Considerations for Antiretroviral Use in Special Patient Populations

Early (Acute and Recent) HIV Infection

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Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all people with HIV, including those with early[a] HIV infection (AI). ART should be initiated as soon as possible after HIV diagnosis (AII). • The goals of ART are to suppress plasma HIV RNA to undetectable levels (AI) and to prevent transmission of HIV (AI). Monitoring of plasma HIV RNA levels, CD4+ T lymphocyte counts, and antiretroviral (ARV) drug-related adverse effects should be done as recommended for people with chronic HIV infection (AII). • A blood sample for genotypic resistance testing should be sent to the laboratory before the initiation of ART (AIII). • ART can be initiated before drug-resistance test results are available. For those without a history of prior use of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP), one of the following ARV regimens is recommended (AIII): o Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC) o Dolutegravir (DTG) with (TAF or tenofovir disoproxil fumarate [TDF])[b] plus (FTC or lamivudine [3TC]) o Boosted darunavir (DRV) with (TAF or TDF)[b] plus (FTC or 3TC) • For those with a history of CAB-LA use as PrEP, genotype testing done before the start of ART should include screening for integrase strand transfer inhibitor (INSTI)-resistance mutations: o A regimen of boosted DRV with (TAF or TDF)[b] plus (FTC or 3TC) is recommended—pending the results of the genotype testing (AIII). o Use of empiric INSTI-containing regimen is not recommended unless genotype testing shows no evidence of INSTI resistance (AIII). This is because INSTI resistance may be present in those who become infected during and possibly after the use of CAB-LA as PrEP. • Pregnancy testing should be performed in persons of childbearing potential before initiation of ART (AIII). • When the results of drug-resistance tests are available, the treatment regimen can be modified if needed (AII). • Providers should inform individuals starting ART of the importance of adherence in achieving and maintaining viral suppression (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed non-randomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

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

[b] TAF and TDF are two forms of tenofovir that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

Introduction

Acute HIV infection occurs soon after transmission and is typically characterized by the lack of anti-HIV antibodies and the presence of viremia, which can be detected by HIV RNA test or p24 antigen test. Recent HIV infection is considered the phase of ≤6 months after infection, during which anti-HIV antibodies become detectable. Throughout this section, the term "early HIV infection" is used to refer to either acute or recent HIV infection. People with acute HIV infection may experience fever, lymphadenopathy, pharyngitis, skin rash, myalgia, arthralgia, and other symptoms; however, illness is generally nonspecific and can be relatively mild or the person can be asymptomatic.[1-6] Clinicians may fail to recognize acute HIV infection, because its manifestations are similar to those of many other viral infections, such as COVID-19, influenza, and infectious mononucleosis. Table 12 below provides clinicians with guidance to recognize, diagnose, and manage acute HIV infection.

Diagnosing Acute HIV Infection

Health care providers should consider a diagnosis of acute HIV infection in a person who has a suggestive clinical syndrome or in asymptomatic individuals who report recent high-risk behavior (see Table 12 below).[7] Individuals may not always disclose high-risk behaviors or perceive that such behaviors put them at risk for HIV acquisition. Thus, even in the absence of reported high-risk behaviors, health care providers should have a low threshold for considering a diagnosis of acute HIV infection. Health care visits to emergency departments provide an opportunity for health care providers to screen for acute or established HIV infection, as well as other sexually transmitted infections. Since 2019, the United States Preventive Services Task Force recommends routine screening for HIV infection in adolescents and adults aged 15 to 65 years (Grade A recommendation). Testing of remnant blood specimens from an emergency department identified acute HIV infection in approximately 5 of 499 (1%) patients presenting with flu-like symptoms.[8] Acute HIV infection also was diagnosed in 7 of 563 (1.2%) patients presenting for evaluation of possible mononucleosis with negative heterophile antibody tests.[9] A study of HIV screening in nine emergency departments in six U.S. cities found that a new HIV diagnosis was made in 0.4% of 214,524 adolescents and adults, of whom 14.5% had acute HIV infection.[10] Current statistics on the prevalence of HIV in geographical areas in the United States can be found on the following websites: AIDSVu and the Centers for Disease Control and Prevention (CDC)'s AtlasPlus.

Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV p24 antigen (Ag/Ab assays) are part of the recommended initial laboratory HIV testing algorithm,[11] primarily due to their enhanced ability to detect acute HIV infection. Specimens that are reactive on an initial 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 result should be tested for quantitative or qualitative HIV RNA; an undetectable HIV RNA test result indicates that the original Ag/Ab test result was a false positive. Detection of HIV RNA in this setting indicates that acute HIV infection is highly likely.[11] Patients presenting to care during the earliest days following HIV infection may have yet to develop a positive p24 Ag response, which typically occurs with viral load levels of >20,000 to 30,000 copies/mL. In clinical settings with a high probability of infection, quantitative or qualitative HIV RNA testing should be considered even if the HIV Ag/Ab test result is negative. HIV infection should be confirmed by repeat quantitative HIV RNA testing or subsequent testing to document HIV antibody seroconversion. People receiving antiretroviral therapy (ART) during acute or very early HIV infection may demonstrate weaker reactivity to screening antibody assays or incomplete HIV antibody evolution; may remain non-

reactive to confirmatory antibody assays; and in the setting of sustained virologic suppression, may have complete or partial seroreversion.[12-16]

Providers should be aware that even a low-positive quantitative HIV RNA level (e.g., <200 copies/mL but detectable) in the setting of a negative or indeterminate antibody test result is consistent with acute HIV infection. When a low-positive quantitative HIV RNA test result is present at this level, the HIV RNA test should be repeated on a new blood specimen to confirm the diagnosis. Repeated false-positive HIV RNA test results are unlikely.[2] HIV RNA levels in acute infection are generally very high (e.g., >100,000 copies/mL)[1,2,4]; however, levels may be <200 copies/mL in the earliest weeks following infection as viral load continues to rise. In rare cases, however, it also may represent a false-positive result. The previously proposed threshold of <3,000 copies/mL is based on historical data, which used laboratory methods that are now considered obsolete.[17] Improvements in plasma viral load methodology suggest that any positive result on a quantitative plasma HIV RNA test in the setting of a negative or indeterminate antibody test result may be consistent with acute HIV infection. Some health care facilities may still be using HIV testing algorithms that test only for anti-HIV antibodies. In such settings, when acute HIV infection is suspected in a patient with a negative or indeterminate HIV antibody test result, a quantitative or qualitative HIV RNA test should be performed. A negative or indeterminate HIV antibody test result and a positive HIV RNA test result (>200 copies/mL)[18] indicate that acute HIV infection is highly likely.

Diagnosing Acute HIV Infection in People Taking Pre-Exposure Prophylaxis

Three antiretroviral (ARV) options, oral emtricitabine (FTC) with either tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), and intramuscular long-acting cabotegravir (CAB-LA) are now available for HIV pre-exposure prophylaxis (PrEP). People who acquire HIV while taking PrEP may sometimes have ambiguous HIV test results. A positive HIV Ag/Ab test result or a positive HIV RNA test result in the setting of a negative HIV antibody test result should prompt immediate confirmation of HIV diagnosis. It is important to collect a new blood specimen to verify the HIV diagnosis before initiating ART. Important considerations include the following:

- In people with HIV RNA level ≥200 copies/mL who are taking PrEP, immediate initiation of an effective HIV treatment regimen[19,20] is recommended while awaiting confirmation of HIV diagnosis **(AIII).**
- In people taking PrEP who have a negative HIV antibody test result and a very low-positive quantitative HIV RNA test result (<200 copies/mL), a confirmatory HIV antibody test and repeat quantitative plasma HIV RNA test should be performed, and results should be available before initiating ART.
- In rare cases, particularly when PrEP is transitioned to an ARV regimen and HIV RNA and antibody diagnostic testing are inconclusive, HIV DNA testing may be of value.[21] Options for confirming HIV infection and managing such cases is an area of evolving science recently summarized by the CDC.[21] Clinicians seeking urgent advice can contact the Clinical Consultation Center's PrEP Service at 1-855-HIV-PREP.

Acute HIV Infection in People Taking Long-Acting Cabotegravir for Pre-Exposure Prophylaxis

In the HPTN 083 trial, a pivotal trial of CAB-LA versus TDF/FTC for HIV PrEP, with more than 2,000 participants enrolled into each arm, 25 incident cases of HIV were identified in the CAB-LA arm.[22,23] Selection of a potent ARV regimen in persons who develop acute HIV infection while taking CAB-LA for PrEP should consider that injectable CAB may remain detectable after treatment discontinuation, for up to 3 years in men and 4 years in women.[24] This long pharmacokinetic tail may contribute to the selection of drug-resistant variants in the setting of incident infection. When diagnosing acute HIV infection in people taking CAB-LA or in people with a history of prior CAB-LA PrEP use, treatment with a non-integrase strand transfer inhibitor (INSTI)-based regimen (see Antiretroviral Regimens for Early HIV Infection below) is recommended **(AIII)** while awaiting confirmation of HIV drug resistance-test results.

Treating Early HIV Infection

The goals of ART during early HIV infection are to suppress plasma HIV RNA to undetectable levels **(AI),** to prevent the transmission of HIV **(AI),** and to preserve immune function **(AIII).**[25-27] Importantly, as with chronic HIV infection, an individual's barriers to ART adherence and appointments should be assessed at the time of ART initiation (see Adherence to the Continuum of Care). ART should be initiated as soon as possible after a positive qualitative or quantitative HIV RNA test result. Same-day or rapid ART initiation in people with acute HIV has been shown to be safe, acceptable, and effective.[28] It is important to collect a new blood specimen for a confirmatory HIV antibody test and quantitative plasma HIV RNA test to verify the HIV diagnosis. Given the sensitivity of current HIV RNA assays,[29] a positive result by quantitative or qualitative plasma HIV RNA testing in the setting of a negative or indeterminate antibody test result indicates that acute HIV infection is highly likely. HIV treatment does not need to be delayed while awaiting confirmation of HIV diagnosis. Some individuals may not accept their diagnosis or may decline ART initially for other reasons. Individuals who do not begin ART immediately should be maintained in care, and every effort should be made to initiate therapy as soon as they are ready.

Clinical trial data indicate that individuals who are treated during early HIV infection may experience immunologic and virologic benefits.[30-42] In addition, early HIV infection is considered a period of high infectivity,[43] and early ART has been shown to substantially reduce the risk of HIV transmission.[44-47]

Drug-Resistance Testing in the Setting of Early HIV Infection

Prior to the widespread use of INSTIs, data from the United States and Europe demonstrated transmitted virus that were resistant to at least one ARV drug in up to 16% of people with HIV.[48,49] In one study, 21% of isolates from persons with acute HIV infection demonstrated resistance to at least one ARV drug, most commonly non-nucleoside reverse transcriptase inhibitors (NNRTIs).[50-52] Therefore, before initiating ART in a person with early HIV infection or low qualitative or quantitative plasma HIV RNA test result (<200 copies/mL), a blood specimen should be sent for drug-resistance testing, although treatment should not be delayed pending resistance-test results. The test results should be used to modify the ARV regimen if necessary **(AII).** The Panel on Antiretroviral Guidelines for Adults and Adolescents does not currently recommend routine genotype testing for INSTI resistance in treatment-naive persons given the low rate of transmitted INSTI resistance and the high barrier to resistance of dolutegravir (DTG) and bictegravir (BIC), unless

transmitted INSTI resistance is a concern **(AIII).** However, the rate of transmitted INSTI resistance has increased (from 0.8% to 1.1%, $P = 0.04$) with the increasing use of INSTIs, indicating a need for ongoing population monitoring.[53,54] Genotype testing for INSTI resistance should be performed for those who become infected during or after the use of CAB-LA as PrEP **(AIII).**[24]

Considerations for Preventing HIV Transmission During Early HIV Infection

People with early HIV infection have a higher likelihood of sexual transmission of HIV to others. Prompt initiation of ART and sustained viral suppression to <200 copies/mL can prevent transmission of HIV to sexual partners. Individuals starting ART should use another form of prevention (e.g., condoms, PrEP for partners who are HIV negative, sexual abstinence) for at least the first 6 months of treatment and until they have a documented viral load of <200 copies/mL **(AII).** Many experts would recommend confirming sustained viral suppression before assuming no risk of sexual transmission of HIV **(AIII)** (see Antiretroviral Therapy to Prevent Sexual Transmission of HIV).

Antiretroviral Regimens for Early HIV Infection

ART should be initiated with one of the combination regimens recommended for people with chronic HIV infection **(AIII)** (see What to Start). Providers should inform individuals starting ART of the importance of adherence in achieving and maintaining viral suppression **(AII).** If available, the results of ARV drug-resistance testing or the resistance pattern of the source person's virus should be used to guide selection of the regimen. All persons of childbearing potential should have a pregnancy test before initiating ART **(AIII).**

If ART is to be initiated before the results of drug-resistance tests are available, one of the following regimens is an appropriate option for individuals who have not received CAB-LA prior to diagnosis of acute HIV **(AIII):**

- DTG with (TDF or TAF plus lamivudine [3TC] or FTC)
- BIC/TAF/FTC
- Boosted darunavir (DRV) with (FTC or 3TC) plus (TAF or TDF)

DTG, BIC, and boosted DRV are all good treatment options, because transmitted resistance to each of these agents is rare, and they all have a high barrier to resistance.

For individuals with acute HIV who become infected during and after the use of CAB-LA as PrEP, use of an INSTI-based regimen **is not recommended (AIII).** The recommended regimen, at least until resistance testing confirms the absence of INSTI-resistance mutations, is a boosted DRV with (FTC or 3TC) plus (TAF or TDF) **(AIII).**

Preliminary data from a birth outcomes surveillance study in Botswana suggested an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception.[55] Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[56] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should perform a pregnancy test. Clinicians should discuss the risks

and benefits of using DTG with persons of childbearing potential to allow them to make an informed decision.

A pharmacologically boosted protease inhibitor (PI)-based regimen (e.g., boosted DRV) is also an option because resistance to PIs emerges slowly, and clinically significant transmitted resistance to PIs is uncommon. Abacavir/3TC **is not recommended** for treatment of acute HIV infection, unless the patient is known to be HLA-B*5701 negative—information that is seldom available when individuals with acute infection are diagnosed. Therefore, TDF/FTC or TAF/FTC is generally recommended in this setting. Baseline laboratory testing recommended for individuals with chronic HIV infection should be performed (see Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy). Individuals with hepatitis B virus/HIV coinfection should receive TDF/FTC or TAF/FTC as part of their ARV regimen.

Given the increasing use of TDF/FTC as PrEP,[57-59] early HIV infection may be diagnosed in some persons while they are taking TDF/FTC. In this setting, drug-resistance test results are particularly important; however, the regimens listed above remain as reasonable treatment options pending drug-resistance test results.

Because the rate of transmitted drug resistance for NNRTIs is relatively high, agents in this drug class **are not recommended** as a component in the regimen of people initiating ART before the results of drug-resistance tests are available.

Treatment Regimens for Early HIV Infection During Pregnancy

All persons of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test **(AIII).** Because early HIV infection, especially in the setting of high-level viremia, is associated with a high risk of perinatal transmission, all pregnant people with HIV should start combination ART as soon as possible to prevent perinatal transmission. Clinicians should refer to the Perinatal Guidelines for information on the safety and efficacy of ARV use in pregnancy.

Follow-Up After Antiretroviral Therapy Initiation

After ART initiation, monitoring of plasma HIV RNA levels, CD4+ T lymphocyte counts, and adverse effects should be performed as described in Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy (i.e., HIV RNA testing 2–8 weeks after ART initiation, then every 4–8 weeks until viral suppression and, thereafter, every 3–4 months) **(AII).**

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

Suspicion of Acute HIV Infection

- Health care providers should consider the possibility of acute HIV infection in individuals with the signs, symptoms, or laboratory findings described below and in asymptomatic individuals with a possible recent (within 2–6 weeks) exposure to HIV.[a]
  - Signs, symptoms, or laboratory findings of acute HIV infection may include, but are not limited to, one or more of the following: fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, diarrhea, pharyngitis, oral ulcers, leucopenia, thrombocytopenia, and transaminase elevation.
  - High-risk exposures include sexual contact with a person who has HIV or a person at risk of HIV infection; sharing needles and syringes to inject drugs, as well as equipment used to prepare drugs for injection; or any exposure in which an individual's mucous membranes or any breaks in the skin come in contact with bodily fluid that potentially carries HIV.

Differential Diagnosis

- The differential diagnosis of acute HIV infection may include, but is not limited to, viral illnesses, such as COVID-19, EBV and non-EBV (e.g., CMV) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis. Diagnosis of any STI should prompt HIV testing and consideration of acute HIV infection.

Testing to Diagnose/Confirm Acute HIV Infection

- Acute HIV infection is defined as detectable HIV RNA or p24 antigen (the specific antigen used in currently available HIV-1/2 Ag/Ab combination assays) in the setting of a negative or indeterminate HIV 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 antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV infection is suspected requires plasma HIV RNA testing to diagnose acute HIV infection.
- A positive result on a quantitative or qualitative plasma HIV RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV infection is highly likely. In this case, the diagnosis of HIV infection should be confirmed by subsequent documentation of HIV antibody seroconversion.
- A positive HIV Ag/Ab test result or a positive HIV RNA test result in the setting of a negative HIV antibody test result in a person taking PrEP should prompt immediate confirmation of HIV diagnosis. It is important to collect a new blood specimen to verify the HIV diagnosis before initiating HIV treatment.

ART After Diagnosis of Early HIV Infection

- ART is recommended for all people with HIV, including those with early HIV infection (AI). ART should be initiated as soon as possible after HIV diagnosis (AII).
- Once initiated, the goals of ART are to achieve sustained plasma virologic suppression and to prevent HIV transmission (AII).
- All persons of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test (AIII).
- Pregnant people with early HIV infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV (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 before resistance-test results are available. If resistance is subsequently identified, treatment should be modified as needed.

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

- ART can be initiated before the results of drug-resistance testing are known. For individuals who do not have a history of prior use of CAB-LA as PrEP, one of the following ARV regimens is recommended (AIII):
  - DTG with (TAF or TDF)[b] plus (FTC or 3TC)
  - BIC/TAF/FTC
  - Boosted DRV with (TAF or TDF)[b] plus (FTC or 3TC)
- For individuals with a history of prior use of CAB-LA as PrEP, genotypic resistance testing done before the start of ART should include screening for INSTI-resistance mutations. Recommended regimens include the following:
  - Boosted DRV with (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype (AIII). Empiric INSTI-containing regimens are not recommended (AIII), because INSTI resistance may be present in those who become infected during the use of CAB-LA and possibly up to 4 years after.
- Pregnancy testing should be performed in persons of childbearing potential before initiation of ART (AIII).
- Preliminary data from a birth outcomes surveillance study in Botswana suggested an increased risk of NTDs (0.9%) in infants born to women who were receiving DTG at the time of conception.[56] Updated data from the same study showed that the prevalence of NTDs in infants born to women on DTG at the time of conception is not significantly different from those on non-DTG regimens at the time of conception.[56] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should discuss the risks and benefits of using DTG to allow them to make an informed decision.

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

[b] TAF and TDF are two forms of tenofovir that are approved in the United States. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

Key: 3TC = lamivudine; Ag/Ab = antigen/antibody; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CAB-LA = cabotegravir long-acting; CMV = cytomegalovirus; DRV = darunavir; DTG = dolutegravir; EBV = Epstein-Barr virus; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; PrEP = pre-exposure prophylaxis; STI = sexually transmitted infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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