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Acute and Recent HIV Infection

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Module 1: Screening and Diagnosis
Lesson 4: Acute and Recent HIV Infection

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Background and Definitions

Background

Following the acquisition of HIV, more than 50% of individuals will develop a transient, symptomatic illness, with nonspecific features, referred to as acute HIV retroviral syndrome.[1,2,3] This illness, also known as primary HIV or acute retroviral syndrome, is frequently mistaken for an alternate viral infection, such as mononucleosis or influenza. Acute HIV represents the time period with an enhanced risk of transmitting HIV to others, primarily because of their very high HIV RNA levels and lack of awareness of HIV status.[4,5,6]. Early antiretroviral therapy arrests the explosive burst of viremia associated with acute HIV infection and thereby reduces symptoms and may improve long-term health outcomes. Furthermore, by reducing HIV RNA levels, which are often extremely elevated during acute infection, treatment decreases the likelihood of transmission to others.[2] Thus, recognition and diagnosis of acute HIV, followed by early initiation of antiretroviral therapy, is critical for both the health of the individual who has acquired HIV and the for prevention of transmission. The following will review the clinical manifestations, diagnosis, and management of persons with acute HIV.

Definitions

- **Eclipse Phase:** The short interval following HIV acquisition in which no diagnostic test is capable of detecting HIV.[7,8] This interval is typically 8 to 10 days in duration (Figure 1).[7,9,10]

- **Seroconversion Window Period**: This term refers to the interval between HIV acquisition and the first detection of anti-HIV antibodies (Figure 2).[8]. 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.

- **Acute HIV Infection**: Defined as the phase of HIV disease that occurs soon after HIV acquisition and is characterized by detectable HIV RNA or HIV p24 antigen in the absence of anti-HIV antibodies (Figure 3).[2] The term acute HIV was previously used interchangeably with the term primary HIV, but acute HIV is now the preferred term.

- **Early HIV Infection**: Early infection is generally used to describe both acute and recent HIV time periods, which extend out to 6 months after HIV acquisition (Figure 4).[11]

- **Acute Retroviral Syndrome**: An acute symptomatic illness that develops in many individuals during the acute HIV infection phase.[12,13]

Immunopathogenesis

The immunopathogenesis of acute HIV infection is best understood within the context of HIV transmission via the genital mucosa and the events that follow transmission in the genital mucosa.[3,14] Therefore, the following discussion will focus on the immunopathogenesis related to the sexual transmission of HIV. 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 5); this illustration shows the transmission of HIV with columnar epithelial cells in the rectum and cervix.[2,3,14,15] In the vagina, ectocervix, and inner side of the penile foreskin, there are thicker barriers consisting of stratified squamous epithelium; in those regions, HIV can also initially infect Langerhans cells (tissue dendritic cells located just below the mucosa).[16] The HIV-Langerhans cell binding occurs via attachment with a CD4 molecule on the surface of the cell, followed by binding to the CCR5 cellular noreceptor; the Langerhans cells express CCR5 coreceptors, but usually not CXCR4 coreceptors.

Initial Inoculation of HIV and Founder Virus

Almost always, the transmitted HIV is R5-tropic, which preferentially binds to these CCR5 co-receptors on CD4 cells, Langerhans cells, and dendritic cells. Although HIV generally exists as a quasispecies or a mixture of mutant strains, usually only one strain (or a few strains) successfully establishes an initial infection; the infecting strain is known as the founder virus (Figure 6).[17,18] Available data indicate this founder virus has unique fitness properties that maximize its transmission capability.[18,19]

Establishment of HIV Infection

The dendritic cells that are infected with HIV can migrate to lymph nodes, where they interact with and potentially fuse with CD4 cells, causing the spread of HIV to deeper tissues.[15] 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).[2,20,21] Investigators have shown that humans typically develop HIV viremia within 11 days of initial transmission.[7,22]

Initial Immune Response

The uncontrolled initial burst of viremia in the acute phase typically causes very high plasma HIV RNA levels, often greater than 200,000 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—referred to as a 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 (Figure 7).[25,26,27] In addition, higher set points are usually associated with more rapid progression of HIV disease, if untreated. These models suggest that despite multiple different strains of HIV interacting with mucosal surfaces, there are typically only 1 or 2 strains of HIV that catalyze the initial HIV infection.

Early Immune Response as Predictor of Disease Progression

Investigators have shown that different individuals have qualitatively distinct 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 8).[28,29,30] More recently, the importance of the epitope-specific type of CD8 T cell response in controlling HIV has been elucidated.[31] In most persons newly infected with HIV, higher initial HIV RNA levels predict an accelerated course of HIV disease progression,[32] but this

correlation is not universal.[28,33] Similarly, several reports have suggested that development of clinically apparent acute retroviral syndrome portends a faster progression to AIDS.[34] One study found that among 218 African women with HIV-1, a higher set point HIV-RNA level or greater severity of acute HIV illness predicted faster progression to death (with each additional symptom of acute HIV contributing to higher mortality).[35]

Clinical Manifestations

Acute Retroviral Syndrome

Acute retroviral syndrome ranges from an asymptomatic infection, to a mild nonspecific viral illness resembling mononucleosis, to a severe systemic illness that requires hospitalization.[12,13] The transient surge of viremia that accompanies acute HIV typically correlates with the timing of the onset of clinical manifestations, which usually begin within 28 days of HIV acquisition.[36] The signs and symptoms are typically nonspecific, protean, and self-limited. Therefore, a high index of suspicion and inquiry into risk factors are generally necessary to identify primary infection.[37] Among persons prospectively followed who have a laboratory diagnosis of acute HIV, the most common manifestations associated with acute HIV are fever, fatigue, myalgia, skin rash, headache, pharyngitis, and cervical adenopathy; some individuals do not develop a symptomatic illness (Table 1).[3,12,38,39,40] The skin rash is typically morbilliform or maculopapular and most often involves the trunk (Figure 9). Less commonly, neurological complications may occur, such as aseptic meningitis, encephalitis, facial palsy, or Guillain-Barré syndrome.[41] Rarely, acute HIV causes such a substantial drop in CD4 cell count that patients may initially present with a major AIDS-defining opportunistic infection. In a study of 216 individuals with acute or recent (within 3 months) HIV infection in Peru, 61% had at least one sign or symptom of acute retroviral syndrome, and 35% had at least three.[36]

Duration of Symptoms

In a study of 46 individuals with acute HIV who did not receive antiretroviral therapy during the acute illness, those who developed a symptomatic illness had a median duration of symptoms of 14 days.[13] The duration of symptoms can range from days to weeks, and the severity and duration of symptoms may correlate with disease progression.[3,38]

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 infection (mononucleosis), secondary syphilis, acute cytomegalovirus, 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

Based on serial blood samples from 99 people who were closely followed after the acquisition of HIV, investigators described 6 stages of early HIV infection that were based on the timing and results of HIV diagnostic tests; the stages identified in this study are referred to as the Fiebig stages of early HIV infection (Figure 10).[7] This study, as well as others, have shown that 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.[1,7,42] The laboratory diagnosis of acute HIV requires a negative HIV antibody assay in combination with either a positive HIV RNA or a positive p24 antigen.[11] 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 8 to 10 days after initial HIV-1 acquisition, plasma HIV-1 RNA levels become detectable.[7,9,10] 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 at about 250,000 copies/mL.[7,42,43] Currently, the APTIMA HIV-1 Qualitative Assay is the only nucleic acid test (NAT) approved by the U.S. Food and Drug Administration (FDA) for the diagnosis of HIV-1, including for acute HIV-1 infection; this test provides only a qualitative detection of HIV-1 RNA.[44] The APTIMA HIV-1 Qualitative Assay can detect all major HIV-1 groups and subtypes, with 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.[45,46] Many clinicians use 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, are more readily accessible, and also provide a quantitative HIV-1 RNA level for positive samples. 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.[47]

HIV-1/2 Antigen-Antibody Tests

Using laboratory-based tests, detection of HIV-1 p24 antigen occurs approximately 1 week after HIV-1 RNA and approximately 1 week prior to detection of IgM/IgG-sensitive antibody test (Figure 11).[48,49,50] The use of a screening test that detects HIV-1 p24 antigen will increase the diagnostic yield of persons with acute HIV-1 infection compared with using antibody tests alone for screening.[8,51] The p24 antigen typically becomes detectable when the HIV RNA level exceeds 10,000-20,000 copies/mL.[7,11] Although the rapid point-of-care Abbott 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 Abbott Determine HIV-1/2 Ag/Ab Combo test).[52,53,54] Among the HIV-1/2 antigen-antibody immunoassays, only a few differentiate the HIV-1 p24 antigen from the anti-HIV antibodies.[55,56] Therefore, for most of the approved assays, a positive result can indicate either the detection of p24 antigen, HIV antibody, or both. From a practical standpoint, a positive HIV-1/2 antigen-antibody immunoassay, followed by a negative differentiation HIV-1/HIV-2 antibody assay, likely indicates positivity of the p24 antigen.

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.[7] 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, individuals with recent HIV acquisition may have incomplete evolution of antibody responses, including rare cases of seroreversion.[57,58,59] 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;[60] this test can help to identify those with recent HIV infection who have already passed through the window period.

Detection of Acute HIV with Routine Screening for HIV

The HIV testing algorithm recommended by the Centers for Disease Control (CDC) and Association of Public Health Laboratories (APHL), which utilizes a laboratory-based HIV-1/2 antigen-antibody immunoassay as the initial screening test, will detect approximately 80 to 85% of persons with acute HIV infection.[8,61,62,63] With this algorithm, persons with acute HIV 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).[8] 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 (as opposed to starting with an antibody-only test, which was the previously used strategy).[8,51] 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.[11] From a practical standpoint, routine screening for HIV infection using an HIV-1 RNA test is not practical due to cost.

Testing for Suspected Very Early Acute HIV Infection

For individuals 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.[11]

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 timing of 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.[64,65,66]

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.[64,65,67,68] 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.[69] 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.[69] Multiple studies, including the Setpoint Study (ACTG A5217), Primo SHM, and SPARTAC, have demonstrated a reduction in viral set point and slower disease progression after initiation of antiretroviral therapy during early HIV infection.[70,71,72] The SABES study in Peru randomized men who have sex with men (MSM) who developed acute or early HIV to receive either immediate or deferred (for 6 months) antiretroviral therapy initiation.[73] Importantly, prompt initiation of antiretroviral had several significant health benefits, including fewer opportunistic infections, fewer respiratory tract infections, higher CD4 cell count rebound at 2 years, and improved inflammatory cytokine profiles.[73]

Impact on Latent Reservoir

One report documented 14 individuals who initiated antiretroviral therapy during acute HIV—and continued therapy for a mean of 36.5 months—who maintained low HIV RNA levels following cessation of therapy.[74] The investigators reported spontaneous control of viremia after treatment interruption in 15% of the group treated during acute infection versus less than 1% of those not treated.[74] These data suggest that treatment during acute infection can significantly reduce latent HIV reservoirs and may aid in future efforts to achieve a 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.[75] In clinical practice, the diagnosis of acute HIV and immediate initiation of a standard antiretroviral therapy regimen is beneficial, and antiretroviral therapy should be continued long-term and not interrupted.

Reduced Risk for HIV Transmission

Individuals with recent acquisition of HIV have a significant increase in risk of transmitting HIV to others due to several factors: (1) they have initial uncontrolled viremia with associated high HIV RNA levels 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.[2,3] In 2016, the CDC estimated that approximately 4% of the new HIV infections in the United States involved transmission from a person with acute HIV.[76] 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 HIV 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 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 significantly reduce HIV transmission during this period.[2,77]

Antiretroviral Treatment Recommendations for Acute HIV

The following summarizes the recommendations from the Adult and Adolescent ART Guidelines regarding the treatment of individuals with acute or recent HIV infection (Table 2).[11]

Treatment Indication and Duration

All persons with acute or recent HIV infection should promptly receive antiretroviral treatment (as soon as the necessary HIV-related tests, such as HIV RNA level and HIV drug-resistance genotype, have been drawn); it is not necessary to wait for the HIV drug resistance genotype result, which typically takes longer than 2 weeks to return.[11] Although several studies have examined the strategy of starting antiretroviral therapy for acute HIV infection and then discontinuing therapy after approximately 6 months, persons with acute or early HIV who start antiretroviral therapy should continue taking it without discontinuation.[11,71,72,78] In addition, persons with HIV at any stage of disease will reduce their risk of transmitting HIV to others if they consistently take antiretroviral therapy.[11] For these reasons, experts recommend continuing antiretroviral therapy indefinitely if started in the acute or early phase.

HIV Drug Resistance Genotypic Testing

All persons diagnosed with acute or recent HIV infection should have an HIV genotypic drug resistance test ordered.[11] The blood sample for the HIV drug resistance genotype 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.[11] When the result of the genotypic drug resistance test returns, which often takes 2 to 4 weeks, the antiretroviral regimen can be modified, if needed.[11]

Antiretroviral Treatment Regimens for Acute (Early) HIV

The following summarizes recommended antiretroviral regimens for persons with acute or recent HIV infection who have not recently taken HIV preexposure prophylaxis (PrEP).[11] These recommended regimens utilize the anchor drugs bictegravir, dolutegravir, or boosted darunavir because of their high potency, relatively high barrier to resistance, and low rates of resistance to these drugs among transmitted HIV strains.[11] Most experts now recommend initiating antiretroviral therapy immediately (ideally on the same day that acute or early HIV is diagnosed). The following regimens are recommended in the Adult and Adolescent ART Guidelines for the treatment of acute or recent HIV in a person who has a drug resistance genotype result pending:[11]

- 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)

For an individual who has never taken HIV PrEP, most clinicians would choose the bictegravir or dolutegravir-anchored options, due to better tolerability and fewer drug interactions than the boosted darunavir-anchored regimen.

Treatment of Acute HIV in Persons Taking HIV Preexposure Prophylaxis

With the increasing use of oral HIV PrEP (tenofovir DF-emtricitabine, tenofovir alafenamide-emtricitabine) and injectable HIV PrEP (long-acting cabotegravir), some individuals will have a diagnosis of acute or early HIV infection in the setting of currently (or recently) taking HIV PrEP. In this situation, the individual with new HIV infection may have acquired drug-resistant HIV (leading to failure of HIV PrEP) or the HIV may have developed resistance mutations due to persistent low HIV PrEP drug levels in the body. Thus, it is essential that a blood sample for genotypic drug resistance testing is collected prior to starting the full antiretroviral treatment

regimen. If the person was receiving injectable cabotegravir, then an integrase drug resistance genotype test should also be obtained prior to starting therapy. While awaiting resistance testing results, the following regimens are recommended in the Adult and Adolescent ART Guidelines for the treatment of acute (or recent) HIV, based on whether the person previously received oral HIV PrEP or long-acting injectable cabotegravir.[11]

Initial Treatment for Persons Recently Taking Oral HIV PrEP

For persons with acute (or recent HIV) who are currently or have recently taken oral HIV PrEP (tenofovir DF-emtricitabine, tenofovir DF-lamivudine, or tenofovir alafenamide-emtricitabine), the initial recommended antiretroviral regimens are the same as those for persons with acute HIV who had not been receiving HIV PrEP (note: the regimen may need to be modified based on the results of the HIV drug resistance genotypic test).[11]

- 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).

In this situation, the most likely resistance mutations present with current or recent use of oral HIV PrEP are the M184V/I mutation or, less likely, the K65R mutation. The recommended initial ART regimens are all likely to be effective even in the setting of these resistance mutations, so all would be reasonable choices, but the regimen may require modification after the genotype resistance assay result returns, especially if the viral load does not decrease appropriately with treatment.

Initial Treatment for Persons who Previously Received Long-Acting Injectable Cabotegravir

For persons with acute (or recent HIV) who are currently or have previously received (at any time) long-acting injectable cabotegravir, the situation is more complicated. Cabotegravir has a very long half-life and may remain at low levels for months or even years.[79] Therefore, if a person acquires HIV after previously receiving cabotegravir, the low levels of cabotegravir may lead to the development of integrase resistance. Clinicians still do not need to wait for the HIV drug resistance genotype test results to return before prescribing antiretroviral therapy in this situation. The recommended regimen in this scenario is boosted darunavir (boosted with ritonavir or cobicistat) with (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine). The rationale for using a boosted-protease inhibitor-based regimen is due to the possibility of integrase resistance-associated mutations that may affect dolutegravir or bictegravir.[11] If an integrase drug resistance genotype confirms full antiviral activity of dolutegravir or bictegravir, then the boosted-protease inhibitor-based regimen can be changed to an integrase inhibitor-based regimen.

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

Summary Points

- Acute HIV is defined as the interval between the detection of HIV RNA and the detection of anti-HIV antibodies. During acute HIV infection, the HIV RNA is always detectable, and the HIV p24 antigen is often positive.
- Symptoms of acute HIV infection are nonspecific and mimic many other viral or bacterial infections. Thus, the diagnosis of acute HIV infection requires a high index of suspicion and a careful medical history to identify recent (within 2 to 6 weeks) possible exposure to HIV.
- Persons with acute HIV have a much higher risk of transmitting HIV to others than when compared with persons who have chronic HIV.
- The diagnosis of acute HIV-1 is confirmed by a 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 (average of about 250,000 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; 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 people with early HIV infection. The rationale for initiating antiretroviral therapy during acute infection is to reduce the level of the set point, slow disease progression, reduce the viral reservoir, and prevent transmission of HIV to others.
- Genotypic HIV drug resistance testing is recommended in all persons with acute or recent HIV infection, but antiretroviral therapy can be initiated prior to obtaining the test results. Regimens can be modified, if needed, following drug resistance testing results.
- Persons with acute HIV who were recently or currently taking long-acting injectable cabotegravir should have an integrase genotypic drug resistance test in addition to the standard HIV drug resistance test.
- The antiretroviral regimen for persons with acute HIV should include an anchor drug that has excellent potency and a strong genetic barrier to resistance. The recommended empiric regimens for early HIV infection are bictegravir-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).
- Persons with acute HIV who who have ever received long-acting injectable cabotegravir should initiate treatment with the regimen darunavir plus (tenofovir alafenamide or tenofovir DF) plus (emtricitabine or lamivudine). In this situation, guidelines recommend against use of an empiric integrase inhibitor-anchored regimen, unless an integrase genotype has confirmed the absence of integrase resistance.

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Figures

Figure 1 HIV Eclipse Phase

Illustration: David H. Spach, MD

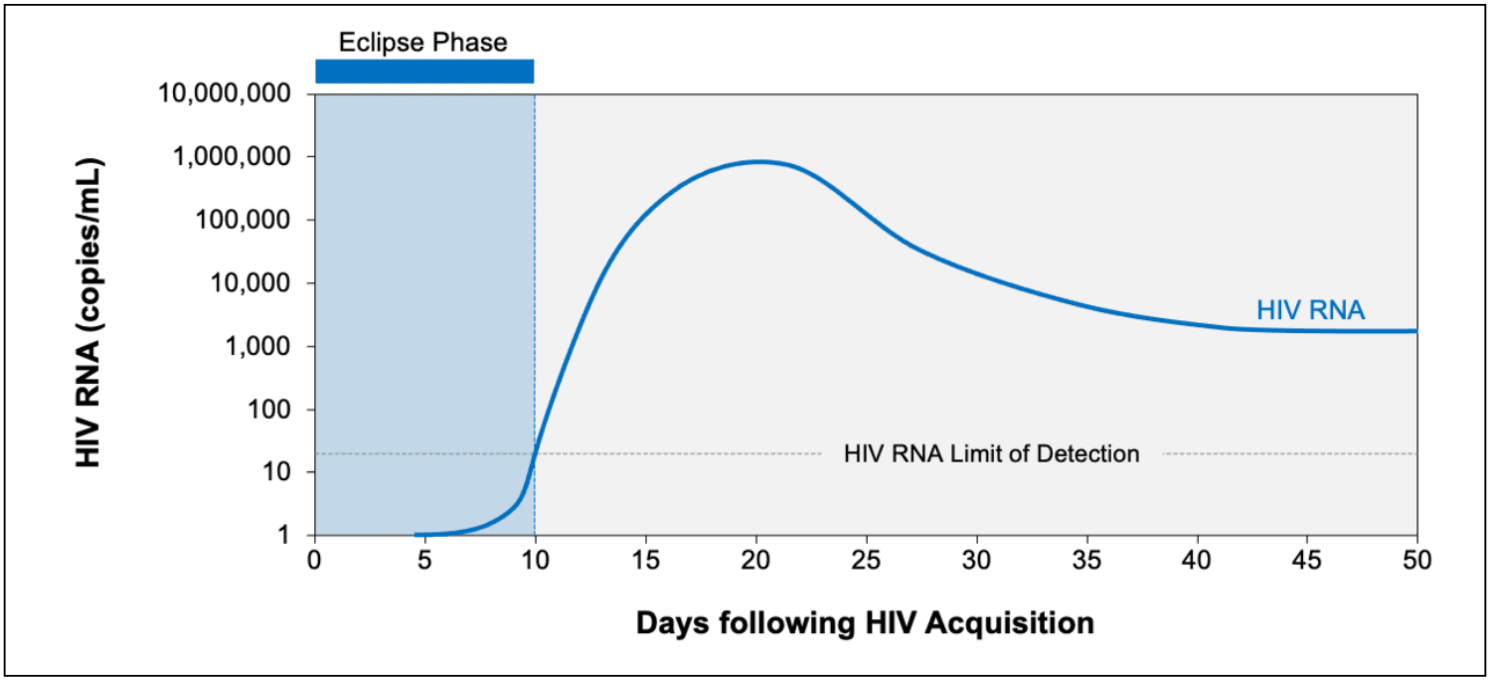

Figure 2 HIV Seroconversion Window Period

Illustration: David H. Spach, MD

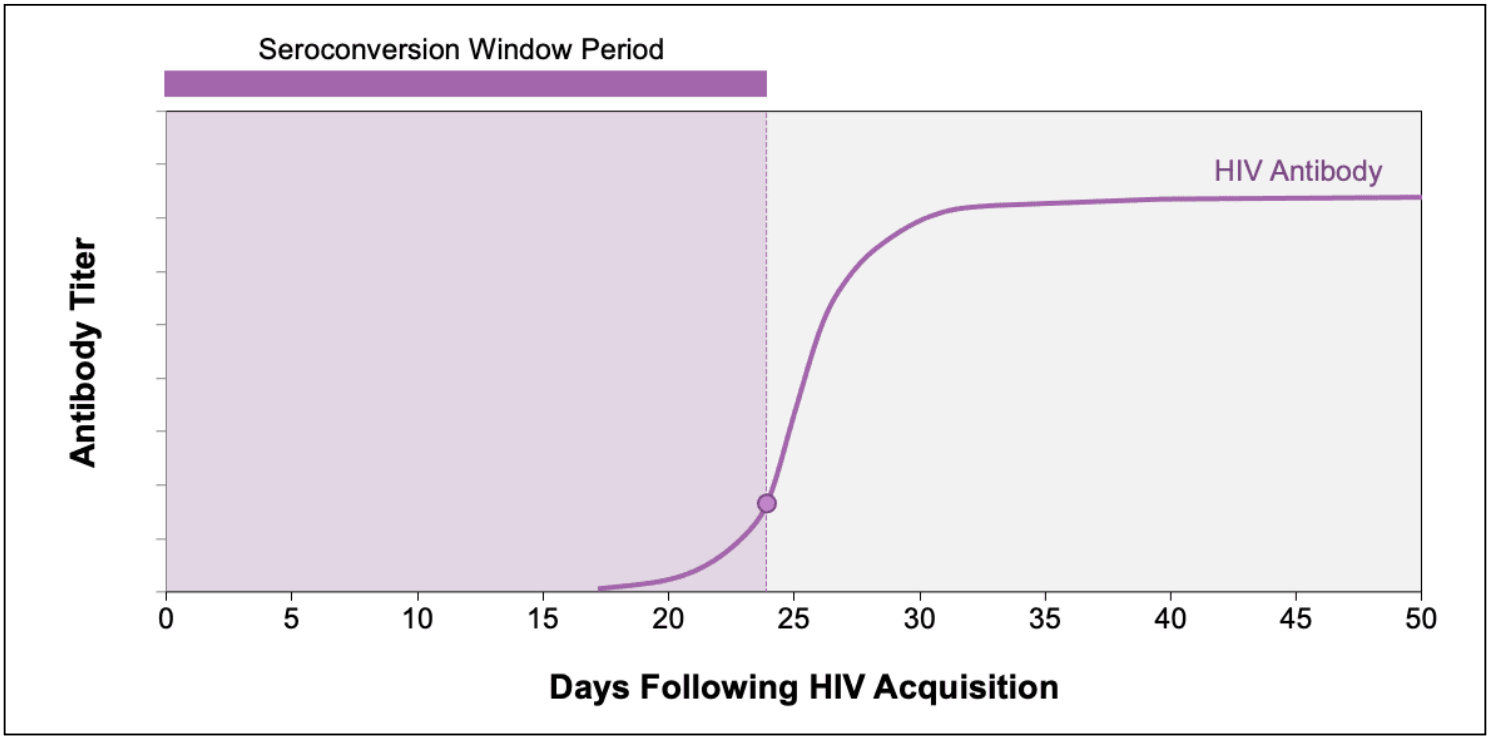

Figure 3 Acute HIV Infection

Th colored circles indicate the typical time for first detection of a positive test after acquisition of HIV.

Illustration: David H. Spach, MD

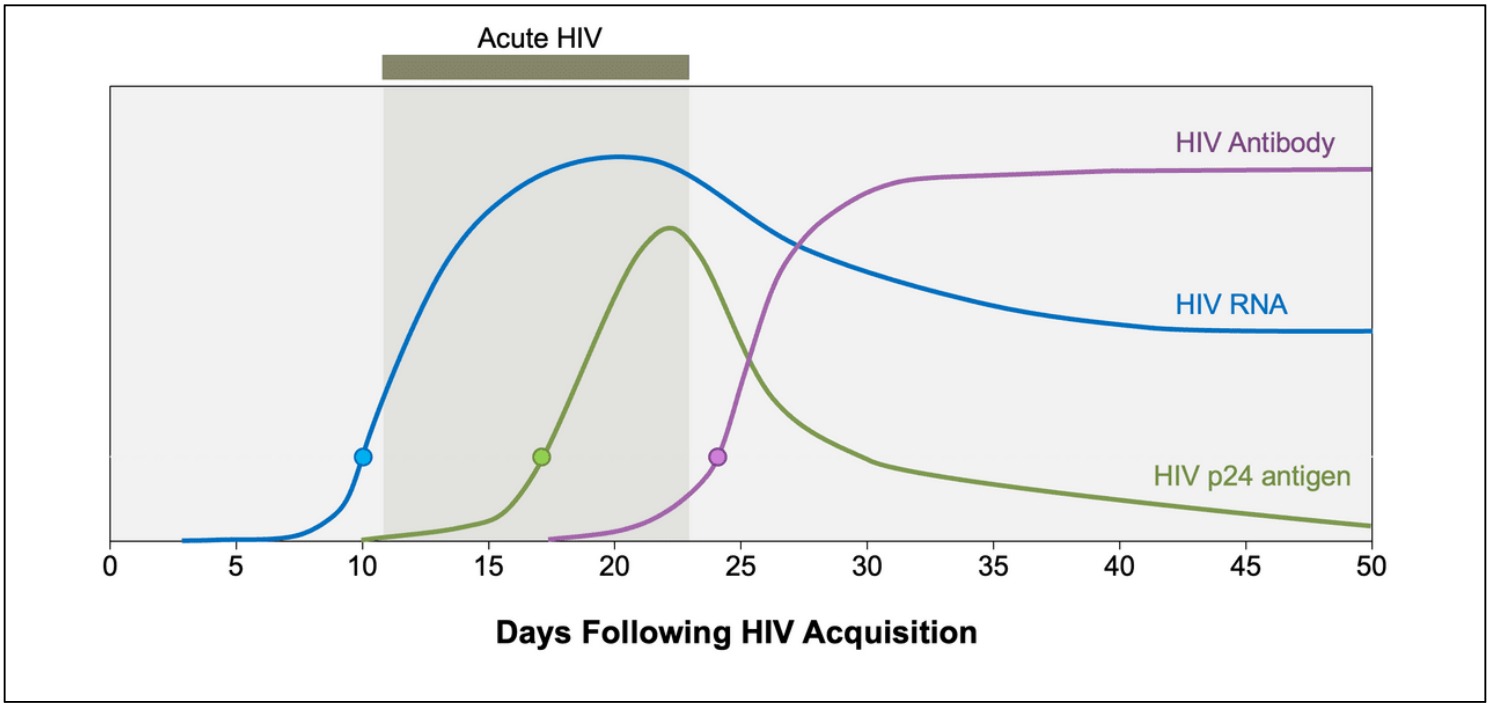

Figure 4 Early HIV Infection

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: early (acute and recent) HIV infection. September 21, 2022. Illustration: David H. Spach, MD

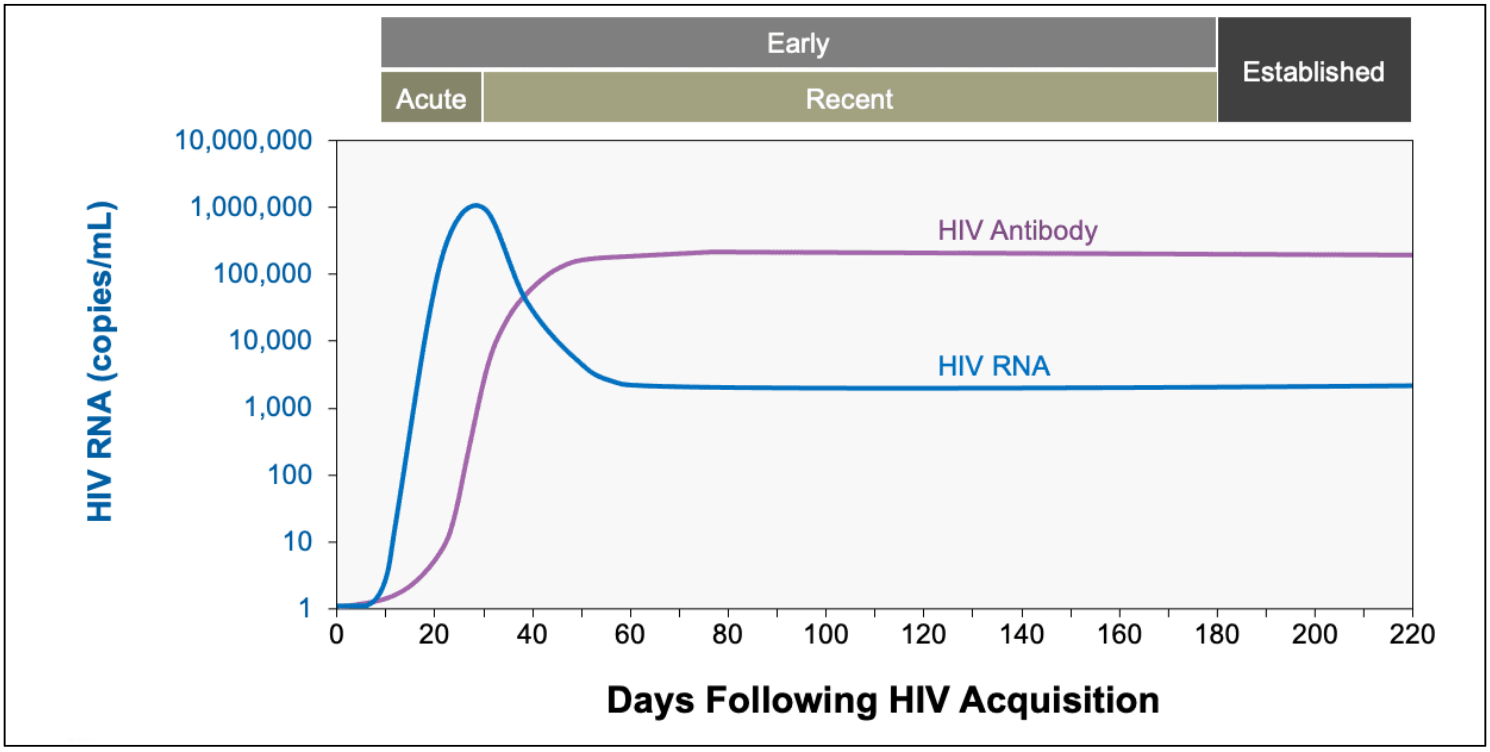

Figure 5 (Image Series) - Model for Sexual Transmission of HIV (Image Series) - Figure 5 (Image Series) - Model for Sexual Transmission of HIV
Image 5A: Exposure Event

Illustration: David H. Spach, MD

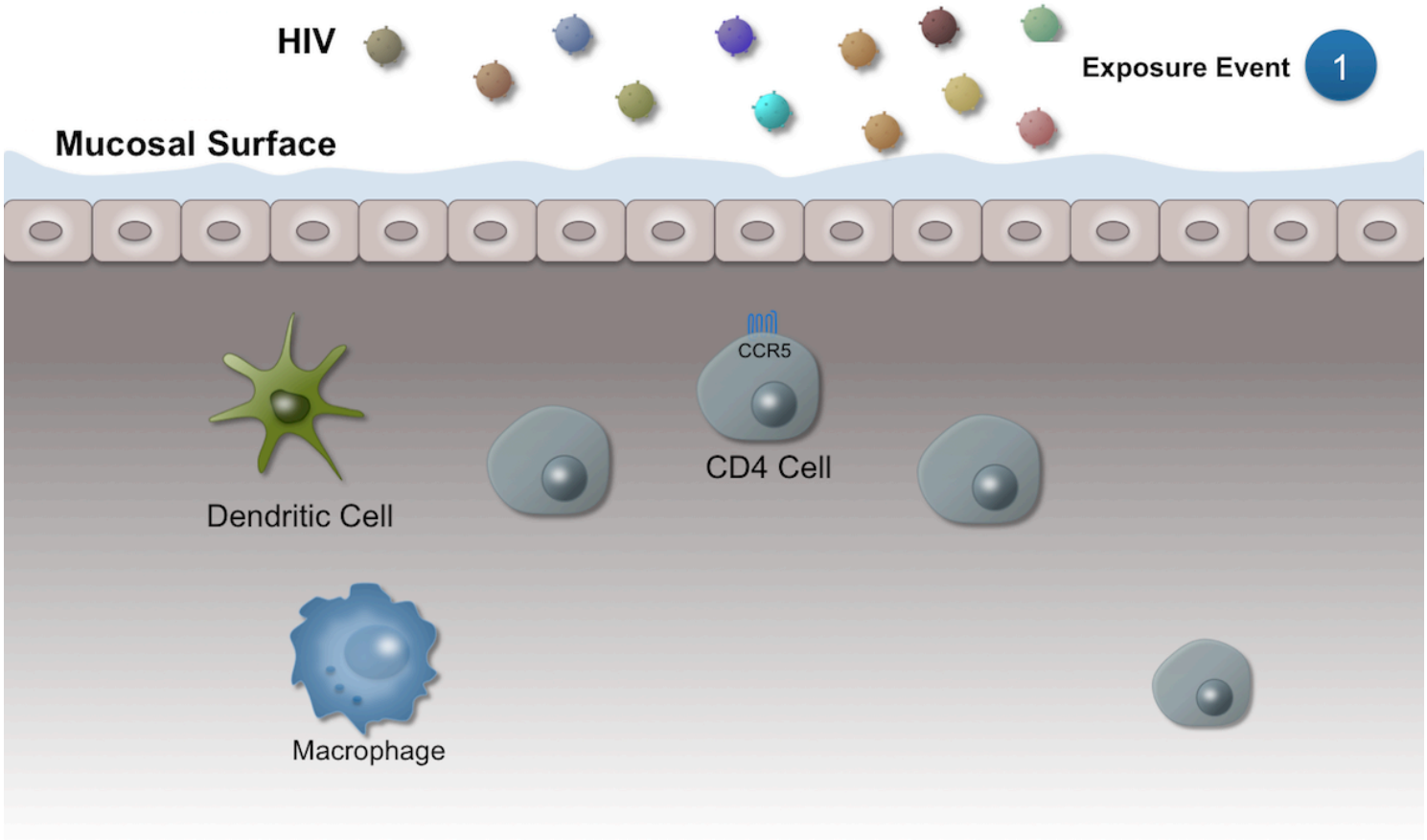

Figure 5 (Image Series) - Model for Sexual Transmission of HIV
Image 5B: Prime Infection with Founder Virus

Illustration: David H. Spach, MD

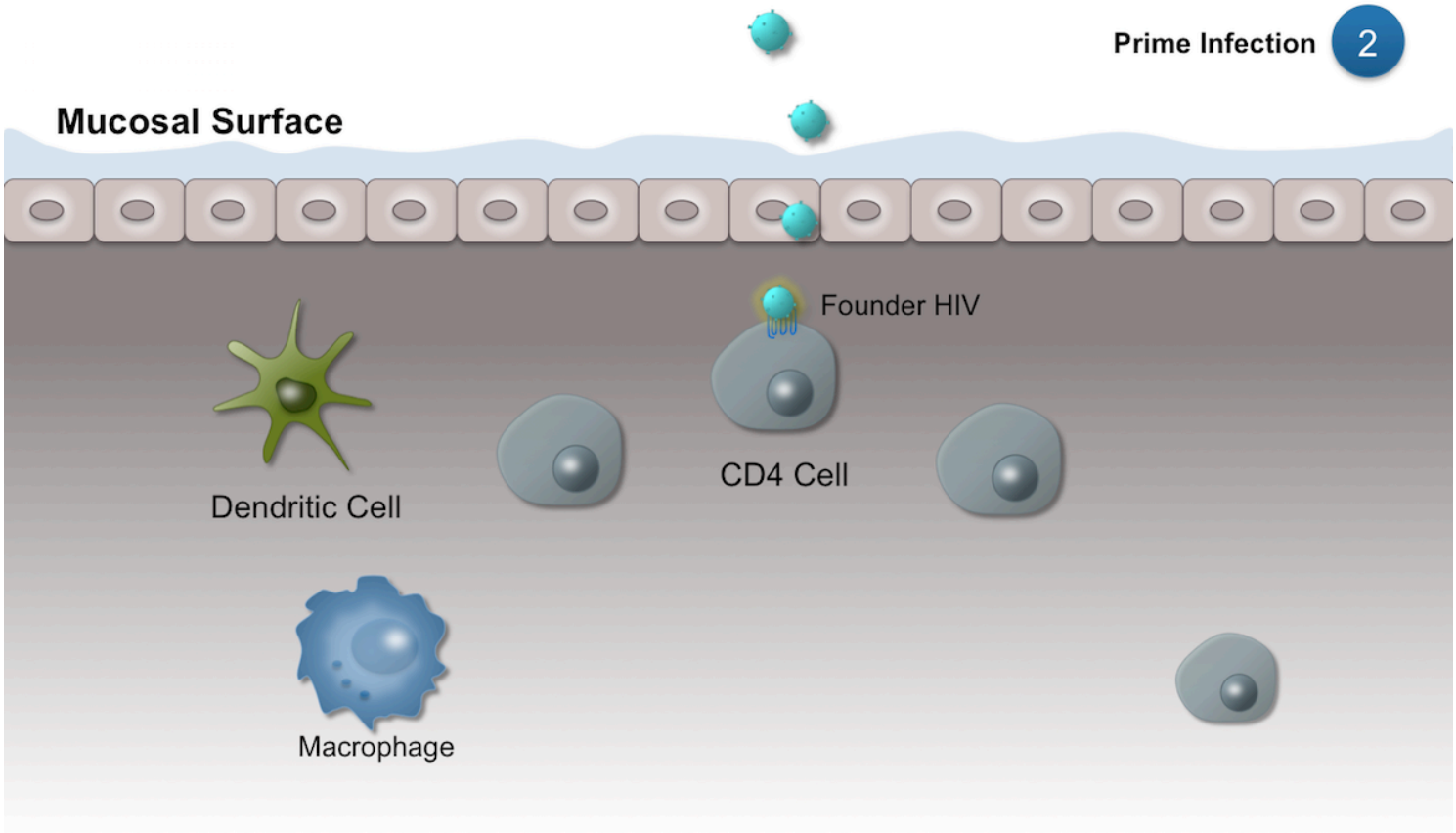

Figure 5 (Image Series) - Model for Sexual Transmission of HIV
Image 5C: Initial Propagation with Small HIV Founder Population

Illustration: David H. Spach, MD

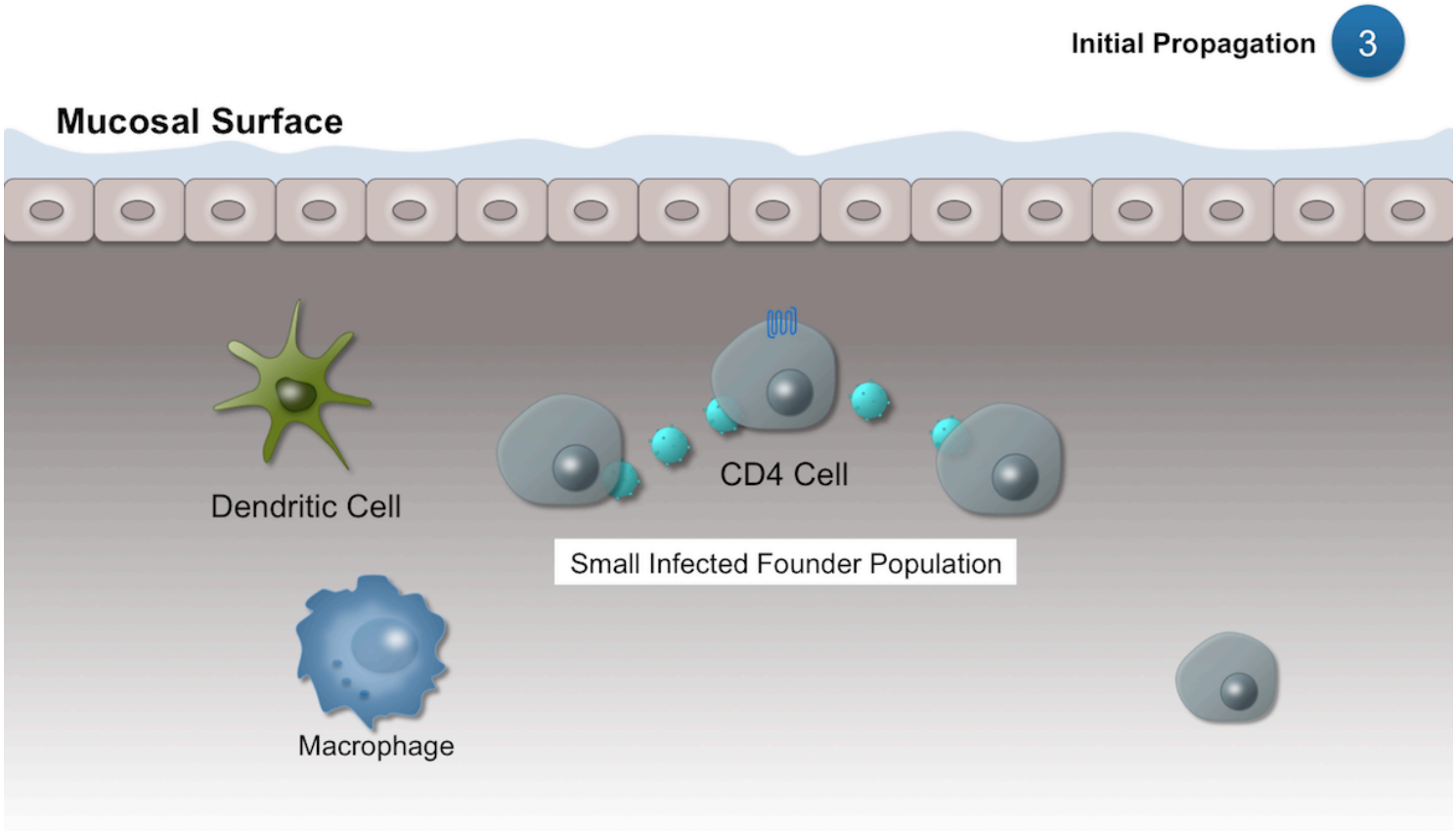

Figure 5 (Image Series) - Model for Sexual Transmission of HIV
Image 5D: Local Expansion

Illustration: David H. Spach, MD

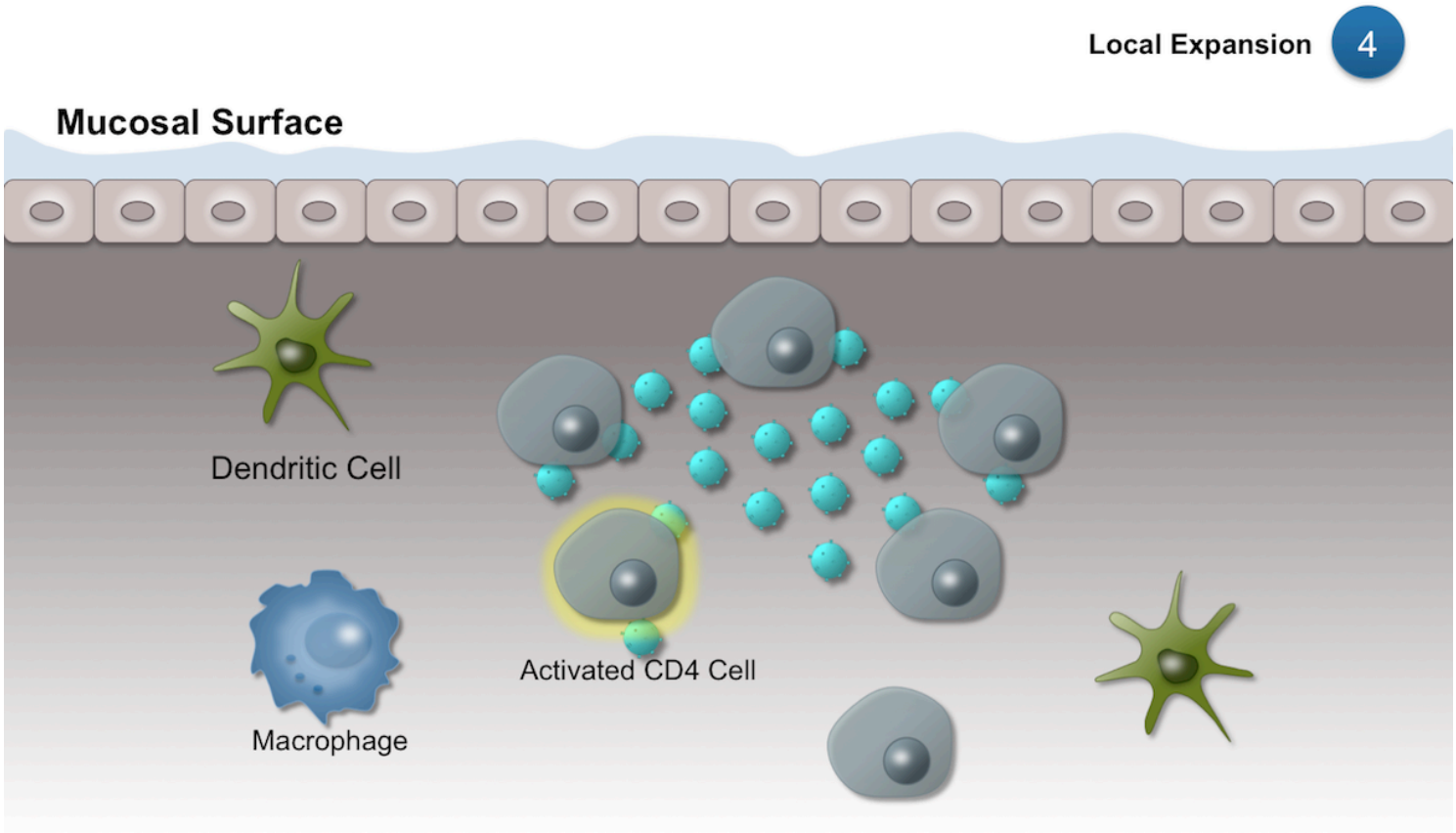

Figure 5 (Image Series) - Model for Sexual Transmission of HIV
Image 5E: Regional Lymphatic Spread

Illustration: David H. Spach, MD

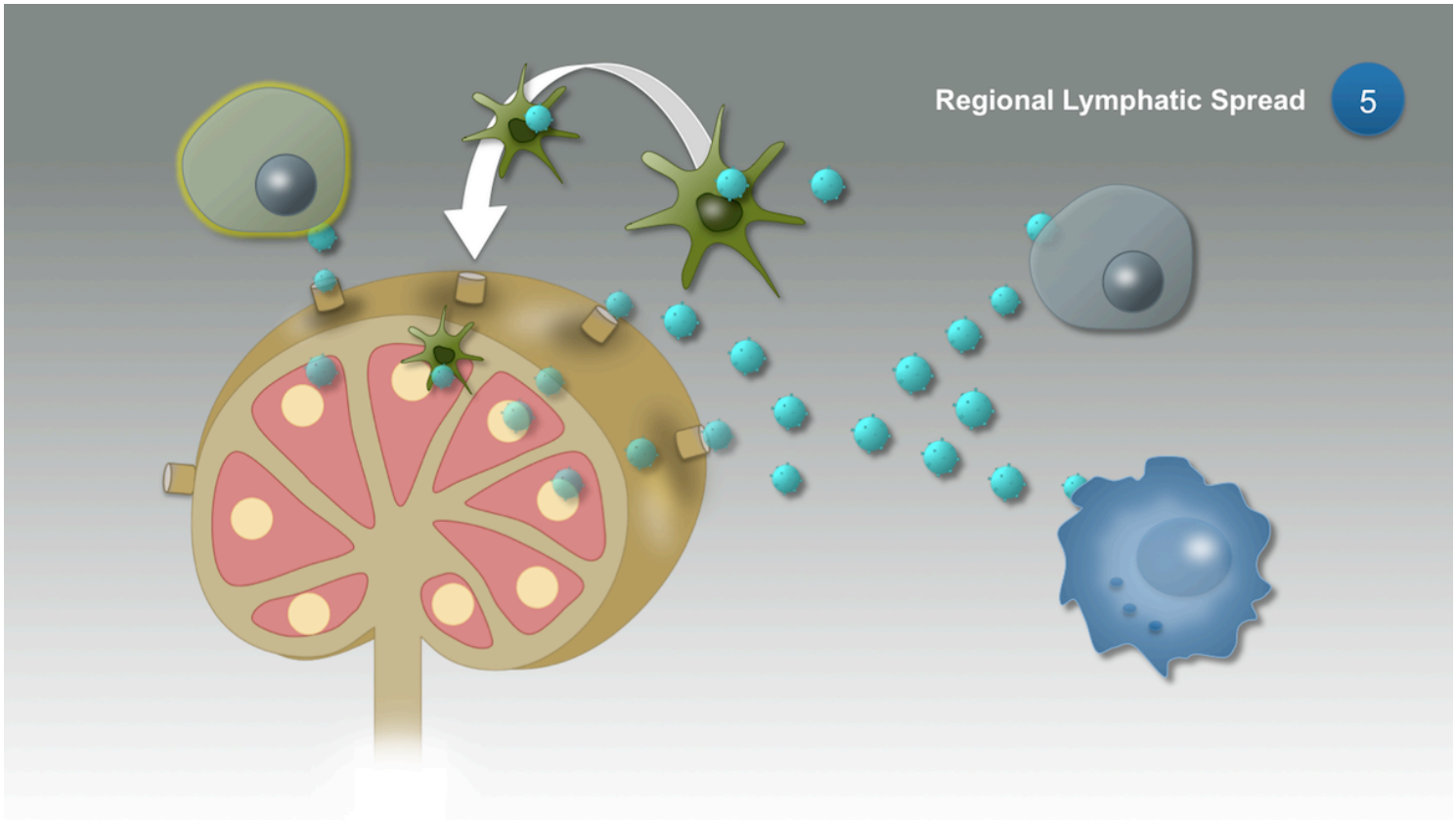

Figure 5 (Image Series) - Model for Sexual Transmission of HIV
Image 5F: Hematogenous Spread

Illustration: David H. Spach, MD

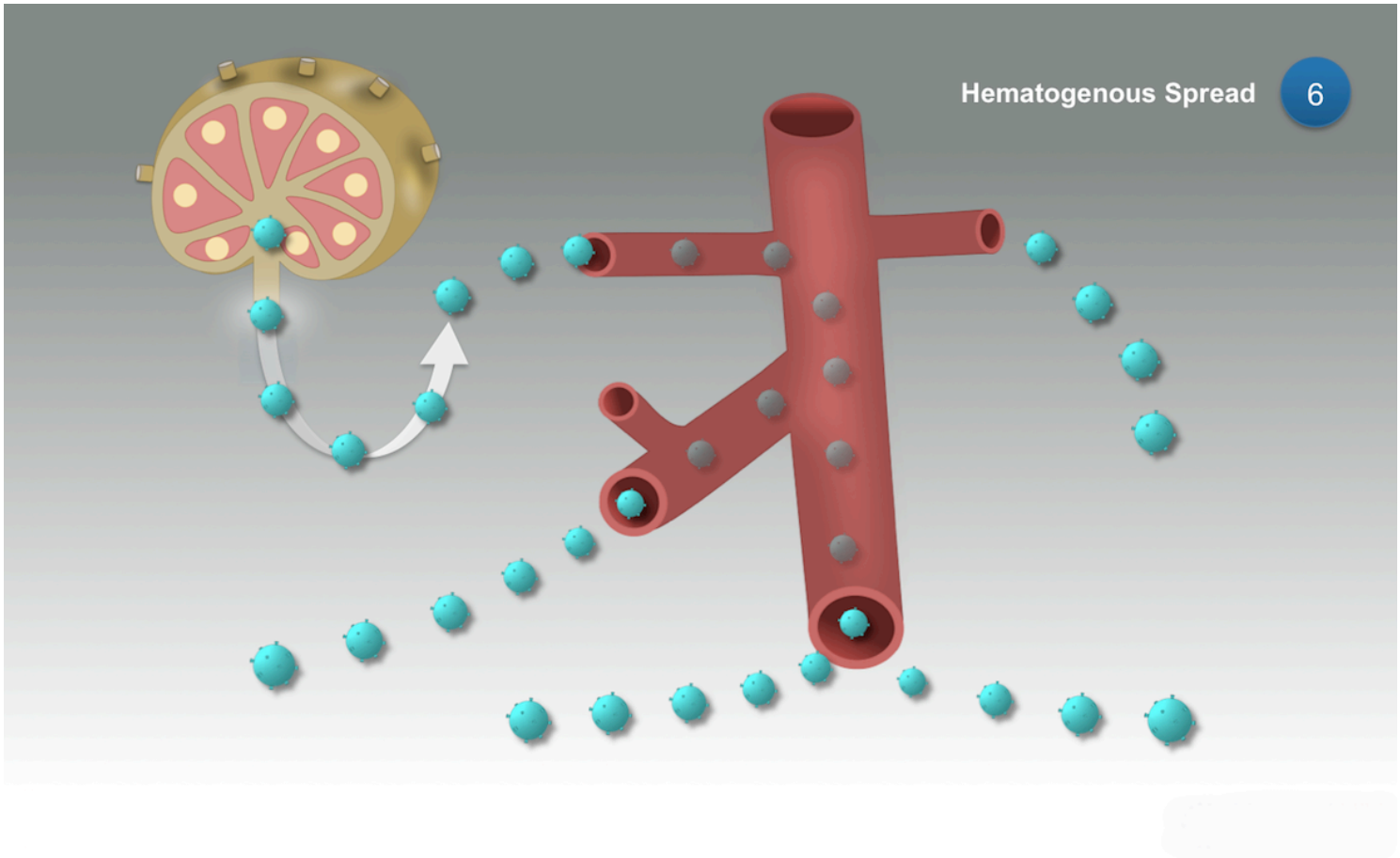

Figure 6 Founder Virus

Source: Keele BF, Giorgi EE, Salazar-Gonzalez JF, et al. Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. Proc Natl Acad Sci U S A. 2008;105:7552-7.
Illustration: David H. Spach, MD

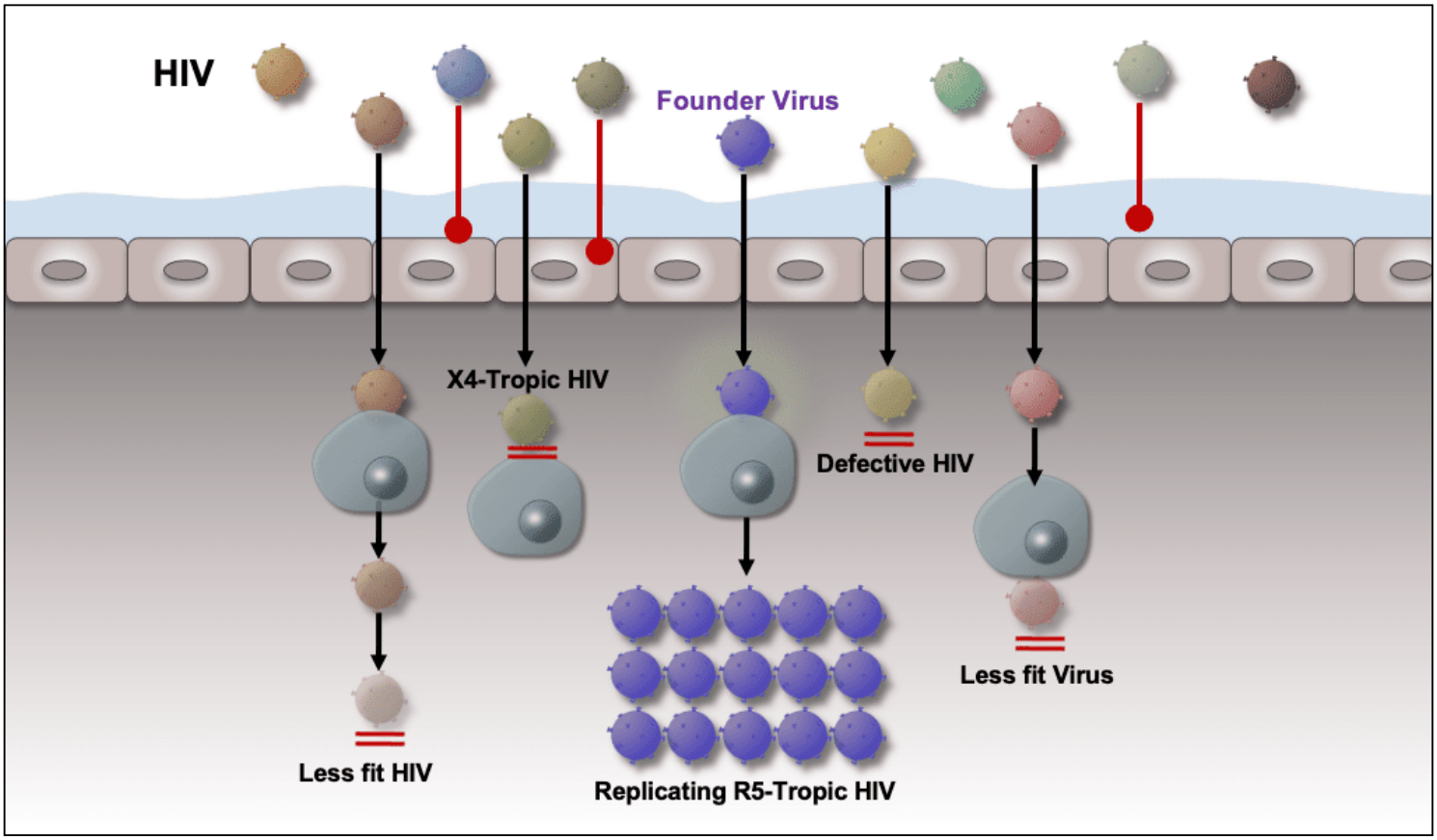

Figure 7 Set Point Following Acquisition of HIV

Illustration: David H. Spach, MD

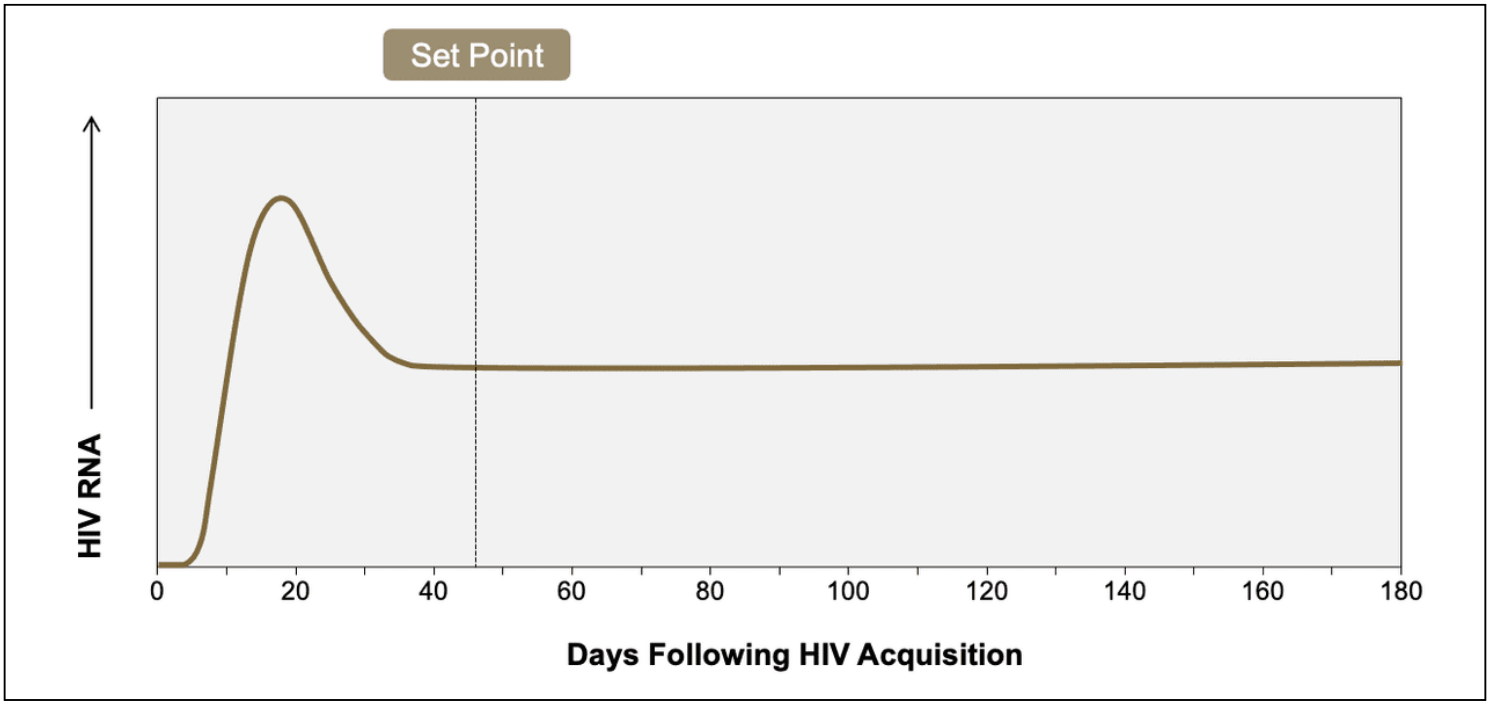

Figure 8 Cytotoxic T-Lymphocyte Response Following Acute HIV Infection

Source: Walker BD, Goulder PJ. AIDS. Escape from the immune system. Nature. 2000;407:313-4.Illustration: David H. Spach, MD

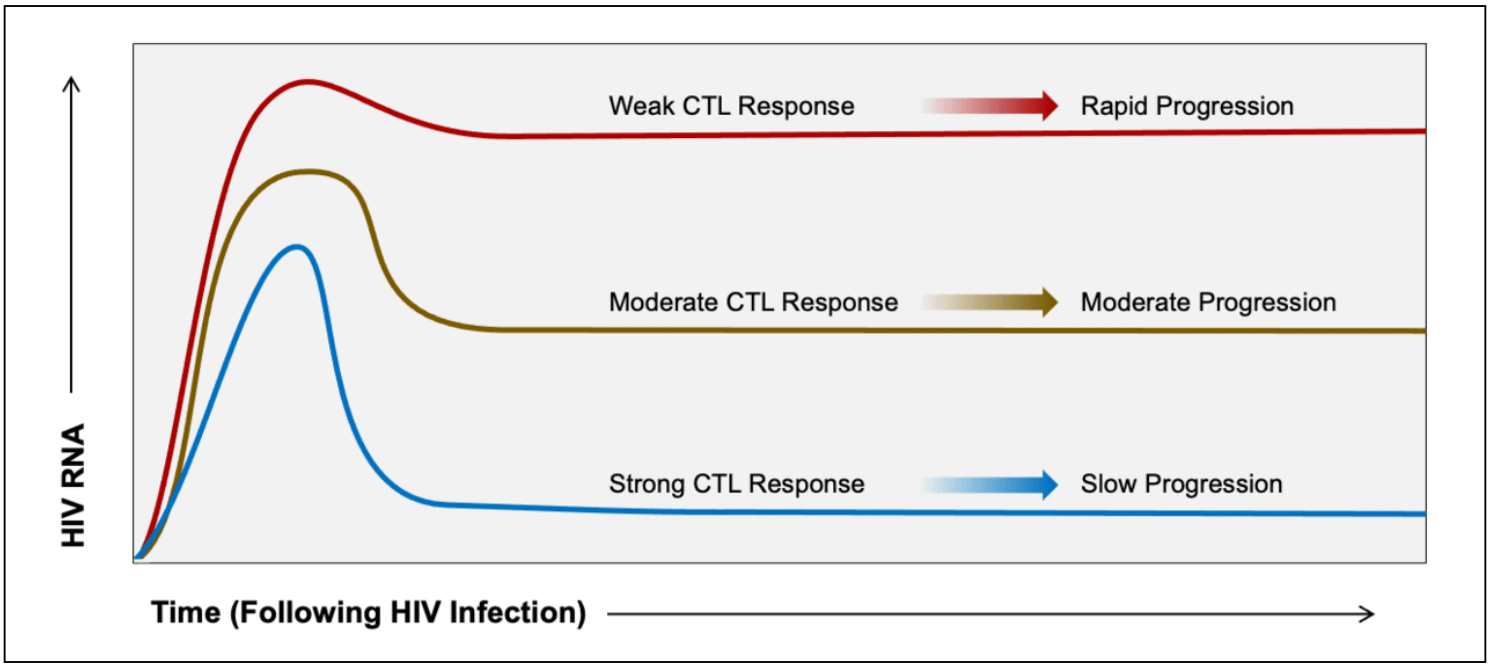

Figure 9 Acute HIV: Skin Rash

Source: photograph by David H. Spach, MD

Figure 10 Fiebig Laboratory Staging of Early HIV Infection

Source: Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS. 2003;17:1871-9.

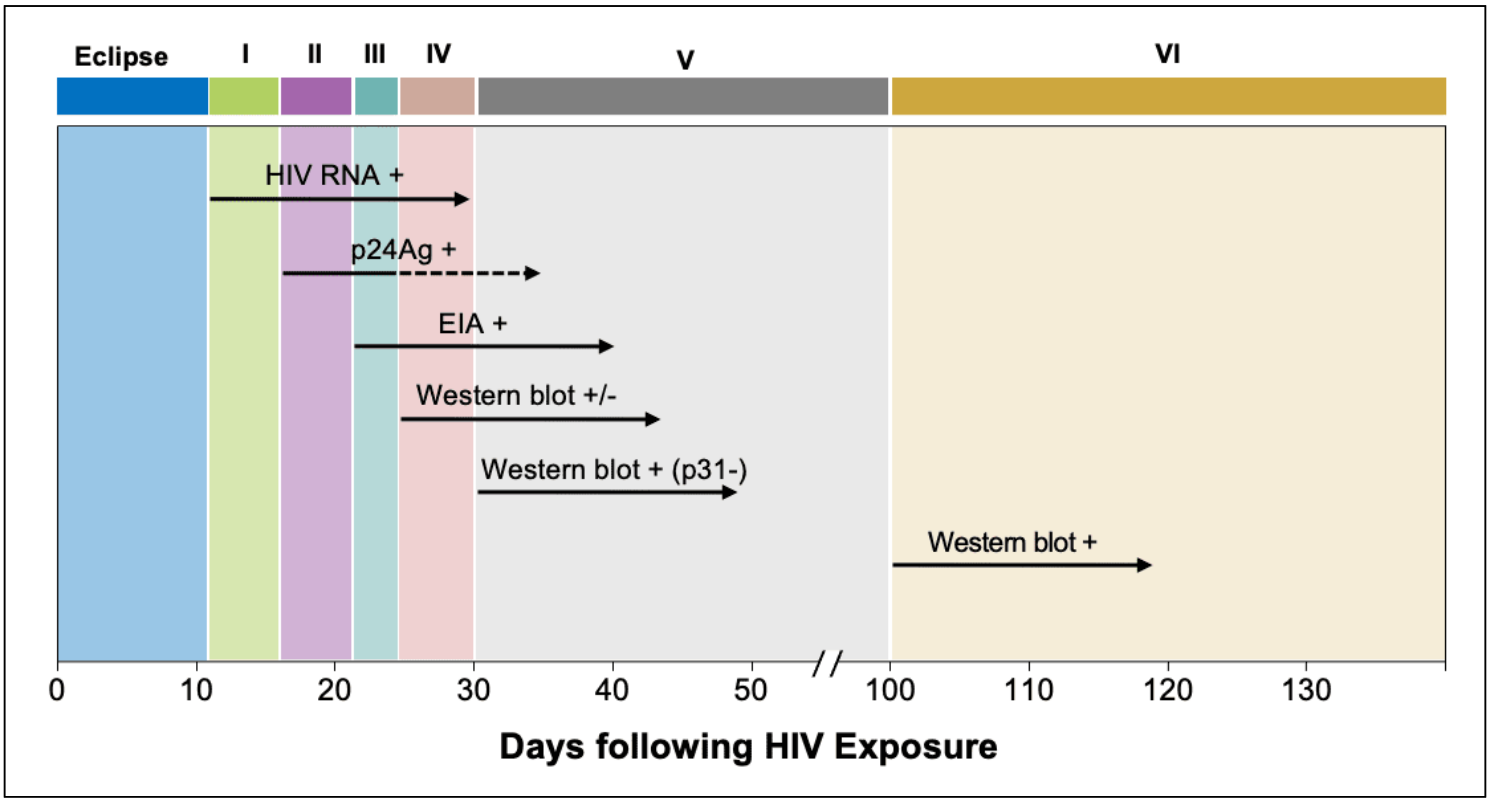

Figure 11 Timing of Positivity for HIV Diagnostic Tests Following Initial HIV Infection

Abbreviation: POC = point-of-care

Source: Illustration by David H. Spach, MD and modified from Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. Published June 27, 2014.

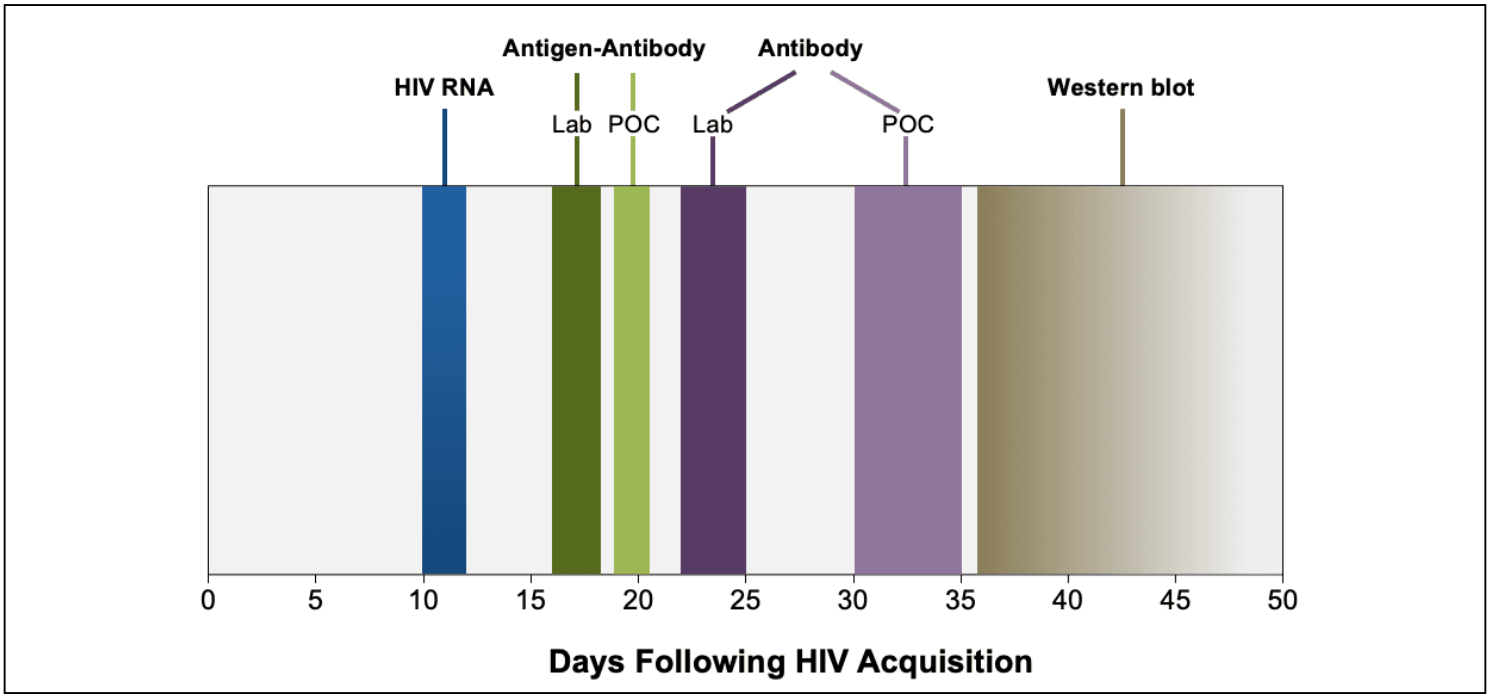

Figure 12 HIV Laboratory Testing Algorithm As Recommended by the CDC and APHL

The rectangles highlighted with yellow border indicate the expected positive tests in a person with acute HIV.

Source: 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.

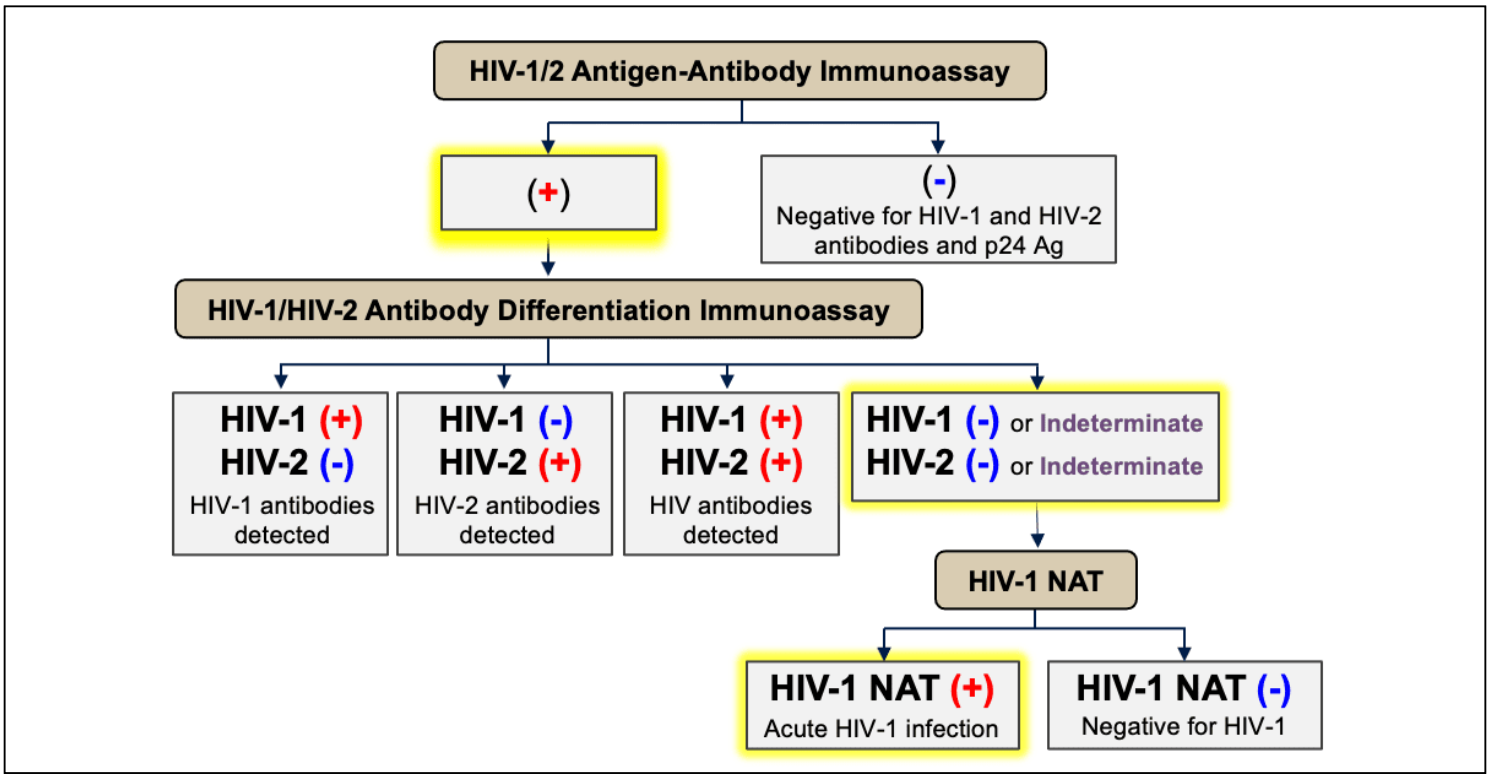

Figure 13 Risk of Sexual Transmission of HIV During Early Infection

Source: Pilcher CD, Tien HC, Eron JJ Jr, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis. 2004;189:1785-92.

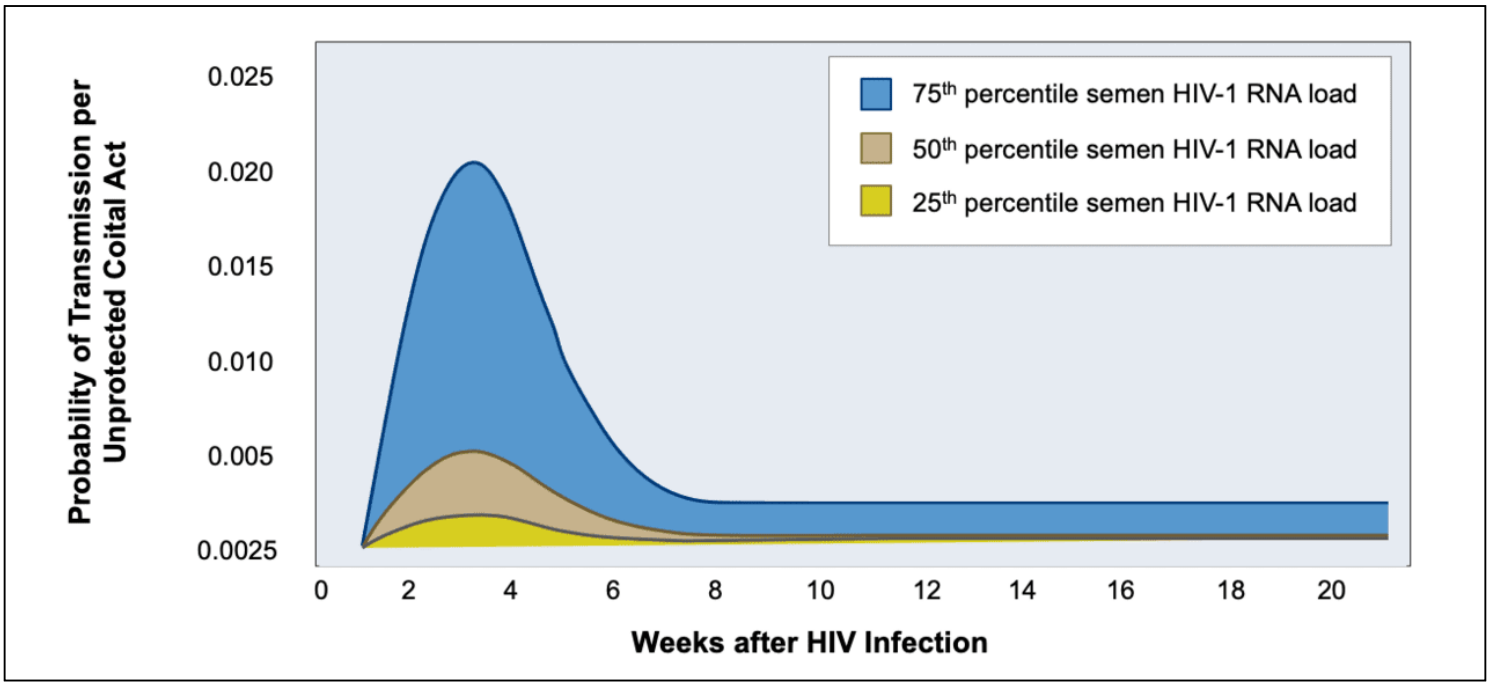

Table 1.

Clinical Signs and Symptoms of Acute HIV Infection

Features (%)	Overall (n=375)	Sex		Route of Transmission	
		Male (n = 355)	Female (n = 23)	Sexual (n = 324)	IDU (n = 34)
Fever	75	74	83	77	50
Fatigue	68	67	78	71	50
Myalgia	49	50	26	52	29
Skin rash	48	48	48	51	21
Headache	45	45	44	47	30
Pharyngitis	40	40	48	43	18
Cervical adenopathy	39	39	39	41	27
Arthralgia	30	30	26	28	26
Night sweats	28	28	22	30	27
Diarrhea	27	27	21	28	23

IDU = Injection drug use

Source:

- US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 Update. A Clinical Practice Guideline. March 2018:1-77. [CDC]

Table 2. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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 goals of antiretroviral therapy 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 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 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).
- For those with a history of long-acting injectable cabotegravir use as HIV PrEP, genotype testing done before the start of antiretroviral should include screening for integrase strand transfer inhibitor (INSTI)-resistance mutations:
  - A regimen of boosted darunavir with (tenofovir alafenamide or tenofovir DF)[b] plus (emtricitabine or lamivudine) is recommended—pending the results of the genotype testing (AIII).
  - 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 injectable cabotegravir as HIV PrEP.
- Pregnancy testing should be performed in women of childbearing potential before initiation of antiretroviral therapy (AIII).
- When the results of drug-resistance tests are available, the treatment regimen can be modified if needed (AII).
- Providers should inform individuals starting antiretroviral therapy 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. Special Populations. Early (Acute and Recent) HIV Infection. September 12, 2024. [HIV.gov]