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

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Considerations for Antiretroviral Use in Special Patient Populations

Acute and Recent (Early) HIV Infection (Last updated October 25, 2018; last reviewed October 25, 2018)

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all individuals with HIV-1 infection **(AI)**, including those with early[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 cell 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. Either boosted darunavir (DRV) or dolutegravir (DTG) with emtricitabine (FTC) plus either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) are recommended regimens in this setting **(AIII)**. The rationales and precautions for these regimens are discussed below.
- A DRV-based regimen is a good option for people with early HIV-1 infection, because resistance to pharmacokinetically enhanced protease inhibitors (PIs) emerges slowly and clinically significant transmitted resistance to PIs is uncommon.
- A DTG-based regimen is also a reasonable option; however, data regarding transmission of integrase strand transfer inhibitor (INSTI)-resistant HIV and the efficacy of DTG regimens in early HIV infection are more limited **(AIII)**.
- Preliminary data from Botswana suggested that infants born to women who were receiving dolutegravir (DTG) at the time of conception have an increased risk of neural tube defects. Until more information are available, DTG **should not be prescribed** for individuals:
  - Who are pregnant and within 12 weeks post-conception;
  - Who are of childbearing potential, who are sexually active, and who are not using effective contraception; *or*
  - Who are contemplating pregnancy.
- 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)**.
- Patients starting ART should be willing and able to commit to life-long treatment and should understand the importance of adherence **(AIII)**. Patients may choose to postpone ART, and providers, on a case-by-case basis, may recommend that patients defer therapy because of clinical 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*

[a] Early infection represents either acute or recent infection.

Definitions: Acute HIV-1 infection, the phase of HIV-1 disease that occurs immediately after transmission, is typically characterized by an initial burst of viremia; although anti-HIV-1 antibodies are undetectable during this phase, HIV-1 RNA or p24 antigen are 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 12 provides practitioners with guidance to recognize, diagnose, and manage acute HIV-1 infection.

Diagnosing Acute HIV-1 Infection

Health care providers should consider a diagnosis of acute HIV-1 infection in patients who have a suggestive clinical syndrome—especially those who report recent high-risk behavior (see Table 12).[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 areas (areas where ≥1% of people have HIV infection). Current statistics on the prevalence of HIV in different geographical areas in the United States can be found at these websites: AIDSVu and the Centers for Disease Control and Prevention (CDC)'s AtlasPlus.

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.[8,9] Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen (often referred to as fourth-generation assays) are now approved by the Food and Drug Administration. The most recent CDC testing algorithm recommends these assays as the preferred assays to use for HIV screening, including in cases of 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.[10] 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.[10] 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).[5-7] 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.[6] The diagnosis of HIV-1 infection should be confirmed by subsequent documentation of HIV antibody seroconversion (see Table 12).

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 immunologic and virologic benefits.[11-19] In addition, because early HIV-1 infection is often associated with high viral loads and increased infectiousness,[20] and the use of antiretroviral therapy (ART) by individuals with HIV reduces the risk of transmission to sexual partners without HIV,[21] treatment during early HIV-1 infection is expected to substantially reduce the risk of HIV-1 transmission.

The START and TEMPRANO trials evaluated the timing of ART initiation (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 the 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 life-long ART. On a case-by-case basis, providers may recommend that patients defer therapy for clinical or

psychosocial reasons. If ART 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 or being re-infected and help them to avoid exposure to sexually transmitted infections (see the CDC's fact sheets on condom effectiveness).

Treating Early HIV-1 Infection During Pregnancy

All patients of childbearing potential who receive a diagnosis of early HIV-1 infection should have a pregnancy test. 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 Regimens 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 (ARV) 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 ARV drug resistance testing should be obtained and the results of the test should be 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 ART 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 ART will be initiated before the results of drug resistance testing are available, a pharmacologically boosted protease inhibitor (PI)-based regimen is an appropriate choice (e.g., boosted darunavir [DRV] plus either tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF] with emtricitabine [FTC]), because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon **(AIII)**.

Dolutegravir (DTG) plus TAF/FTC or TDF/FTC can also be used in certain patients **(AIII)**. Although data regarding the efficacy of a DTG-based regimen in persons with acute/early HIV infection are limited, there are several reasons why DTG is a good treatment option—transmission of DTG-resistant HIV is rare, and DTG's barrier to resistance exceeds that of raltegravir (RAL) and elvitegravir (EVG). On the basis of data from *in vitro* studies and clinical trials in ART-naive patients, it is anticipated that, like DTG, bictegravir (BIC) has a high barrier to resistance. However, clinical data and experience are relatively limited at this time.

Preliminary data from Botswana suggested that infants born to women who were receiving dolutegravir (DTG) at the time of conception have an increased risk of neural tube defects.[26,27] DTG is therefore **not recommended** for persons with acute/early HIV who are pregnant and within 12 weeks post-conception **(AII)**. DTG is also not recommended for individuals of childbearing potential who are sexually active and cannot use effective contraception or who are contemplating pregnancy **(AII)**. These patients should receive a boosted PI-based regimen. It is unknown whether this possible risk of neural tube defects is shared by other INSTIs (i.e., whether this is a class effect). BIC is structurally similar to DTG, and there are no safety data on the use of BIC around the time of conception. For individuals who are of childbearing potential and who are not pregnant, an approach similar to that outlined for DTG should be taken before considering BIC-containing ART.

Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Abacavir/lamivudine is not recommended as part of an 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. Therefore, TDF/FTC or TAF/FTC is generally recommended as a backbone in this setting.

Given the increasing use of TDF/FTC as pre-exposure prophylaxis (PrEP) in HIV-negative individuals,[28-30] early infection may be diagnosed in some patients while they are taking TDF/FTC for PrEP. In this setting, drug resistance testing should be performed; however, as described above, use of a boosted PI (e.g., boosted DRV) or DTG plus TDF/FTC or TAF/FTC remain reasonable treatment options pending resistance testing results, while keeping in mind the caveats discussed above concerning DTG use among patients who are pregnant or of childbearing potential (see also What to Start).

Patient Follow-Up

Testing for plasma HIV-1 RNA levels, CD4 T lymphocyte cell counts, and toxicity monitoring should be performed as described in Laboratory Testing for Initial Assessment and Monitoring (e.g., HIV-1 RNA should be assessed at initiation of ART, after 2 to 8 weeks, and 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, following the guidelines for patients with chronic infection. A large randomized controlled trial of patients with chronic HIV-1 infection found that treatment interruption was harmful, leading to increased risk of AIDS and non-AIDS events in these patients compared to those who continued ART,[31] and that this strategy was associated with increased markers of inflammation, immune activation, and coagulation.[32] For these reasons, and the potential benefit of ART in reducing the risk of HIV-1 transmission, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends indefinite continuation of ART in patients treated for early HIV-1 infection **(AIII)**.

Table 12. Identifying, Diagnosing, and Treating Acute and Recent HIV-1 Infection

Suspicion of Acute HIV-1 Infection:

- Health care providers should consider the possibility of acute HIV-1 infection in individuals with signs, symptoms, or the laboratory findings described below and recent (within 2 to 6 weeks) high risk of exposure to HIV-1.[a]
  - 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, and 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 that potentially carries HIV-1.
- **Differential Diagnosis:** The differential diagnosis of HIV-1 infection may include but is not limited to viral illnesses such as 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 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 this case, the diagnosis of HIV-1 infection should be later confirmed by subsequent documentation of HIV-1 antibody seroconversion.

Antiretroviral Therapy After Diagnosis of Early HIV-1 Infection:

- ART is recommended for all individuals with HIV-1 **(AI)** and should be offered to all patients with early HIV-1 infection.
- A pregnancy test should be performed for all individuals who receive a diagnosis of early HIV infection and who are of childbearing potential **(AIII)**.
- Pregnant patients with early HIV-1 infection should begin ART as soon as possible for their own 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 ART should be initiated 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)**.
- Preliminary data from Botswana suggested that infants born to women who were receiving DTG at the time of conception have an increased risk of neural tube defects. Until more information is available, DTG **should not be prescribed** for individuals:
  - Who are pregnant and within 12 weeks post-conception **(AII)**;
  - Who are of childbearing potential, who are sexually active, and who are not using effective contraception **(AII)**; *or*
  - Who are contemplating pregnancy **(AII)**.
- 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)**.
- Once initiated, the goal of ART should be sustained plasma virologic suppression, and ART should be continued indefinitely **(AIII)**.

[a] 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: Ag/Ab = antigen/antibody; ART = antiretroviral therapy; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EBV = Epstein-Barr virus; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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