Perspective

Treatment of Acute HIV Infection and the Potential Role of Acutely HIV-Infected Persons in Cure Studies

Diagnosis of acute HIV infection is important for accurate estimation of HIV incidence, identifying persons who are unaware of their HIV infection, and offering immediate treatment and risk-reduction strategies. The higher viral loads associated with acute HIV infection are associated with an increased risk of transmission. Current treatment recommendations are the same for acute and established infections. Studies of acute HIV infection indicate that initiation of antiretroviral therapy during this period may allow greater recovery of CD4+ T-cell count and function and may result in a smaller latent viral reservoir and a skewing of infection away from central memory CD4+ T cells toward shorter-lived transitional memory CD4+ T cells. This article summarizes a presentation by Susan J. Little, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, *held in Los Angeles, California, in April 2015.*

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Acute HIV infection is defined as the earliest phase of infection following acquisition of virus and before seroconversion (ie, the period in which the patient is HIV RNA positive and antibody negative). The duration of this phase varies depending on the diagnostic assays used to detect infection. Acute HIV infection is characterized by a markedly elevated peak viral load in blood and genital secretions. Screening for acute HIV infection is not routinely performed, primarily because of difficulties in case finding and cost of the diagnostic assays. Diagnosis of acute HIV infection is dependent on direct detection of virus through testing for the p24 antigen or increasingly through nucleic acid testing (or test; NAT), although there are currently no point-of-care HIV NATs approved by the US Food and Drug Administration (FDA) for HIV diagnosis, and the only FDA-approved diagnostic assay for detecting the p24 antigen has poor sensitivity for detecting acute HIV infection.[1]

Importance of Diagnosing Acute HIV Infection

Data vary regarding the influence of acute HIV infection on HIV transmission, but it has been estimated that 25% to 50% of HIV transmission is associated with sexual exposure to an individual with acute infection.[2-4] Plasma viral load is the greatest predictor of HIV transmission risk, with higher viral load associated with higher risk of transmission. However,

the greater infectivity of persons with acute HIV infection may not be exclusively related to higher plasma viral load levels. Ma and colleagues demonstrated that plasma from macaques with acute simian immunodeficiency virus (SIV) infection was at least 750 times more infectious per virion than plasma from macaques with chronic SIV infection.[5] This difference may be related in part to the absence of neutralizing antibodies in the acutely infected animals; the addition of heat-inactivated plasma to plasma from acutely infected macaques blocked infection.

The laboratory screening algorithm to detect acute or chronic HIV infection published in 2014 recommends the use of a fourth-generation HIV-1/2 antigen/antibody combination assay to initiate HIV screening (Figure 1).[6] A negative result on an antigen/antibody test indicates an absence of HIV infection within approximately the last 17 days (ie, the window period for detection of HIV-1 p24 antigen, a structural protein product of the HIV-1 *gag* gene).[7] Because a positive result on an antigen/antibody test does not differentiate antibody from antigen (only 2 fourth-generation assays were FDA approved when the laboratory testing algorithm was being developed in 2011), the sample is then tested using an HIV-1/2 antibody differentiation immunoassay, which has replaced the Western blot from earlier testing algorithms, to differentiate HIV-1 antibodies from HIV-2 antibodies. If results are negative for antibody, an NAT is performed, with a positive result indicating acute infection.

In contrast to the laboratory HIV screening algorithm, field-based HIV screening methods rely primarily on point-of-care assays that do not typically detect acute HIV infection (the sensitivity of the HIV-1/2 antigen/antibody point-of-care combination assay approved by the FDA in 2013 does not support its use for detection of acute HIV infection[1]). For example, a positive rapid antibody test result could be confirmed using a fourth-generation immunoassay followed by an HIV-1/2 antibody differentiation immunoassay, but this algorithm would not detect acute HIV infection in persons who are HIV antibody negative. A challenge for field-based screening programs that wish to identify persons with acute HIV infection is the decision regarding use of alternative testing for those who are antibody negative. The decision depends somewhat on the risk level of a population, the cost of the diagnostic assays, and the prevalence of acute infection in the population (likely unknown in settings in which screening for acute infection has not been performed). Although there is 1 FDA-approved fourth-generation point-of-care assay, it is substantially less sensitive than the fourth-generation assays approved for use in the laboratory screening algorithm (Figure 1). The overall prevalence of HIV infection is not well correlated with the prevalence of acute infection, as

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suggested by the yield of acute HIV screening programs in many international settings.[8] Thus, a relatively low overall HIV prevalence does not indicate that screening for acute infection is unnecessary. There are many point-of-care NATs in development that may markedly simplify and improve point-of-care screening approaches for acute HIV infection.

Detection of acute HIV infection is crucially important for 1) accurate estimation of HIV incidence; 2) identifying persons who are unaware of their infection; 3) offering immediate treatment and risk-reduction strategies; 4) identifying HIV transmission hot spots (geographic regions with high HIV transmission rates); and 5) tailoring prevention services to individual behaviors and risks associated with acute infection.

Treatment of Acute HIV Infection

According to current guidelines on antiretroviral therapy from the US Department of Health and Human Services and the IAS–USA, antiretroviral therapy is recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV transmission.[9,10] Persons initiating antiretroviral therapy should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence.

Data on treatment as prevention demonstrate that earlier versus later initiation of antiretroviral therapy substantially reduces the risk of HIV transmission. Mathematical models of the impact of increasing use of antiretroviral therapy on population HIV incidence (new infections by country) further support treatment as prevention as a strategy to reduce HIV transmission. Preliminary estimates from 53 low- and middle-income countries demonstrate a correlation between antiretroviral therapy coverage (the percentage of all people living with HIV infection who are receiving antiretroviral therapy) and population HIV incidence.[11] Additionally,

a South African study recently reported a 1.1% reduction in HIV incidence for every 1% increase in antiretroviral therapy coverage.[12]

Recommended antiretroviral regimens do not differ for treatment of acute and established HIV infections. Recommended initial regimens are the integrase strand transfer inhibitor–based regimens of 1) dolutegravir, abacavir, and lamivudine (only in individuals who are negative for the HLA-B*5701 allele); 2) dolutegravir plus tenofovir disoproxil fumarate and emtricitabine; 3) elvitegravir, cobicistat, tenofovir disoproxil fumarate, and emtricitabine (only if baseline creatinine clearance > 70 mL/min); 4) elvitegravir, cobicistat, tenofovir alafenamide, and emtricitabine (the fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide was approved for use in antiretroviral therapy–naive persons in November 2015); and 5) raltegravir plus tenofovir disoproxil fumarate and emtricitabine; and the protease inhibitor–based regimen of ritonavir-boosted darunavir plus tenofovir disoproxil fumarate and emtricitabine.[9] Genotypic drug-resistance testing is recommended regardless of whether antiretroviral therapy is initiated immediately or is deferred.[10]

In the SPARTAC (Short Pulse Antiretroviral Therapy at Seroconversion) study, which investigated when to initiate treatment for newly HIV-infected persons (< 6 months), 2 short-course antiretroviral regimens of 12 weeks and 48 weeks were compared with no immediate treatment, the standard of care at the time for this population.[13] The primary end point was the combined measure of time to a CD4+ cell count of less than 350/μL or initiation of long-term antiretroviral therapy. The 48-week regimen (hazard ratio [HR], 0.63; $P = .01$) but not the 12-week regimen (HR, 0.93; $P = .67$) was associated with a significant delay in time to the primary end point compared with no immediate treatment. However, the delay in progression with the 48-week regimen was roughly equivalent to the time spent on treatment, arguing against any benefit to be gained by interrupting treatment. There was no evidence of adverse outcomes in terms of drug resistance or impaired CD4+ cell recovery after initiation of long-term antiretroviral therapy.

Researchers in San Diego, California, performed a retrospective study to determine if there is a crucial period following acute HIV infection during which initiation of antiretroviral therapy can maximize the potential for restoration of normal immune function.[14] The study included 468 recently infected, antiretroviral therapy–naive individuals in whom CD4+ cell count trajectories were observed over 48 months during which some initiated therapy. An estimated date of infection was calculated for each participant using virologic and serologic data at time of presentation. A total of
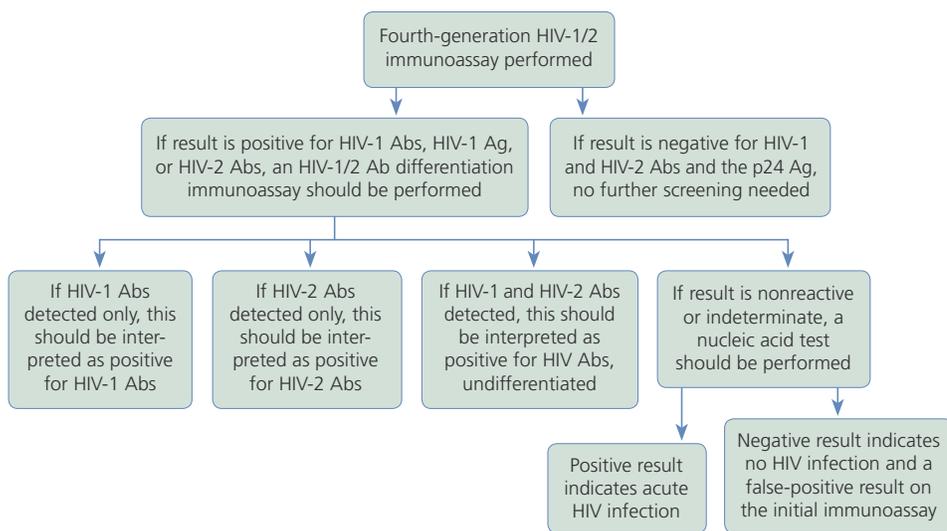

Figure 1. Laboratory screening algorithm for diagnosis of HIV infection. Ab indicates antibody; Ag, antigen. Adapted from Centers for Disease Control and Prevention.[6]
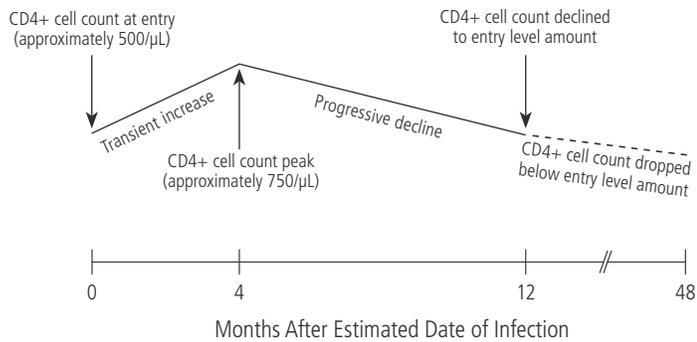
Figure 2. Changes in CD4+ cell count following estimated diagnosis of HIV infection in individuals who did not initiate antiretroviral therapy. Adapted from Le et al.[14]

136 remained antiretroviral therapy naive for the duration of the study, and the remainder initiated therapy. Among those who did not initiate immediate therapy, mean CD4+ cell count spontaneously increased from approximately 500/µL at baseline to approximately 750/µL in approximately 4 months (a period during which natural immunologic recovery appeared to be occurring) followed by a progressive decline (Figure 2). Outcomes were assessed in 6 groups, based on the timing of initiation of antiretroviral therapy and the CD4+ cell count at the time therapy was initiated. Individuals in groups 1 and 4 initiated therapy within 4 months of the estimated date of HIV infection, at CD4+ cell counts above 500/µL and below 500/µL, respectively; those in groups 2 and 5 initiated therapy between 4 months and 12 months after the estimated date of HIV infection, at CD4+ cell counts above 500/µL and below 500/µL, respectively; and those in groups 3 and 6 initiated therapy more than 12 months after the estimated date of HIV infection, at CD4+ cell counts above 500/µL and below 500/µL, respectively. A normal CD4+ cell count was defined as 900/µL or higher. Based on the hypothesis that initiation of antiretroviral therapy during this period might improve immunologic recovery, outcomes were compared among groups of individuals who exhibited durable viral suppression after initiation of therapy (Figure 3). Individuals who initiated therapy within 4 months of HIV infection at CD4+ cell counts above 500/µL exhibited a robust early CD4+ cell response, and individuals who initiated therapy within 12 months of HIV infection at CD4+ cell counts above 500/µL eventually achieved similar CD4+ cell counts of 900/µL or greater. The individuals who initiated therapy within 4 months of HIV infection, but at a starting CD4+ cell count below 500/µL, demonstrated a statistically significantly lower potential for achieving a normal CD4+ cell count within the study period.

Overall, the study showed that the probability of achieving a CD4+ cell count above 900/µL while taking antiretroviral therapy was greatest for those who initiated therapy within 4 months of the estimated date of HIV infection with a CD4+ cell count of greater than 500/µL. Each month that antiretroviral therapy was delayed reduced the probability of achieving a normal CD4+ cell count by approximately 10%;

the probability of achieving a normal CD4+ cell count was reduced by 94% if CD4+ cell count was below 500/µL at the time of initiation of antiretroviral therapy, regardless of the estimated date of HIV infection. Overall, less than 25% of antiretroviral therapy–naive individuals maintained a CD4+ cell count of 500/µL or higher for more than 12 months after their estimated date of infection.

Treatment of Acute Infection and HIV Cure

An unanswered question related to the timing of antiretroviral therapy during acute HIV infection is whether earlier initiation of antiretroviral therapy might help limit the latent viral reservoir. Viral latency is established early and preferentially in nondividing and minimally activated cells. Only a small fraction of resting memory CD4+ T cells carry integrated viral genomes, and levels of latently infected cells remain relatively stable during antiretroviral treatment.[15,16] A subset of latently infected cells may persist indefinitely, even in individuals who initiate antiretroviral therapy during acute HIV infection.[17]

One case that initially raised hope of eradication or spontaneous control of the latent viral reservoir was that of the Mississippi baby.[18] The baby's mother was diagnosed with HIV infection during labor, and the newborn infant was found to be HIV infected at 30 hours of life. Antiretroviral treatment with zidovudine, lamivudine, and nevirapine was initiated at 30 hours of life and at 1 week of life was switched to zidovudine, lamivudine, and ritonavir-boosted lopinavir. The baby achieved an undetectable viral load at day 30 and maintained viral suppression during follow-up. The mother discontinued the child's therapy sometime between 15 months and 18 months, after which the infant continued to exhibit viral suppression. Unfortunately, the child's HIV RNA level rebounded to 16,000 copies/mL at 27 months. In retrospect, single-copy levels of HIV RNA were observed at months 24 and 26 and HIV DNA was detected at 24 weeks. Thus, although the virus was not eradicated, this case does suggest that sustained virologic control might be achieved by very early initiation of antiretroviral treatment in at least some individuals even after interruption of therapy.

The VISCONTI (Viro-Immunological Sustained Control after Treatment Interruption) cohort comprises participants from French studies who exhibited posttreatment virologic control.[19] To be considered posttreatment controllers, individuals had to be identified during acute HIV infection (before development of the immunoglobulin M antibody), had to initiate antiretroviral treatment within the first 3 months of infection, and had to continue treatment for at least 24 months. A total of 14 individuals who had initiated antiretroviral therapy early, achieved rapid and sustained virologic suppression, and maintained durable suppression of viremia for several years after stopping therapy were identified. Overall, these individuals had an undetectable viral load at a median of 3 months of antiretroviral therapy (0.5 months to <8 months) and a median duration of therapy of 36.5 months. Most of these posttreatment controllers lacked the
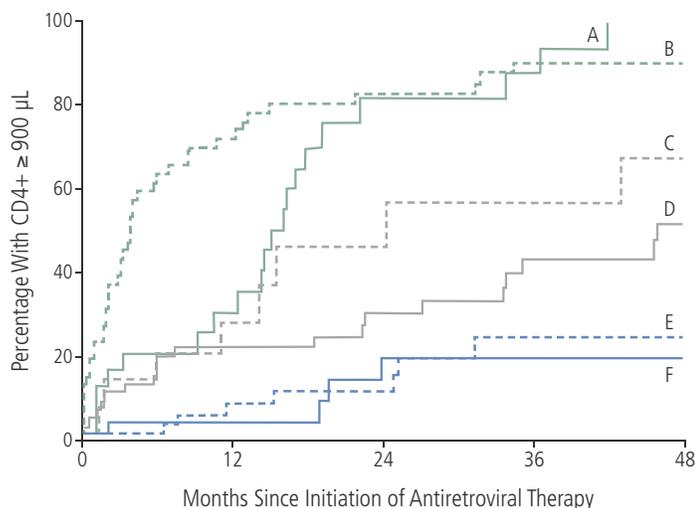
Figure 3. CD4+ cell count recovery in HIV-infected individuals who initiated antiretroviral therapy within 4 months of estimated date of infection (EDI) at CD4+ cell counts (A) above 500/μL or (D) below 500/μL; 4 months to 12 months after EDI at CD4+ cell counts (B) above 500/μL or (E) below 500/μL; or more than 12 months after EDI at CD4+ cell counts (C) above 500/μL or (F) below 500/μL. Adapted from Le et al.[14]

protective HLA-B*5701 allele overrepresented in individuals who spontaneously control HIV. The viral reservoirs in the posttreatment controllers had lower total levels of HIV DNA than those found in individuals who did not exhibit post-treatment control, with lower levels of integrated HIV in their naive CD4+ T-cell populations and a skewed distribution of infection toward shorter-lived transitional memory CD4+ T cells within the resting memory CD4+ cell population.

A similar finding regarding the potential skewing of infection to shorter-lived memory CD4+ T cells was observed in the RV254/SEARCH010 study (a collaboration of the US Military HIV Research Program and the South East Asia Research Collaboration with Hawaii [SEARCH]) in Thailand in which acutely HIV-infected participants initiate antiretroviral therapy at diagnosis of HIV infection.[20] Initiation of antiretroviral therapy within 2 weeks of infection was associated with undetectable HIV DNA in long-lived memory CD4+ T cells in 100% of participants, compared with 63% of participants who initiated therapy at 2 weeks to 4 weeks and 0% of participants who initiated therapy at 24 weeks or later. These findings suggest that earlier treatment limits persistence of virus in long-lived central memory CD4+ T cells.

Conclusion

It is unclear whether or to what degree antiretroviral treatment during acute HIV infection might lead to HIV cure. Most individuals are infected with a single viral variant or a few highly related variants, and ensuing viral genetic diversity in those who do not begin antiretroviral treatment makes attempts at immunologic interventions (eg, vaccines) and antiretroviral therapy more challenging. HIV-specific CD4+

cell responses may be preserved by early antiretroviral therapy, and early therapy may result in diminished levels of persistent immune activation. Although HIV reservoirs may become smaller with earlier antiretroviral treatment, infection generally persists in memory CD4+ T cells. However, antiretroviral therapy during acute HIV infection may protect central memory CD4+ T cells from infection and may skew the distribution of latently infected cells to shorter-lived memory CD4+ T cells.[17] Even if early antiretroviral treatment cannot effect a cure, individuals treated during acute infection should prove the best candidates for HIV cure interventions, because they have smaller viral reservoirs and better-preserved immune systems than individuals who initiate antiretroviral therapy later during infection.

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