Background and Definitions

Background

Following acquisition of HIV, more than 50% of individuals will develop a transient, symptomatic illness, with nonspecific features, that often goes undiagnosed.\[1, 2, 3\] This illness, also known as acute retroviral syndrome, is frequently mistaken for an alternate viral infection, such as mononucleosis or influenza. Early antiretroviral therapy arrests the explosive burst of viremia associated with acute infection and thus may improve long-term health outcomes for individuals with acute HIV and also decrease the likelihood of viral transmission.\[2\] Most individuals in the acute phase of HIV infection have high risk of transmitting HIV to others with condomless sex, primarily because of very high HIV RNA levels and lack of awareness of their HIV status.\[4, 5, 6\]. Thus, accurate and timely detection of primary HIV infection is important— for the future health of the individual who has acquired HIV and for reducing HIV transmission risk. The following will review the manifestations and diagnosis of acute retroviral syndrome, as well as explore considerations for treatment in such instances.

Definitions

- **Acute HIV**: Defined as the phase of HIV disease that occurs immediately after HIV acquisition and is characterized by detectable HIV RNA or HIV p24 antigen in the absence of anti-HIV antibodies (Figure 1).\[2\] The term acute HIV was previously used interchangeably with the term primary HIV, but acute HIV is now the preferred term.
- **Acute Retroviral Syndrome**: An acute symptomatic illness that develops in many individuals during the acute HIV infection phase.\[7, 8\]
- **Early HIV Infection**: Refers to the initial 6-month time period following HIV acquisition; this term encompasses three phases—the time from infection until acute HIV, acute HIV infection, and recent HIV infection (Figure 2).\[9\]
- **Eclipse Phase**: The short interval following HIV acquisition in which no diagnostic test is capable of detecting HIV.\[10, 11\] This interval is typically 10 to 12 days in duration and the HIV RNA is the first test to detect HIV (Figure 3).
- **Fiebig Stages of Early HIV Infection**: The classification system used to describe various stages of early HIV infection and based on the timing and results of diagnostic tests (Figure 4).\[10\]
- **Founder Virus**: The initial virus (or small cluster of viruses) that succeeds in catalyzing HIV mucosal infection (Figure 5).\[12\]
- **Seroconversion Window Period**: The seroconversion window period specifically refers to the interval between HIV acquisition and the first detection of anti-HIV antibodies (Figure 6).\[11\]. The duration of the window period depends on the sensitivity of the antibody assay used, with IgM/IgG-
sensitive HIV antibody tests detecting HIV sooner than IgG-sensitive HIV antibody tests.

- **Set point:** The relatively stable HIV RNA level reached about 1 to 2 months after the peak HIV RNA levels associated with acute HIV infection. Without antiretroviral therapy, the HIV RNA levels tend to chronically remain near the set point established early in HIV infection (Figure 7).[13,14]
Immunopathogenesis

Initial Infection

The immunopathogenesis of acute HIV infection is best understood with regard to transmission via the genital mucosa.[1, 15] Studies of intravaginal inoculation of simian immunodeficiency virus (SIV) in rhesus monkeys helped generate a model for early events of human sexual transmission of HIV (Figure 8).[1, 2, 15, 16] In the proposed model, HIV first infects Langerhans cells (tissue dendritic cells located just below the mucosa).[17] On the surface of the Langerhans cell, HIV initially binds to the CD4 molecule, followed by binding to the CCR5 cellular coreceptor; the Langerhans cells express CCR5 coreceptors, but usually not CXCR4 coreceptors. Most often, the transmitted HIV is macrophage-tropic HIV (also known as R5 HIV), which preferentially binds to the CCR5 coreceptor. The infected dendritic cells can migrate to lymph nodes, where they interact with and potentially fuse with CD4 cells, causing spread of HIV to deeper tissues.[16]

Within a few days of inoculation, HIV is present within gut-associated lymphoid tissue and other tissues of the lymphoreticular system, causing irreversible depletion of helper T cells and establishment of viral latency (integration into the genome of resting T cells).[2, 18, 19] Although HIV generally exists as a quasispecies or a mixture of mutant strains, usually only one strain (or a small number of strains) successfully establishes initial infection; the infecting strain is known as the founder virus.[12, 20] Data indicate that selection bias leads to transmission of virus species with greater relative fitness.[21] Investigators have shown that humans typically develop HIV viremia within 11 days of initial transmission.[10, 22]

Initial Immune Response

The uncontrolled initial burst of viremia in the acute phase typically causes very high plasma HIV RNA levels, often greater than 100,000 copies/mL, and is associated with a surge of inflammatory cytokines.[2] Although antibody responses against HIV are generated, the initial neutralizing antibodies have weak neutralizing activity against primary HIV isolates and thus probably contribute very little to the initial control of HIV.[23] The initial burst of viremia is followed by a decrease in HIV RNA levels, predominantly as a result of a potent CD8 cytotoxic lymphocyte response targeted against HIV.[23, 24] The HIV RNA levels reach a steady state, or so called "set point", within 3 months after infection and, if untreated, remain at a similar level for years thereafter; the set point in men is typically higher than in women.[25, 26, 27] In addition, higher set points are usually associated with more rapid progression of HIV disease, if untreated.

Early Immune Response as Predictor of Disease Progression

Investigators have shown that individuals have qualitatively different immune responses to primary HIV infection.[28] Several research groups have shown that persons with strong initial CD8 T cell (cytotoxic T-lymphocyte) responses have lower HIV RNA levels after 6 to 12 months, and subsequently experience a slower progression of their HIV disease (Figure 9).[14, 28, 29] More recently, the importance of the epitope-specific type of CD8 T cell response in controlling HIV has been elucidated.[30] In most persons newly infected with HIV, higher initial HIV RNA levels predict an accelerated course of HIV disease progression,[31] but this correlation is not universal.[28, 32] Similarly, several reports have suggested that development of clinically apparent acute retroviral syndrome portends a faster progression to AIDS.[33] One study found that among 218 African women with HIV-1, a greater set point viral load or greater severity of acute HIV illness predicted faster progression to death (with each additional symptom of acute HIV contributing to a higher mortality).[34]
Clinical Manifestations

Acute Retroviral Syndrome

The transient surge of viremia and associated drop in CD4 cell count that accompany primary HIV infection cause most of the manifestations of acute disease. Acute retroviral syndrome ranges from an asymptomatic infection, to a mild nonspecific viral illness resembling mononucleosis, to a severe illness that requires hospitalization.[7,8] The signs and symptoms are nonspecific, protean, and self-limited. Therefore, a high index of suspicion and inquiry of risk factors are generally necessary to identify primary infection.[35] Symptoms of primary HIV typically begin within 28 days of infection, with the most common manifestations consisting of fever, fatigue, myalgia, skin rash, headache, pharyngitis, and cervical adenopathy (Table 1).[1,7,36,37,38] The skin rash is typically morbilliform or maculopapular and most often involves the trunk (Figure 10). Less commonly, neurological complications may occur, such as aseptic meningitis, facial palsy, or Guillain-Barré syndrome.[39] Rarely, acute infection causes such a substantial drop in CD4 T-cell count that patients may initially present with oral candidiasis or even major AIDS-defining opportunistic infections.

Duration of Symptoms

In a study of 46 individuals with primary infection in which 89% developed a symptomatic illness, the median duration of symptoms was 14 days.[8] The duration of symptoms can range from days to weeks and the severity and duration of symptoms may correlate with disease progression.[1,36]

Differential Diagnosis

A high index of suspicion is necessary to correctly identify nonspecific symptoms as acute HIV and differentiate it from other common illnesses with similar symptoms. For example, acute Epstein-Barr virus (EBV) infection (mononucleosis), secondary syphilis, acute cytomegalovirus (CMV), acute toxoplasmosis, acute hepatitis B, streptococcal pharyngitis, influenza, and enterovirus infection can all present with symptoms comparable to those seen in patients with acute HIV. Routine laboratory studies taken from persons acutely infected with HIV may show leukopenia, thrombocytopenia, and increases in hepatic aminotransferase levels, all of which are also nonspecific and can be seen with a number of other illnesses and infections.
Laboratory Diagnosis

Individuals who present with symptomatic acute HIV infection typically have a very high HIV RNA level and a negative HIV antibody test; most will also have a positive p24 antigen test.[3] The laboratory diagnosis of acute HIV requires a negative HIV antibody assay plus either a positive HIV RNA or a positive p24 antigen test.[9] Since the vast majority of new HIV infections in the United States are HIV-1 infections, the following discussion will focus on the diagnosis of acute HIV-1 infection.

HIV-1 RNA Tests

Approximately 10 days after initial HIV-1 acquisition, plasma HIV-1 RNA levels become detectable.[10] At around day 10, the HIV-1 RNA levels begin to rapidly ramp up, reaching very high levels in the subsequent 1-2 weeks and typically peaking above 200,000 copies/mL.[10] Currently, the APTIMA HIV-1 Qualitative Assay is the only nucleic acid test (NAT) approved by United States Food and Drug Administration (U.S. FDA) for the diagnosis of HIV-1, including acute HIV-1 infection; this test provides a qualitative detection of HIV-1 RNA, but no quantitative value.[40] The APTIMA HIV-1 Qualitative Assay can detect all major HIV-1 groups and subtypes, and has a manufacturer reported detection rate of 98.5% for 30 copies/mL, 82.6% for 10 copies/mL, and 42.5% for 3 copies/mL.[41,42] Some clinicians have used a quantitative HIV-1 RNA assay (those typically used for monitoring response to treatment with chronic HIV-1 infection) for making a diagnosis of acute HIV-1, since these tests have similar lower limits of detection and also provide a quantitative HIV-1 RNA level for positive samples. Persons with acute HIV-1 typically have quantitative HIV-1 RNA levels greater than 100,000 copies/mL.[43,44] The use of HIV-1 RNA testing on pooled samples, in conjunction with HIV antibody testing, has also been utilized as a cost-effective strategy to screen for acute HIV-1 infection.[45]

HIV-1/2 Antigen-Antibody Tests

Since laboratory-based detection of HIV-1 p24 antigen occurs approximately 1 week prior to detection of anti-HIV antibodies, use of a screening test that detects HIV-1 p24 antigen will increase the diagnostic yield of persons with acute HIV-1 infection. Since 2014, the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL) have recommended use of HIV-1/2 Antigen-Antibody immunoassays as the preferred initial HIV screening test, primarily in an effort to enhance the detection of persons with acute HIV-1 infection.[11,46] The United States FDA has approved six laboratory-based HIV-1/2 antigen-antibody immunoassays:

- ADVIA Centaur HIV Ag/Ab Combo (CHIV) Assay,
- ARCHITECT HIV Ag/Ab Combo,
- BioPlex 2200 HIV Ag-Ab Assay,
- Elecsys HIV Combi PT,
- GS HIV Combo Ag/Ab EIA, and
- VITROS HIV Combo Test

These assays detect HIV approximately 1 week after HIV RNA can be detected and about 1 week prior to laboratory-based HIV IgM/IgG-sensitive antibody tests (Figure 11).[47,48,49] Although the rapid point-of-care Alere Determine HIV-1/2 Ag/Ab Combo test is more sensitive for detecting early HIV infection than HIV IgM/IgG-sensitive antibody tests, it is not as sensitive as the laboratory-based HIV-1/2 antigen-antibody assays (the laboratory-based assays detect HIV p24 antigen about 3 to 5 days before the point-of-care Alere Determine HIV-1/2 Ag/Ab Combo test).[50,51,52] Among the HIV-1/2 antigen-antibody assays, only the laboratory-based BioPlex 2200 HIV Ag-Ab Assay and the point-of-care Alere Determine HIV-1/2 Combo assays differentiate the HIV-1 p24 antigen from the anti-HIV antibodies.[53,54]

HIV Antibody Tests
Laboratory-based IgG/IgM-sensitive HIV-1 antibody tests first turn positive at approximately 23 days after acquisition of HIV, with laboratory-based IgG-sensitive HIV antibody tests and point-of-care HIV antibody tests typically turning positive about 4 to 5 weeks after infection. The characteristic formation of anti-HIV antibodies may be altered in persons with acute HIV infection who receive antiretroviral therapy prior to seroconversion; in this scenario, recently infected individuals may have incomplete evolution of antibody responses and rarely may have a seroreversion. A modified, less sensitive HIV antibody test, the so-called "detuned" assay, has been used in research settings to differentiate those with recent HIV infection (acquired HIV within the previous 4 to 5 months) from those with well-established chronic HIV infection; this test can help to identify those with recent HIV infection who have already passed through the window period.

**Recommended Testing to Diagnosis Acute HIV**

**Detection of Acute HIV with Routine Screening for HIV**

The HIV testing algorithm recommended by the CDC and APHL, which utilizes a laboratory-based HIV-1/2 antigen-antibody immunoassay as the initial screening test, will detect approximately 85% of persons with acute HIV infection. With this algorithm, persons with acute HIV would typically have a positive initial screening test with the HIV-1/2 antigen-antibody immunoassay, followed by a negative HIV-1/HIV-2 antibody differentiation immunoassay, and then a positive HIV-1 RNA test (Figure 12). The ability of this routine screening algorithm to detect most persons with acute HIV is one of the primary reasons the CDC now advocates using this HIV testing approach for routine screening. In the situation where the routine screening testing algorithm detects HIV, follow-up antibody testing in 3 to 6 months should be performed to document seroconversion. From a practical standpoint, routine screening for HIV infection using HIV NAT is not practical due to cost considerations.

**Testing for Suspected Very Early Acute HIV Infection**

For patients in whom there is a strong clinical suspicion of acute HIV infection, but initial testing with the HIV-1/2 antigen-antibody immunoassay is negative, additional testing should be performed with an HIV-1 RNA assay. The rationale for this approach is that individuals with very early HIV infection can have a negative HIV-1 p24 antigen test and the only assay that would detect HIV in that setting is an HIV-1 RNA. Persons are presumptively diagnosed with acute HIV infection if they have a positive HIV RNA (especially at a high level) and negative or indeterminate HIV antibody assay; in this scenario, they should have follow-up antibody testing in 3 to 6 months to document seroconversion.

**Testing for Recent HIV Infection**

For individuals with a positive HIV antibody test and suspected recent infection, it is important to try and determine the last negative HIV test. In this setting, a negative HIV-1/2 antigen-antibody immunoassay (or negative HIV antibody test) in the prior 6 months would support a diagnosis of recent HIV infection. From a research standpoint, the detuned HIV antibody assay could confirm recent infection, but this test is not widely available in clinical settings.
Rationale for Treatment of Acute HIV Infection

The potential benefits of initiating antiretroviral therapy for patients with acute and recent HIV infection include (1) accelerated resolution of symptomatic acute retroviral syndrome, (2) minimized immunologic damage, (3) diminished size of the latent HIV reservoir pool, and (4) prevention of HIV transmission to others.[61,62]

Preservation of Immune Function and Delayed Disease Progression

Early antiretroviral therapy can help preserve immune function and slow HIV disease progression by slowing CD4 decline and reducing HIV RNA levels.[61,62,63,64] One study analyzed differences between a group of individuals who started antiretroviral therapy within 2 weeks of seroconversion (acute treatment arm), a group who started between 2 weeks and 6 months of seroconversion (early treatment arm), and a group who declined to initiate therapy; individuals in the acute and early treatment arms took therapy for at least 3 months then stopped.[65] At 6 months after treatment interruption, groups who initiated treatment had lower HIV RNA levels and higher CD4 counts, with the greatest benefit seen in those who initiated within 2 weeks of seroconversion.[65] Multiple studies, including the Setpoint Study (ACTG A5217),[13] Primo SHM[66], and SPARTAC,[67] have demonstrated a reduction in viral set point and slower disease progression after initiation of antiretroviral therapy during early HIV infection.

Impact on Latent Reservoir

One report documented 14 individuals who initiated antiretroviral therapy during primary infection (with continuation of therapy for a mean 36.5 months) and were able to control viremia on their own following cessation of therapy (so-called “post-treatment controllers”); the investigators reported a likelihood of spontaneous control of viremia after treatment interruption among 15% in the group who were treated during acute infection, as opposed to less than 1% of those not treated.[68] These data suggest that treatment during acute infection can significantly reduce latent HIV reservoirs and may aid in future efforts to achieve functional cure. In one study, use of a potent five-drug regimen did not have a greater impact on HIV reservoirs when compared with a standard triple-drug antiretroviral regimen.[69]

Reduced Risk for HIV Transmission

In the acute phase, newly infected persons have a significant increase in risk of transmitting HIV to others due to several factors: (1) they have initial uncontrolled viremia with associated high levels of HIV in the genital tract, (2) their initial HIV quasispecies is less varied and probably better adapted for transmission than later in the course of HIV infection, and (3) they are often unaware of their HIV status.[1,2] For the year 2016, the CDC estimated that among the 38,700 new HIV infections in the United States, 1,500 (4%) involved transmissions from persons with acute HIV.[70] The Duke-UNC-Emory Acute HIV Consortium examined viral dynamics at different phases of HIV disease and found markedly higher semen and blood HIV RNA levels in men during acute HIV infection than in men with chronic HIV, thus providing a biologic basis for the reported increases in HIV transmission during early infection.[5] This same group also generated models for calculating probabilities of male-to-female HIV transmission per coital act that projected a markedly higher risk of HIV transmission during acute HIV infection than in the subsequent months after acute infection (Figure 13).[6] In addition, other groups of investigators have shown that for every 10-fold increase in viral load, the risk of transmission increases by a factor of 2.5, so a prompt reduction in the very high HIV RNA levels with acute or early HIV infection could be a key in preventing HIV transmission.[2,71]
Antiretroviral Treatment Recommendations

The following summarizes the recommendations from the Adult and Adolescent ARV Guidelines regarding treatment of individuals with acute or recent HIV infection [Table] Panel's Recommendations for Acute and Recent (Early) HIV Infection.[9]

Treatment Indication and Duration

All persons with acute or recent HIV infection should receive antiretroviral treatment.[9] Several studies have examined the strategy of starting antiretroviral therapy for acute HIV infection and then discontinuing therapy after approximately 6 months.[13,66,67,72] Although this strategy has shown beneficial impact on immune status when compared with no treatment during acute HIV, other studies have shown that treatment interruption in patients with chronic HIV results in increased in laboratory markers of inflammation, immune activation, and coagulation, as well as an increase in risk of clinical AIDS and non-AIDS-related events.[73,74] In addition, persons with HIV at any stage of disease will reduce their risk of transmitting HIV to others if they are consistently taking recommended antiretroviral therapy. For these reasons, experts recommend continuing antiretroviral therapy indefinitely if started in the acute or early phase.

Genotypic Drug Resistance Testing

All persons diagnosed with acute or recent HIV infection should have a genotypic drug resistance test ordered.[9] The laboratory sample for the genotypic drug should be obtained prior to the individual taking their first dose of antiretroviral therapy, but initiation of antiretroviral therapy can occur prior to the availability of the results from the genotypic drug resistance test result. When the genotypic drug resistance result returns, which often takes 3 to 5 weeks, the antiretroviral regimen can be modified, if needed.

Antiretroviral Treatment Regimens

The recommended antiretroviral regimens for persons with acute and recent HIV infection utilize the anchor drugs (bictegravir, dolutegravir, or boosted darunavir) because of their highly potency very high barrier to resistance, and low rate of resistance among transmitted HIV strains.[9] Most experts now recommend initiating antiretroviral therapy immediately (ideally on the same day as acute or early HIV is diagnosed). The following regimens are recommended for the treatment of persons with acute or recent HIV in whom genotypic drug resistance data are not available:

- Bictegravir-tenofovir alafenamide-emtricitabine
- Dolutegravir with (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine)
- Boosted darunavir with (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine)

The Adult and Adolescent ARV Guidelines has updated recommendation on the use of dolutegravir and other INSTIs in persons of child-bearing potential (Table 3).[75]

Treatment in Persons on Preexposure Prophylaxis

With increasing use of tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine for preexposure prophylaxis (PrEP), some individuals will have a diagnosis of acute or early HIV infection in the setting of currently (or recently) taking PrEP. In this situation, the individual with new HIV infection may acquire emtricitabine-resistant HIV (and possibly tenofovir-resistant HIV). Thus, it is essential that genotypic drug resistance testing is obtained prior to starting on a full antiretroviral treatment regimen. While awaiting resistance testing results, it is reasonable to use one the recommended regimens as noted above.[9] Some experts, however, would consider utilizing a more aggressive four-drug initial regimen, such as darunavir (boosted with cobicistat or ritonavir) plus dolutegravir plus either tenofovir alafenamide-emtricitabine or tenofovir DF-emtricitabine, until results from the genotypic drug resistance test became available.
Summary Points

- Symptoms of acute HIV are nonspecific and mimic many other viral or bacterial infections. Thus, the diagnosis of acute HIV infection requires a high index of suspicion and careful history taking to identify recent (within 2 to 6 weeks) high-risk exposure to HIV.
- Acute HIV infection is defined as detectable HIV RNA (or HIV p24 antigen) combined with a negative HIV antibody test. The diagnosis of acute HIV-1 is confirmed by negative HIV-1 antibody test in conjunction with a positive HIV-1 RNA assay or p24 antigen assay. Acute HIV is generally associated with high HIV RNA levels (above 100,000 copies/mL).
- The HIV testing algorithm recommended by the CDC and APHL uses HIV-1/2 antigen-antibody immunoassays as the initial HIV screening test and will detect most, but not all, persons with acute HIV. The characteristic algorithm pattern with acute HIV-1 infection is a positive HIV-1/2 antigen-antibody immunoassay, a negative HIV-1/HIV-2 antibody differentiation immunoassay, and a positive HIV-1 RNA test.
- The detection of acute HIV is critical for timely initiation of antiretroviral therapy. Antiretroviral treatment is recommended for all person with early HIV infection. The rationale for initiating antiretroviral therapy during acute infection is to reduce the level of the set point, slow progression of disease, reduce the viral reservoir, alleviate symptoms, and prevent transmission of HIV to others.
- Genotypic drug resistance testing is recommended in all persons with acute or recent HIV infection, but antiretroviral therapy can be initiated prior to the test results, with regimens modified if needed.
- The antiretroviral regimen should include an anchor drug that has excellent potency and a strong genetic barrier to resistance. Specific recommended regimens for early HIV infection in the setting of pending drug-resistance testing data are bictegraavir-tenofovir alafenamide-emtricitabine; dolutegravir with (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine; or boosted darunavir with (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine).
Citations


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25. Sterling TR, Vlahov D, Astemborski J, Hoover DR, Margolick JB, Quinn TC. Initial plasma HIV-1 RNA

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[PubMed Abstract] -


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[PubMed Abstract] -


[PubMed Abstract] -


[PubMed Abstract] -


[PubMed Abstract] -


[PubMed Abstract] -


40. U.S. Food and Drug Administration. APTIMA HIV-1 RNA Qualitative Assay [U.S. FDA] - 


46. Centers for Disease Control and Prevention and Association of Public Health Laboratories. 2018 Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. Published January 27, 2018. [CDC] - 


50. Duong YT, Mavengere Y, Patel H, et al. Poor performance of the determine HIV-1/2 Ag/Ab combo


54. U.S. Food and Drug Administration. Alere Determine HIV-1/2 Ag/Ab Combo.


References

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

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Figures

Figure 1 Acute HIV Infection

Acute HIV infection is defined as the phase of HIV disease that occurs immediately after HIV acquisition and is characterized by detectable HIV RNA or HIV p24 antigen in the absence of detectable anti-HIV antibodies.
**Figure 2 Early HIV Infection**

Early HIV infection is the 6-month time period following initial HIV infection. This period encompasses both the acute and recent period.

**Figure 3 HIV Eclipse Phase**

The HIV eclipse phase is defined as the time from acquisition to the time HIV RNA is detectable in plasma. The eclipse phase is typically about 10 days.

Figure 4 Fiebig Laboratory Staging of Early HIV Infection

Figure 5 Founder Virus

Despite presence of a diverse quasispecies of HIV present in semen, cervicovaginal secretions, or blood, a single virion (or a few virions) is usually responsible for catalyzing the initial HIV infection that results in a productive infection.

Figure 6 HIV Seroconversion Window Period

The HIV seroconversion window is the time from acquisition of HIV to time anti-HIV antibodies are detectable.

Figure 7 Set Point Following HIV Infection

Days following HIV Infection

HIV RNA

Set Point
Figure 8A: Exposure Event

- HIV
- Mucosal Surface
- Dendritic Cell
- CD4 Cell
- Macrophage
- Exposure Event 1
Figure 8 (Image Series) - Model for Sexual Transmission of HIV
Image 8B: Prime Infection with Founder Virus
Figure 8 (Image Series) - Model for Sexual Transmission of HIV
Image 8C: Initial Propagation with Small HIV Founder Population
Figure 8 (Image Series) - Model for Sexual Transmission of HIV
Image 8D: Local Expansion

Mucosal Surface

Dendritic Cell

Activated CD4 Cell

Macrophage

Local Expansion 4
Figure 8 (Image Series) - Model for Sexual Transmission of HIV
Image 8E: Regional Lymphatic Spread
Figure 8 (Image Series) - Model for Sexual Transmission of HIV
Image 8F: Hematogenous Spread
Figure 9 Cytotoxic T-Lymphocyte Response Following Acute HIV Infection

Figure 10 Acute HIV: Skin Rash

Source: photograph by David H. Spach, MD
**Figure 11 Timing of Positivity for HIV Diagnostic Tests Following Initial HIV Infection**

Abbreviation: POC = point-of-care

Figure 12 HIV Laboratory Testing Algorithm As Recommended by the CDC and APHL

This graphic shows the HIV testing algorithm as recommended by the Centers for Disease Control and Prevention and Association of Public Health Laboratories. The rectangles highlighted with yellow border indicate the expected positive tests in a person with acute HIV infection.

Figure 13 Risk of Sexual Transmission of HIV During Early Infection

Table 1.

**Clinical Signs and Symptoms of Acute HIV Infection**

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<th>Features</th>
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<th>Male (n = 355)</th>
<th>Female (n = 23)</th>
<th>Sexual (n = 324)</th>
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IDU = Injection drug use

Source:

### Key Considerations and Recommendations for Acute and Recent (Early\(^a\)) HIV Infection

- Antiretroviral therapy is recommended for all individuals with HIV including those with early\(^a\) HIV infection (AI). Antiretroviral therapy should be initiated as soon as possible after HIV diagnosis (AII).

- The goal of antiretroviral therapy is to suppress plasma HIV RNA to undetectable levels (AI) and to prevent transmission of HIV (AI). Testing for plasma HIV RNA levels, CD4 T lymphocyte cell counts, and toxicity monitoring should be performed as recommended for persons with chronic HIV infection (AII).

- A sample for genotypic testing should be sent before initiation of antiretroviral therapy (AIII). Antiretroviral therapy can be initiated before drug resistance testing and HLA B*5701 test results are available. In this setting, one of the following antiretroviral regimens is recommended (AIII):
  - Bictegravir-tenofovir alafenamide-emtricitabine
  - Dolutegravir with (tenofovir alafenamide or tenofovir DF)\(^b\) plus (emtricitabine or lamivudine)
  - Boosted darunavir with (tenofovir alafenamide or tenofovir DF)\(^b\) plus (emtricitabine or lamivudine).

- Pregnancy testing should be performed in individuals of childbearing potential before initiation of antiretroviral therapy (AIII).

- Data from an observational study in Botswana suggest there may be an increased risk of neural tube defects in infants born to individuals who were receiving dolutegravir at the time of conception. Before initiating an integrase strand transfer inhibitor-based regimen in a person of childbearing potential, clinicians should review the table Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors as Initial Therapy for Persons of Childbearing Potential for information to consider when choosing an antiretroviral therapy regimen.

- As there are no safety data for bictegravir use around the time of conception, an approach similar to that outlined for dolutegravir should be considered for bictegravir-containing antiretroviral therapy (AIII).

- When the results of drug resistance and HLA-B*5701 testing are available, the treatment regimen can be modified if needed (AII).

- Providers should inform individuals starting ART of the importance of adherence to achieve and maintain viral suppression (AIII).

\(^a\) Early infection represents either acute or recent infection

\(^b\) Tenofovir alafenamide and tenofovir DF are two forms of tenofovir that are approved in the United States. Tenofovir alafenamide has fewer bone and kidney toxicities than tenofovir DF, while tenofovir DF is associated with lower lipid levels. Safety, cost, and accessibility are among the factors to consider when choosing between these drugs.

**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

**Source:**
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Considerations for antiretroviral use in special patient populations: acute and recent (early) HIV infection. December 18, 2019. [AIDSSinfo]
Table 3. **Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV**

**Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors (INSTIs) as Initial Therapy for Persons of Child-Bearing Potential**

Before Initiating an INSTI-Containing Regimen in a Person of Childbearing Potential:

- A pregnancy test should be performed (AIII).
- To enable individuals of childbearing potential to make informed decisions, providers should discuss the benefits and risks of using dolutegravir around the time of conception, including the low risk of neural tube defects and the relative lack of information on the safety of using other commonly prescribed antiretroviral drugs, including other INSTIs, around the time of conception (AIII).
- For individuals who are trying to conceive, the Panel recommends initiating one of the following regimens, which are designated as Preferred regimens during pregnancy in the Perinatal Guidelines: use of an anchor drug (raltegravir, or atazanavir boosted with ritonavir, or darunavir boosted with ritonavir) plus a 2-drug backbone (tenofovir DF-emtricitabine, or tenofovir DF plus lamivudine, or abacavir-lamivudine). Dolutegravir would be an Alternative, rather than a Preferred, option (BII).
- For individuals who are not planning to conceive but who are sexually active and not using contraception, consider a regimen’s effectiveness and tolerability, the available data on potential teratogenicity, and the person’s preferences (e.g., low pill burden) when choosing among regimens recommended for initial therapy. In this situation, dolutegravir would be an Alternative, rather than Preferred, option (BII). If the person becomes pregnant, changes to the antiretroviral regimen may be warranted. In this situation, clinicians should refer to the Perinatal Guidelines or recommendations.
- For individuals who are using effective contraception, a dolutegravir-based regimen is one of the recommended options; however, clinicians should discuss the risks and benefits of using dolutegravir with patients to allow them to make an informed decision (AIII).
- An approach similar to that outlined for dolutegravir should be considered for bictegravir-containing antiretroviral therapy (AIII).
- Regimens that contain elvitegravir-cobicistat should not be used during pregnancy because of inadequate drug concentrations of elvitegravir in the second and third trimesters (AII).
- Clinicians should refer to the Perinatal Guidelines when prescribing antiretroviral therapy for a pregnant persons with HIV.

**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, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

**Source:**
