
- When results of drug resistance testing are available, the treatment regimen can be modified if warranted (AII). In patients without transmitted drug-resistant virus, ART should be initiated with one of the combination regimens that is recommended for patients with chronic HIV-1 infection (see What to Start (AII).
- Once initiated, the goal of ART should be sustained plasma virologic suppression; ART should be continued indefinitely (AIII).

In some settings, behaviors that increase the risk of HIV-1 infection may not be recognized or perceived as risky by the health care provider or the patient or both. Thus, even in the absence of reported high-risk behaviors, symptoms and signs consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV-1 infection.
References


