Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

Downloaded from https://aidsinfo.nih.gov/guidelines on 3/18/2018

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at https://aidsinfo.nih.gov/e-news.
Considerations for Antiretroviral Use in Special Patient Populations

Acute and Recent (Early\(^*\)) HIV Infection  (Last updated October 17, 2017; last reviewed October 17, 2017)

<table>
<thead>
<tr>
<th>Panel’s Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antiretroviral therapy (ART) is recommended for all individuals with HIV-1 infection (AI) including those with early(^*) HIV-1 infection.</td>
</tr>
<tr>
<td>• Once initiated, the goal of ART is to suppress plasma HIV-1 RNA to undetectable levels (AII). 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).</td>
</tr>
<tr>
<td>• Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen (AII).</td>
</tr>
<tr>
<td>• 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, a boosted darunavir (DRV) and emtricitabine (FTC) plus either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) are recommended regimens in this setting (AII). For similar reasons, dolutegravir (DTG) and FTC plus either TDF or TAF are also reasonable options, although data regarding transmission of integrase strand transfer inhibitor (INSTI)-resistant HIV and the efficacy of DTG regimens in early HIV infection is more limited (AIII).</td>
</tr>
<tr>
<td>• 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) (AIII).</td>
</tr>
<tr>
<td>• 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 or psychosocial factors.</td>
</tr>
</tbody>
</table>

**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

---

\(^*\) Early infection represents either acute or recent infection.

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

Although some patients with acute HIV-1 infection experience fever, lymphadenopathy, pharyngitis, skin rash, myalgia, arthralgia, and other symptoms,\(^1,6\) a recent prospective study shows that most patients have nonspecific and relatively mild signs and symptoms.\(^7\) Primary care clinicians may fail to recognize acute HIV-1 infection because its manifestations are often similar to those of many other viral infections, such as influenza and infectious mononucleosis. 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 for acute HIV-1 infection in patients who have a suggestive clinical syndrome—especially in those who report recent high-risk behavior (see Table 11).\(^8\) Patients may not always disclose high-risk behaviors or perceive that such behaviors put them at risk for HIV-1 acquisition. Thus, even in the absence of reported high-risk behaviors, practitioners should have a low threshold for considering a diagnosis of acute HIV-1 infection, especially in high prevalence (≥1%) areas. Current statistics on the HIV prevalence in different geographical areas in the United States can be found at these websites: AIDSVu (http://aidsvu.org/) and the Centers for Disease Control and Prevention (CDC)’s...
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. Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen (often referred to as “4th Generation” assays) are now approved by the Food and Drug Administration, and the most recent CDC 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; an undetectable 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. HIV-1 infection should be confirmed later 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 (but not always) 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 because repeated false-positive HIV-1 RNA tests are unlikely. 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. However, a number of studies suggest that individuals who are treated during early infection may experience potential immunologic and virologic benefits. In addition, because early HIV-1 infection is often associated with high viral loads and increased infectiousness, and ART use by individuals with HIV reduces transmission to uninfected sexual partners, treatment during early HIV-1 infection is expected to substantially reduce the risk of HIV-1 transmission.

The START and TEMPRANO trials evaluated timing of initiation of antiretroviral therapy (see Initiation of Antiretroviral Therapy). Although neither trial collected specific information on patients with early infection, the strength of the two studies’ overall results 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 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. Patients should also be reminded regularly of the importance of using condoms consistently and correctly during sex. The consistent use of condoms will reduce a patient’s risk of transmitting HIV infection and help them to avoid exposure to sexually transmitted infections.
**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 pregnant women with HIV-1 infection should start combination ART as soon as possible to prevent perinatal transmission of HIV-1.22

**Treatment Regimen for Early HIV-1 Infection**

Prior to the widespread use of integrase strand transfer inhibitors (INSTIs), data from the United States and Europe demonstrated that transmitted virus may be resistant to at least one antiretroviral drug in up to 16% of patients.23,24 In one study, 21% of isolates from patients with acute HIV-1 infection demonstrated resistance to at least one drug.25 Therefore, before initiating ART in a person with early HIV-1 infection, a specimen for genotypic antiretroviral (ARV) drug resistance testing should be obtained and the results of the test used to help guide selection of an ARV regimen (AII). However, treatment initiation itself should not be delayed pending resistance testing results. Once the resistance test results are available, the treatment regimen can be modified if warranted (AII).

As in 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. Since therapy for early HIV infection is often started before the results of drug resistance testing are available, a pharmacologically boosted protease inhibitor (PI)-based regimen may be an appropriate choice (e.g., boosted darunavir [DRV]) because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon (AIII). For similar reasons, dolutegravir (DTG) plus emtricitabine (FTC) and either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) are also reasonable treatment options, although data regarding transmission of INSTI-resistant HIV and the efficacy of DTG plus TDF/FTC in patients with acute/early infection are more 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 TDF/FTC as pre-exposure prophylaxis (PrEP) in HIV-negative individuals,26-28 early infection may be diagnosed in some patients while they are taking TDF/FTC for PrEP. In this setting, resistance testing should be performed; however, as described above, use of a pharmacologically boosted PI (e.g., boosted DRV) and FTC plus either TDF or TAF—or DTG and FTC plus either TDF or TAF—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 (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. 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,29 and that the strategy was associated with increased markers of inflammation, immune activation, and coagulation.30 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

### Suspicion of Acute HIV-1 Infection:
- 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.
- 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.
- High-risk exposures include sexual contact with a person who has HIV-1 infection 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.
- **Differential diagnosis:** The differential diagnosis of 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.

### 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, in which case, the diagnosis of HIV-1 infection should be later confirmed by subsequent documentation of HIV antibody seroconversion.

### Antiretroviral Therapy After Diagnosis of Early HIV-1 Infection:
- ART is recommended for all individuals with HIV (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 (AI).
- A blood sample for genotypic drug resistance testing should be obtained before initiation of ART to guide the selection of the regimen (AII), but the initiation of ART should be done as soon as possible, often prior to availability of resistance test results. If resistance is subsequently identified, treatment should be modified appropriately.
- If no resistance data are available, then a pharmacologically boosted PI-based regimen is recommended because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. **Boosted DRV (DRV/r or DRV/c) plus FTC and either TDF or TAF** is a recommended regimen in this setting (AIII). For similar reasons, DTG plus FTC and either TDF or TAF are reasonable options although the data regarding transmission of INSTI-resistant HIV and the efficacy of this regimen in early HIV infection are limited (AIII).
- In patients without transmitted drug-resistant virus, ART should be initiated with one of the combination regimens recommended for patients with chronic HIV-1 infection (see **What to Start**) (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.*

**Key to Acronyms:**
- ART = antiretroviral therapy; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate
References


