Introduction

Acute HIV infection is the phase of HIV disease that occurs immediately after transmission, which is typically characterized by viremia as detected by the presence of HIV RNA or p24 antigen. Anti-HIV antibodies are not yet detectable early during this phase of HIV infection. Recent HIV infection is generally considered the phase of HIV disease ≤6 months after infection, during which anti-HIV antibodies develop and become detectable. Throughout this section, the term “early HIV infection” is used to refer to either acute or recent HIV infection. Persons 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. Clinicians may fail to recognize acute HIV infection because its manifestations are often similar to those of many other viral infections, such as influenza and infectious mononucleosis. Table 12 provides practitioners 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—especially those who report recent high-risk behavior (see Table 12). 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, practitioners should have a low threshold for considering a diagnosis of acute HIV infection, especially in high-prevalence areas (areas where ≥1% of people have HIV infection). Health care encounters in an emergency department create an opportunity to screen for acute or established HIV infection, as well as other sexually transmitted infections. Testing of remnant blood specimens from emergency departments identified acute HIV in approximately 1% of patients presenting with flu-like symptoms and in 1% presenting for evaluation of possible mononucleosis with negative heterophile antibody tests. A retrospective analysis of nine emergency departments in six U.S. cities using a laboratory-based, fourth generation antigen-antibody screening algorithm found that a new HIV diagnosis was made in 0.4% of 214,524 adolescents and adults screened. Among those with newly diagnosed HIV, 14.5% had acute HIV infection. Current statistics on the prevalence of HIV in 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 infection is usually defined as detectable HIV RNA or p24 antigen in serum or plasma in the setting of a negative or indeterminate HIV antibody test result. Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV p24 antigen (Ag/Ab assay) are now the preferred initial HIV screening test, primarily due to their enhanced ability to detect acute HIV infection. The recommended laboratory testing algorithm is initiated using an HIV-1/2 Ag/Ab assay for HIV screening. 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 results 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. HIV infection should be confirmed by repeat quantitative HIV RNA test or subsequent testing to document HIV antibody seroconversion.

Persons receiving antiretroviral therapy (ART) during acute or very early HIV infection may demonstrate weaker reactivity to screening antibody assays or incomplete HIV antibody evolution; remain non-reactive to confirmatory antibody assays; and in the setting of sustained virologic suppression, may have complete or partial seroreversion. Persons who acquire HIV while taking PrEP may sometimes also have ambiguous HIV test results. Options for confirming HIV infection and managing such cases is an area of evolving science recently summarized by CDC. Clinicians seeking urgent advice can contact the Clinical Consultation Center’s PrEP Service at 1-855-HIV-PREP.

Some health care facilities may still be using HIV testing algorithms that only recommend testing 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 indicate that acute HIV infection is highly likely. Providers should be aware that a low-positive quantitative HIV RNA level (e.g., <10,000 copies/mL) may represent a false-positive result, because HIV 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 RNA test result is obtained, the HIV RNA test should be repeated using a different specimen from the same patient, because repeated false-positive HIV RNA tests are unlikely. The diagnosis of HIV infection should be confirmed by subsequent documentation of HIV antibody seroconversion.

**Treating Early HIV Infection**

As in chronic HIV infection, the goal of ART during early HIV infection is to suppress plasma HIV RNA to undetectable levels (AI) and to prevent the transmission of HIV (AI). Importantly, as with chronic infection, persons with early HIV infection must be willing and able to commit to life-long ART. Individuals who do not begin ART immediately should be maintained in care and every effort made to initiate therapy as soon as they are ready.
Clinical trial data regarding the treatment of early HIV infection are limited. However, a number of studies suggest that individuals who are treated during early infection may experience immunologic and virologic benefits. In addition, early HIV infection is often associated with high viral loads and increased infectiousness, and the use of ART at this stage of infection to achieve and maintain a viral load <200 copies/mL is expected to substantially reduce the risk of HIV transmission.

The START and TEMPRANO trials evaluated the timing of ART initiation (see Initiation of Antiretroviral Therapy). Although neither trial collected specific information on participants with early infection, the strength of the overall results from both studies and the evidence from the other studies described above strongly suggest that, whenever possible, persons with HIV should begin ART upon diagnosis of early infection.

Drug Resistance Testing in the Setting of Early HIV 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 persons with HIV. In one study, 21% of isolates from persons with acute HIV infection demonstrated resistance to at least one ARV drug, with transmitted resistance consistently most common to non-nucleoside reverse transcriptase inhibitors (NNRTIs). Therefore, before initiating ART in a person with early HIV infection, a specimen should be sent for drug resistance testing, though 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 high barrier to resistance of dolutegravir (DTG) and bictegravir (BIC), unless transmitted INSTI resistance is a concern (AIII). However, with the increasing use of INSTIs in recent years, the rate of transmitted INSTI resistance has increased (from 0.8% to 1.1%, \( P = 0.04 \)), indicating a need for ongoing population monitoring.

Considerations for Preventing HIV Transmission During Early HIV Infection

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

Treatment Regimens for Early HIV Infection

ART should be initiated with one of the combination regimens recommended for persons with chronic HIV infection (AIII) (see What to Start). Providers should inform individuals starting ART of the importance of adherence to achieve and maintain 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 child-bearing potential should have a pregnancy test before initiating ART (AIII).

If ART is to be initiated before the results of drug resistance and HLA-B*5701 testing are available, one of the following regimens are appropriate options (AIII):

- DTG with (emtricitabine [FTC] or lamivudine [3TC]) plus (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF])
- BIC/TAF/FTC
• Boosted darunavir (DRV) with (FTC or 3TC) plus (TAF or TDF)

DTG is a good treatment option because transmission of DTG-resistant HIV is rare, and DTG has a higher barrier to resistance than raltegravir and elvitegravir. Based on data from in vitro studies and clinical trials in ART-naive participants, it is anticipated that BIC, like DTG, also has a high barrier to resistance. However, clinical data and experience defining the BIC barrier to resistance are relatively limited at this time.

Preliminary data from Botswana suggested that there is an increased risk of neural tube defects (NTDs) (0.9%) in infants born to women who were receiving DTG at the time of conception. Follow-up data, however, showed that the prevalence of NTDs in association with DTG exposure at conception is lower (0.3%), but still slightly higher than with non-DTG containing ARV regimens (0.1%). Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when in choosing an ART regimen.

A pharmacologically boosted protease inhibitor (PI)-based regimen (e.g., boosted DRV) is also an option, as resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. Abacavir/3TC is not recommended as part of an empiric 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 present for care. Therefore, TDF/FTC or TAF/FTC is generally recommended as a backbone 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 HBV/HIV coinfection should remain on TDF/FTC or TAF/FTC as part of their ART regimen.

Given the increasing use of TDF/FTC as pre-exposure prophylaxis (PrEP) in individuals who are HIV negative, early infection may be diagnosed in some persons while they are taking TDF/FTC for PrEP. In this setting, drug resistance results are particularly important; however, the regimens listed above remain as reasonable treatment options pending resistance testing results.

### Treatment Regimens for Early HIV Infection During Pregnancy

All individuals 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 individuals 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 ART Initiation

After ART initiation, testing for plasma HIV RNA levels and CD4 T lymphocyte cell counts, and toxicity monitoring should be performed as described in Laboratory Testing for Initial Assessment and Monitoring of Patients with HIV Receiving Antiretroviral Therapy (e.g., HIV RNA testing 2 to 8 weeks after ART initiation, then every 4 to 8 weeks until viral suppression, and thereafter, every 3 to 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 recent (within 2 to 6 weeks) high risk of 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, 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 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 or early 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 later confirmed by subsequent documentation of HIV antibody seroconversion.

ART After Diagnosis of Early HIV Infection:

- ART is recommended for all individuals with HIV, including those with earlya 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 individuals of childbearing potential who receive a diagnosis of early HIV infection should have a pregnancy test (AIII).
- Pregnant individuals with early HIV infection should begin ART as soon as possible for their own health and to prevent perinatal transmission of HIV (A).
- 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.
- ART can be initiated before the results of drug resistance testing are known. In this setting, one of the following ART 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)
- Pregnancy testing should be performed in individuals of childbearing potential before initiation of ART (AIII).
- Preliminary data from Botswana suggested that there is an increased risk of NTDs (0.9%) in infants born to women who were receiving DTG at the time of conception.a Follow-up data, however, showed that the prevalence of NTDs in association with DTG exposure at conception is lower (0.3%), but still slightly higher than with non-DTG containing ARV regimens (0.1%).46,47 Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review Table 6b for information to consider when choosing an ART regimen.

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


