Primary HIV Type 1 Infection

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Emerging evidence suggests that early events in human immunodeficiency virus type 1 (HIV-1) infection may play a critical role in determining disease progression. Although there is limited evidence on which to base medical decisions, the diagnosis and treatment of acute HIV-1 infection may have virologic, immunologic, and clinical benefits. In addition, rapid diagnosis of infection may prevent unknowing transmission of HIV-1 during a period of high-level viremia. We review the basic principles of primary HIV-1 infection, clinical and diagnostic markers of acute seroconversion, approaches to management, and new therapeutic strategies.

EARLY EVENTS

Infection with HIV type 1 (HIV-1) typically occurs across mucosal surfaces or by direct inoculation. The virus first encounters dendritic cells (DCs), which subsequently facilitate spread of HIV-1 to CD4+ T lymphocytes. DC-SIGN, an HIV-specific DC receptor, binds HIV-1 at its gp-120 domain without requiring direct infection of the cell, and transports HIV-1 to lymphoid tissue [1]. Infected and uninfected cells traffic to regional lymph nodes, where HIV-1 resides and replicates for days to weeks [2, 3]. DCs act as potent antigen-presenting cells, priming naive T cells and enabling rapid infection of T cells.

HIV-1 entry into host cells requires docking and binding at 2 separate sites: the CD4+ T cell receptor and a 7-transdomain chemokine coreceptor. Genetic mutations in the CCR5 coreceptor have afforded relative protection from infection with macrophage-tropic strains of HIV-1 in both homozygous and heterozygous individuals [4]; highly exposed and persistently seronegative patients have been shown to carry the CCR5Δ32 genotype more frequently [5]. This mutation has been associated with slower disease progression and is more prevalent among patients with long-term nonprogressive disease than among those with progressive disease [4].

Once HIV-1 infects a cell, the virus integrates into host genetic material and either begins cycles of replication or remains inactive, causing latent infection in cellular reservoirs. The dissemination of HIV-1 into cellular and anatomic sanctuaries such as the CNS occurs early in infection [6, 7]. Several studies have confirmed the presence of replication-competent virus reservoirs in resting CD4+ T cells, lymphoid tissue, and other sequestered sites in patients receiving potent antiretroviral therapy (ART) [8, 9]. Rapid viral replication in actively infected cells results in widespread dissemination. Estimated time to initial viremia has been reported to be as early as 4–11 days [3]; clinically detectable viremia may be more delayed.

During the period of rapid replication, the host immune response attempts to control dissemination and eradicate the virus. Peak viremia can reach levels of several million viral copies, which is higher than any other period during the natural history of infection [3]. Activation of HIV-1–specific cytotoxic T lymphocytes (CTLs) appears to be a critical immunologic response, and their emergence is temporally associated with a decreased HIV-1 load [2, 10, 11].

Primary HIV-1 infection (PHI) involves a highly dynamic relationship between virus and host. The development of symptoms of acute retroviral syndrome typically coincides with high-level viremia and the host’s initial immunologic response. Although the exact mechanisms causing clinical symptoms are not known, theories include direct cytopathic effects of the virus and/or immune-mediated toxicity. The classic mononucleosis-like symptoms of acute HIV-1 infection may last several days to several weeks. The formation of HIV-1–specific antibodies marks the completion of seroconversion; antibodies are generally detectable by weeks 3–12 of infection but may take up
to 6–12 months to form [12]. Acute HIV infection is typically defined as the time from virus entry to completion of seroconversion. Early-stage HIV infection is less well defined but generally refers to the interval between seroconversion and the establishment of the virus load set point, which usually occurs 6–12 months after infection. The magnitude of the virus load set point is prognostic for disease progression [13].

**PRESENTING SYNDROMES**

It is estimated that 40%–90% of patients with PHI experience an acute retroviral syndrome [3, 6]. Symptoms typically occur 2–6 weeks after exposure to HIV-1 and commonly include fever, fatigue, pharyngitis, weight loss, night sweats, lymphadenopathy, myalgias, headache, nausea, and diarrhea [3, 6, 14]. Leukopenia, thrombocytopenia, or mild transaminitis are frequently associated laboratory findings; however, these are nonspecific findings and are only supportive of the diagnosis. Rash or mucosal ulcers in patients with a mononucleosis-like illness can offer important clues in the presence of specific epidemiologic factors. Neurological presentations include aseptic meningitis (present in 24% of patients in one series [6]), CN VII palsy, and radiculopathy. Other unusual presentations of PHI include myopericarditis, acute renal failure, and opportunistic infections such as candidiasis, cytomegalovirus infection, and *Pneumocystis jirovecii (Pneumocystis carinii)* pneumonia. The significance of the relative severity of seroconversion symptoms is not known, but presence of seroconversion symptoms has been correlated with more-rapid disease progression [3, 7]. Seroconversion symptoms typically last 14 days but may persist for as long as 10 weeks [6].

The nonspecific nature of acute symptoms of PHI often makes the diagnosis challenging. In a cohort of 46 patients with PHI, >85% sought medical attention for acute retroviral syndrome in various settings, including primary care facilities (48%), urgent care facilities (21%), and emergency departments (31%) [6]. Of note, only 25% received a correct diagnosis. The differential diagnosis is broad (figure 1), and a high index of suspicion is necessary to obtain appropriate history; to perform appropriate risk factor assessment and thorough physical examination, with attention to diagnostic “flags” associated with acute HIV-1 disease (such as rash, mucosal ulcers, pharyngitis, generalized lymphadenopathy, and abnormal neurologic findings); and to order appropriate diagnostic tests.

**DIAGNOSIS**

Testing strategies for PHI are based on the temporal events in the natural history of acute infection. Because antibody may not have yet formed at the time of peak viremia and onset of symptoms, positive results of a p24 antigen assay or a detectable virus load, along with negative or weakly positive EIA results and negative or evolving results of Western blot analysis, are common diagnostic markers. Plasma HIV-1 load or a p24 antigen assay must therefore be ordered (in addition to an HIV antibody test) to establish the diagnosis of PHI. Virus loads are typically very high in patients with acute infection, often exceeding 1 million copies/mL [15]. The presence of low plasma levels of HIV-1 RNA in patients with seroconversion symptoms does not rule out acute infection but may suggest a false-positive test result. The sensitivity of the p24 antigen assay is time dependent; antigenemia may wane during PHI [12]. Some health care professionals prefer assays that measure HIV-1 load, because of the greater sensitivity of such tests. HIV-1 load specificity is improved in laboratories using robotic tests and by using a threshold of >5000 copies/mL for interpretation of test positivity [16]. Detection of HIV-1 plasma RNA by PCR is not currently approved by the US Food and Drug Administration for the diagnosis of HIV-1 infection; therefore, a follow-up antibody EIA and Western blot analysis are necessary to confirm the diagnosis.

The HIV-1 and HIV type 2 (HIV-2) EIA detects antibodies to HIV-1 and HIV-2, but the routine confirmatory Western blot is specific to HIV-1. The p24 band is often the first to be detected by Western blot testing; when present alone, the HIV antibody test is considered to be indeterminate. This finding is not infrequent during seroconversion and should prompt correlation with the HIV-1 plasma RNA level. For patients who initially present with a positive HIV-1 antibody test and a recent history of acute retroviral syndrome or high-risk exposure, a

<table>
<thead>
<tr>
<th>Viral</th>
<th>Epstein-Barr virus</th>
<th>Cytomegalovirus</th>
<th>Primary herpes simplex virus</th>
<th>Influenza</th>
<th>Early-stage hepatitis</th>
<th>Parvovirus B19</th>
<th>Rubella</th>
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<tr>
<td>Bacterial</td>
<td>Streptococcal disease</td>
<td>Secondary syphilis</td>
<td>Lyme disease</td>
<td>Rickettsial disease</td>
<td>Disseminated gonococcal infection</td>
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<tr>
<td>Parasitic</td>
<td>Acute toxoplasmosis</td>
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<td>Noninfectious</td>
<td>Adult Still disease</td>
<td>Systemic lupus erythematosus</td>
<td>Systemic vasculitides</td>
<td>Drug reaction</td>
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less sensitive (i.e., “detuned”) ELISA can be used to identify recent seroconversion. Results of the detuned assay generally become positive a mean of 129 days after infection [17]. A nonreactive result suggests infection in the past 18 weeks and can help identify potential candidates for early therapy. The typical time course of evolving clinical, immunologic, and laboratory features of PHI is shown in figure 2.

CD4+ T cell counts are not generally reliable markers of immune status during the first 6 months of infection, because they can transiently decrease during acute infection. The utility of using laboratory markers for Epstein-Barr virus (EBV) mononucleosis to identify patients with acute HIV-1 infection has been investigated; false-positive results of an EBV heterophile antibody assay can occur but are infrequent [14]. Atypical lymphocytes are seldom encountered [3], and this finding does not discriminate between HIV-1 and other viral infections. Negative results of an EBV heterophile antibody assay for patients with mononucleosis-like symptoms can be a positive predictor for HIV-1 disease. In a cohort of 563 patients with mononucleosis-like illness and negative results of a monospot test, 7 (1.2%) were found to have acute HIV-1 infection [18]. This finding suggests that clinicians should consider the diagnosis of acute HIV-1 infection for patients in whom EBV infection is suspected.

Advantages of making an early diagnosis of PHI include opportunities to enhance immune response on the individual level and to reduce transmission on the population level. Preventing the “unknowing spread” of HIV-1 during acute infection is of particular public health significance because of the extremely high virus loads typical of this stage of infection [19]. However, early diagnosis of acute infection often creates a dilemma for clinicians with regard to treatment. Potential benefits of early treatment have been suggested, but differences in morbidity or mortality have not been proven. The theoretical benefits that are frequently discussed must be weighed against the significant risks of long-term medication toxicities and costs.

**TREATMENT OF PHI: REDEFINING OPPORTUNISM?**

An emerging hypothesis is that the “seroconversion window” represents a unique opportunity for early modulation of the host’s immune response to HIV-1. Treatment of PHI may be a potential way to achieve a more effective immune response to the virus, delaying or preventing decreased immune function and vulnerability to opportunistic infections. Because of the relative paucity of clinical trial data, the advantages and disadvantages of initiating therapy for PHI continue to be debated (table 1). Potential benefits include mitigation of acute retroviral symptoms, early prevention of abnormal helper T cell function, decreasing the initial virus load set point, limiting viral evolution and diversity, and reducing the risk of transmission at a time of extraordinarily high virus levels. Risks include increased cost, adverse effects and abnormal metabolic

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**Figure 2.** Generalized immunologic and virologic patterns in the natural history of acute HIV type 1 infection. Rapid, moderate, and slow progression of disease is schematically represented at different relative virus load (VL) set points. WB, Western blot; CTL, cytolytic T lymphocytes; Detuned, detuned ELISA; nAb, neutralizing antibody.
**Table 1. Potential advantages and disadvantages of treating primary HIV type 1 (HIV-1) infection.**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Preservation of HIV-1–specific cellular immune responses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Toxocities and unknown long-term risks</td>
</tr>
<tr>
<td>Opportunity for structured treatment interruption&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Short- and long-term clinical benefits are not well-defined</td>
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<tr>
<td>Lowering of HIV-1 set point&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Resistance acquisition</td>
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<tr>
<td>Limitation of viral evolution and diversity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Limitation of future antiretroviral therapy options</td>
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<tr>
<td>Decreased transmission&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Quality of life impact</td>
</tr>
<tr>
<td>Mitigation of acute retroviral symptoms&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cost</td>
</tr>
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<sup>a</sup> Evidence based.  
<sup>b</sup> Hypothesized.

findings, drug resistance, long-term challenges to adherence, and unknown long-term toxicities or expected duration of benefit.

**IMMUNOLOGIC EFFECTS OF ART IN PATIENTS WITH PHI**

Randomized, placebo-controlled studies of early therapy in patients with PHI are limited. A previous study compared disease progression over a 6-month period in 77 patients receiving zidovudine monotherapy or placebo. The treatment arm showed a lower incidence of opportunistic infection and a greater increase in CD4<sup>+</sup> T cells [20].

These quantitative findings were followed by reports of functional, HIV-1–specific benefits of early therapy. An inverse relationship between the level of viremia and HIV-1–specific CD4<sup>+</sup> cell proliferative responses has been shown [21], and treatment of PHI in small cohorts of patients allowed for preservation of these responses [21–23]. An observational prospective study of 85 patients with PHI investigated the effect of early ART on CD4<sup>+</sup> T cell and CTL proliferative responses. Several findings emerged. First, HIV-specific CD4<sup>+</sup> T cell proliferative responses were found in both treated and untreated subjects during the first 18 months of infection but were markedly increased in treated subjects who maintained virologic control. Second, suppression of virus load was correlated with diminishing CTL responses, and patients with incompletely controlled viremia had stronger CTL responses, suggesting that persistence of viral antigens is an important determinant in the maintenance of HIV-1–specific CTL response. Finally, favorable immunologic responses were attainable in patients treated up to 3 months after infection [24].

In a cohort of 16 HIV-1–infected individuals who received their diagnosis at the time of seroconversion and who started ART <=72 h later, robust HIV-1–specific CD4<sup>+</sup> T cell proliferative responses were again observed [18]. Initiation of ART in patients with PHI appears to preserve virus-specific CD4<sup>+</sup> T helper cell responses to a degree that is not typically observed with treatment initiated during chronic infection [21, 24, 25], but the long-term clinical benefit of preserving this immune response has never been demonstrated. Virus suppression during acute HIV-1 infection appears to limit the evolution of HIV-1–specific CTL responses, resulting in narrowly focused responses of modest magnitude. Institution of therapy in patients with PHI may afford the opportunity for interface with a less diversified virus before the emergence of more difficult-to-target quasispecies during chronic infection [25]. A growing number of studies support the use of ART in patients with PHI [3, 11, 15, 20–22, 24–26], but data proving beneficial effect on survival are lacking.

**WHEN TO INITIATE THERAPY**

Initiation of therapy for patients in whom acute HIV-1 infection has been diagnosed remains controversial. The US Department of Health and Human Services (DHHS) recommends consideration of treatment for patients who received their diagnosis <=6 months after infection. The British HIV Association (BHIVA) guidelines recommend treatment of PHI with ART only for relief of symptoms of acute retroviral syndrome; BHIVA comments that there is presently insufficient evidence to support treatment for other indications [27]. The International AIDS Society (IAS)–USA guidelines do not comment specifically about treatment of individuals with PHI, except for mentioning the potential role of structured treatment interruption (STI) in this population of patients [28]. The temporal window of opportunity for the treatment of acute infection is not well defined. Studies have demonstrated immunologic benefit associated with ART initiation up to 3–4 months after infection [23, 24], although long-term effects on morbidity and mortality are unknown. Most clinicians who elect to treat individuals with PHI will extend the window for treatment to the first 6 months after seroconversion, which is consistent with DHHS guidelines [29]. We propose an algorithmic approach to evaluation and management of patients with suspected acute or early-stage HIV-1 infection (figure 3).
SELECTING A STARTING REGIMEN

For patients who initiate ART during the acute phase of infection, the optimal starting regimen has not been well defined. Some clinicians favor combination therapy with ≥3 drugs initially, until results of resistance tests are available and virus loads have significantly decreased. A regimen containing a potent protease inhibitor or nonnucleoside reverse-transcriptase inhibitor is favored, because triple nucleoside regimens do not appear to perform as well in patients with very high virus loads, and data are limited regarding the use of entry inhibitors or nucleoside/nucleotide reverse-transcriptase inhibitor regimens for treating PHI.

The patient’s preparedness and commitment to starting treatment must be carefully assessed before initiating therapy; poor adherence to treatment may do more harm than no treatment at all. The mutational capacity of a rapidly replicating virus makes adherence critical to the success of PHI treatment, and this factor must be emphasized with all patients. Adherence is also an important consideration for patient-specific regimen selection and requires individualized attention to the patient’s lifestyle, pill burden tolerance, dietary habits, and comorbidities. Efavirenz has been shown to be better tolerated than some protease inhibitors [30] but carries a greater risk of resistance acquisition due to a single mutational event if doses are missed. There is also theoretical concern that primary resistance to nonnucleoside reverse-transcriptase inhibitors due to a K103N mutation that effectively reduces susceptibility of the virus to all drugs in the class may be more common than primary resistance to other drug classes, because the mutation does not hinder viral fitness. However, genotypic resistance has been documented in all drug classes in a minority of primary HIV-1 isolates [31].

Most clinicians favor genotype testing before initiation of therapy for acute HIV-1 infection, which is consistent with IAS-USA guidelines [28]. The result of this test should not delay treatment but can be useful to inform any subsequent necessary changes in the initial regimen. Genotype testing of HIV-1 isolates from patients with PHI also assists surveillance of overall

Figure 3. Testing algorithm for diagnosis of primary HIV type 1 infection (PHI). DDx, differential diagnosis; VL, virus load; Ab, antibody; SC, seroconversion; Rx, treatment; wk, week; +, positive; (−), negative.
resistance patterns and incidence of resistance transmission. Diagnostic testing and postexposure prophylaxis should be considered for recent sexual partners, particularly in light of typically high virus levels in the acutely infected index patient [32].

EXPECTED OUTCOMES OF EARLY THERAPY

Typical responses of virus load to treatment in patients with chronic HIV-1 infection show decreases to undetectable levels during an 8–20-week period of potent ART. Time to virus suppression in patients with PHI has not been well characterized. Higher initial virus loads in patients with acute infection may prolong the time to virus suppression. Alternatively, a relatively intact immune system and a lower total body virus burden in patients with early-stage infection may decrease time to suppression. The pattern and potency of individual immunologic responses likely reflect a number of host factors, including HLA class I type, initial antibody response, CTL and T helper cell responses, and chemokine receptor polymorphisms.

STI

Indefinite continuation of therapy once primary viremia is suppressed is being debated. Treatment of PHI may allow for interruption or discontinuation of therapy. STI may sustain or augment immune responses, minimize cost, and decrease toxicity due to long-term ART, but ideal schedules and long-term benefits have not yet been determined. In addition, risks of adopting an STI strategy include (recurrent) development of an acute retroviral syndrome, emergence of resistance, and immunologic damage sustained during periods of permissive viremia (i.e., rising virus loads during STI). The first documented example of STI was seen in 1998 in an individual recognized for his ability to control HIV-1 infection after discontinuing therapy [33]. After additional anecdotal reports of sustained control of viremia in patients initially treated for acute HIV-1 disease who then stopped therapy, the concept of STI gained attention. A study of 8 patients undergoing STI after at least 8 months with undetectable virus loads showed sustained virologic suppression for up to 18 months in 3 patients [15]. Accompanying immunologic findings showed a marked increase in the magnitude and breadth of CTL responses and the maintenance of HIV-1–specific CD4+ T cell proliferative responses.

The early reported successes of STI are in keeping with current theories of virologic control. HIV-1–specific CD8+ cell responses have been shown to decrease with suppression of viremia, suggesting that at least low-level antigenic stimulation is necessary to maintain a strong CTL response to HIV-1 infection. Intermittent low-level exposure of the immune system to virus during STI may allow the host to strengthen HIV-1–specific CTL response, while minimizing the immunologic damage by controlled reinitiation of ART when the virus load increases or the CD4+ T cell count decreases. Studies are currently under development to assess clinical outcomes and optimal methods of STI. Until more data are obtained, the IAS-USA recommends that interruptions in therapy should only be performed in the context of a clinical trial [28].

NOVEL TREATMENTS

The role of neutralizing antibodies in PHI is not clear. Initial enthusiasm about the therapeutic potential for antibodies directed primarily at the HIV-1 envelope to neutralize the virus before it enters the cell stemmed from the discovery that some acutely infected individuals who control the infection after stopping therapy have notably strong neutralizing antibody responses [34]. However, escape mutations (i.e., mutations that allow the virus to escape this form of immunologic control) have been demonstrated. RNA interference is being explored as a therapeutic means to silence the activity of post-transcriptional mRNA in patients with HIV-1 infection. Adjunctive immunomodulatory therapies currently under study include mycophenolate mofetil, cyclosporine, IL-2, and various vaccination strategies, including those involving follicular dendritic cells. Recently demonstrated cases of super-infection have raised important concerns about the breadth and competency of an early optimized immune response. Whether boosting the immune system effectively improves host defenses in the face of antigenic challenge from previously unencountered strains of HIV-1 remains to be seen.

CONCLUSIONS

Early recognition and diagnosis of acute HIV-1 infection can provide important benefits on the individual level, because the potential for early initiation of treatment may allow for preserved immune-system control of the virus, and on the public health level, because the risk of transmission may be decreased. The decision to initiate therapy must involve careful consideration of potential risks and benefits on a case-by-case basis. Once stable virologic suppression is achieved, STI may prove a beneficial strategy in patients treated at the time of PHI; currently it is best pursued in the context of a clinical trial. Other adjunctive approaches such as vaccine-based strategies may help sustain HIV-1–specific responses and long-term virologic suppression and deserve further study.

References