Primary Human Immunodeficiency Virus Type 1 Infection

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Primary human immunodeficiency virus type 1 (HIV-1) infection represents the initial stage of disease that immediately follows viral entry into the body. Primary infection is frequently accompanied by an acute retroviral syndrome with associated high levels of plasma HIV-1 RNA and the development of host immune responses. The identification of subjects during this period requires a high index of suspicion and an understanding of how to make the diagnosis, as standard HIV-1 antibody tests can initially be negative. Identifying these people provides a unique opportunity for early counseling to reduce further transmission, facilitates entry into care, and allows for further study of the immunopathogenesis of disease and the potential role of early antiretroviral therapy.

Introduction

There are currently approximately 40 million people infected with the human immunodeficiency virus type 1 (HIV-1) around the world. While there has been a substantial decline in cases of AIDS and AIDS-related mortality in the United States associated with the introduction of potent antiretroviral therapy, the incidence of HIV-1 infection has increased among men having sex with men and heterosexuals [1]. Moreover, as many as 25% of HIV-1-infected people in the United States are unaware of their infection status [2].

Primary HIV-1 infection and the associated acute retroviral syndrome occur shortly after viral entry into the body and are associated with the development of HIV-1-specific immune responses. Although the clinical presentation can be dramatic, the diagnosis of primary infection is often missed because of the lack of specificity of symptoms and because the usual markers of HIV-1 infection can be negative or inconclusive. Consequently, identification of subjects during this stage of the disease requires a high index of suspicion and an understanding of how to utilize select diagnostic tests. Identifying these individuals provides a unique opportunity to further study the natural history of disease, allowing for early referral into medical care, counseling regarding risk reduction behavior, and the potential role of early antiretroviral therapy. This article will summarize the clinical manifestations of primary HIV-1 infection, how it can be diagnosed, and the immunopathogenesis of this stage of disease. In addition, recent data related to superinfection and the potential role of antiretroviral therapy will be analyzed.

Defining Primary HIV-1 Infection

Different studies have utilized variable criteria for defining primary HIV-1 infection. Some include subjects identified at the time of an evolving humoral immune response, while others include those documented to have been previously HIV-1 antibody negative in the preceding 6 to 12 months. How primary infection is defined has implications regarding which tests need be used to make the diagnosis and is highly relevant when considering studies of immunopathogenesis and the potential role of early antiretroviral therapy. Those infected for days to weeks will have high level viremia and undetectable or evolving HIV-1 antibodies, and therefore diagnosis requires use of virologic assays. In contrast, those infected for months will be HIV-1 antibody positive and thus documentation of primary HIV-1 infection requires either previous evidence of a negative test or the use of an assay that can distinguish between early and late infection. From a pathogenesis perspective, those in the first weeks to months of infection are of particular interest in defining the evolution of HIV-1–specific immune responses. Similarly, the influence of antiretroviral therapy on viral evolution and host immune response, as discussed below, may differ by stage of disease.

Although the acute retroviral syndrome has classically been described as a mononucleosis-like illness with fever, sore throat, lymphadenopathy, and occasional rash, individuals can be asymptomatic or have relatively mild to very severe symptoms that are nonspecific and indistinguishable from other acute illnesses [3–5]. Vanhems *et al.* [4] showed in a cohort of over 200 subjects that the most common symptoms were fever (~77%), lethargy and malaise (~66%), diffuse maculopapular rash (~56%), myalgias (~54%), sore throat (~45%), cervical lymphadenopathy (~39%), arthralgias (~31%), and headache (~51%).

Other relatively common symptoms include oral and genital ulcers and thrush. In addition, unusual manifestations such as pancreatitis, Guillain-Barre syndrome, facial nerve palsies, brachial neuritis, myelopathy, peripheral neuropathy, and acute meningoencephalits have been reported. Common laboratory abnormalities during primary infection include anemia, leucopenia, thrombocytopenia, and transaminase elevation. Because of the varied symptoms and the complexity in defining and diagnosing the syndrome, it is often missed in clinical practice. In fact, one recent study [6•] showed that only five of 29 (17%) individuals with primary HIV-1 infection were diagnosed at the time of initial presentation to medical care. While further education of the community regarding this stage of disease may help, the diagnosis often will remain elusive because no signs or symptoms are sufficiently sensitive or specific to provide guidance to those caring for patients [5].

Diagnosing Primary HIV-1 Infection

The diagnosis of primary HIV-1 infection depends upon identifying patients who are at risk and knowing what tests to use in those presenting with symptoms consistent with the acute retroviral syndrome. Risk factors for acquisition of HIV-1 include unprotected sexual intercourse and intravenous drug use by needle sharing. Other factors associated with increased risk of acquiring HIV-1 infection are incarceration, concomitant sexually transmitted diseases, especially in the presence of genital ulcerations, depression, and exchange of sex for drugs or money [2,7]. Others become infected as a result of exposures generally thought to be of lower risk such as oral sex and insertive intercourse [8•]. Since patients with primary HIV-1 infection are likely to be highly infectious, with high levels of circulating HIV-1 RNA in their blood and genital secretions, diagnosing infection allows for the opportunity to interrupt potential transmission to others.

Several studies have looked at the relationship between the timing of infection and the development of laboratory markers used to identify primary infection. After infection, it is estimated that it takes approximately 12 days for the detection of HIV-1 RNA, 17 days for p24 core antigen, and 22 days for the emergence of detectable HIV-1 antibodies [9••]. Consequently, the diagnostic tests needed to identify primary infection will vary depending upon the time from infection. Those in the first days of infection will be HIV-1 antibody enzyme immunoassay (EIA) negative, and the diagnosis will depend upon tests for circulating virus such as p24 core antigen, plasma HIV-1 RNA, or proviral DNA from peripheral blood mononuclear cells. The most frequently utilized of these virologic tests is the quantitative assay for plasma HIV-1 RNA which is likely to be very sensitive. Nevertheless, all virologic tests must be used with caution because of the potential to report false positive results. In general, those with primary HIV-1 infection have plasma HIV-1 RNA levels in excess of 100,000 copies per mL, while those with false positive results are usually less than 5000 copies per mL, making it easy to distinguish false from true positives in those HIV-1 antibody negative presenting with a suspected acute retroviral syndrome [5,10].

Some studies have suggested that a substantial number of people presenting for routine HIV-1 antibody testing do so with symptoms consistent with primary HIV-1 infection. Thus, it has been proposed that those HIV-1 antibody negative may benefit from routine testing for HIV-1 RNA [11]. Such testing strategies are standard in blood banks and could be applied to people presenting for screening HIV-1 testing [12]. Nevertheless, the majority will present weeks, months, or years after infection, at which time they all are HIV-1 antibody positive. In this case there is interest in defining which are incident cases of infection. In this situation novel antibody tests have been developed to identify those in the first weeks to months of infection. One such test is the insensitive EIA or detuned assay, an investigational test that is generally used for epidemiological purposes to identify subjects infected during the preceding 4 to 6 months [13].

Immunopathogenesis: Viral and Immunologic Events

Several studies have confirmed that HIV-1 infection initiated at the level of mucosa is mediated by infection of dendritic cells followed by spread to regional lymph nodes, widespread dissemination throughout the body, and the development of host immune responses. The high levels of plasma HIV-1 RNA observed during primary HIV-1 infection ultimately nadir as the infected person enters the asymptomatic phase of disease. Initial infection is generally with a relatively homogenous population of CCR5-tropic viruses [14]; however, some data suggests that those acquiring more heterogeneous populations or strains that are CXCR4-tropic experience more rapid disease progression [15,16].

The initial decrease in plasma HIV-1 RNA is temporally associated with the evolution of HIV-1-specific cytotoxic T lymphocytes (CTL) [17,18]. In addition, the magnitude and breadth of CTL responses have been associated with viral set-point and disease progression and there is evidence of rebound in plasma HIV-1 RNA occurring in association with mutations in CTL epitopes [19••,20]. This type of data strongly supports the clinical relevance of the CTL response in controlling HIV-1 infection. Other immunologic factors such as natural killer (NK) cells and soluble suppressive factors have also been shown to potentially play a role in viral control in vivo [21,22]. Recent attention has focused on the role HIV-1-specific CD4+ T cells play in orchestrating immune responses, how they might modulate the natural history of disease, and how this part of the host immune response might be influenced by the early initiation of antiretroviral therapy. A landmark study by Rosenberg *et al.* [23••]

Table 1. Potential benefits and disadvantages of initiating antiretroviral therapy during primary HIV-1 infection

Potential benefits	Potential disadvantages
Higher CD4+ T cells	Short- and long-term toxicities
Preservation of HIV-1 specific immune responses	Restrict immune responses
Reduction of viral set point upon discontinuation of therapy	Development of drug resistance mutations
Delayed clinical progression	Increased cost
Decrease the rate of viral evolution	Development of acute retroviral syndrome upon discontinuation of therapy
Decreasing duration of the acute retroviral syndrome	
Reduce risk of transmission	

showed that long term nonprogressors tended to have preserved HIV-1-specific CD4+ T-cell responses that were found to be weak or absent in most others with chronic infection. Moreover, this group demonstrated that treatment during primary HIV-1 infection preserved these immune responses. The importance of this aspect of host immunity to HIV-1 is further supported by recent work of Gloster *et al.* [24] showing that the plasma HIV-1 RNA setpoint is lower in those with more vigorous HIV-1-specific CD4+ T-cell responses.

Transmission of Antiretroviral Drug-Resistant HIV-1

Transmission of drug resistant virus was first described shortly after the introduction of zidovudine into clinical practice. As combination therapy became available, it was inevitable that there would be increasing frequency of drug-resistant and even multidrug-resistant virus transmitted to newly infected individuals. Many groups from around the world have assessed the prevalence of drug resistant virus in treatment-naïve subjects, including those presenting with primary infection. Studies demonstrate drug-resistant virus present in less than 5% to as high as 30% of newly infected individuals [25,26]. Further study of those acquiring resistant virus has shown that these strains can persist for prolonged periods of time [27], and that up to 10% of chronically infected, antiretroviral-naïve individuals have evidence of drug resistant virus [28••]. Some studies show that there may be trends towards increasing transmission of resistance [25,26], and others have suggested that viruses with unique resistance patterns may be transmitted with different frequencies [29]. While further investigation is needed to define the natural history of transmitted drug resistant virus, at the very least this data supports current recommendations that resistance testing be performed on all subjects with primary HIV-1 infection and be strongly considered in those with chronic infection considering therapy for the first time [30,31].

Antiretroviral Therapy during Primary HIV-1 Infection

There has been considerable interest over the years in the potential impact that treatment during primary HIV-1 infection might have on the natural history of disease. Nearly a decade ago, Kinloch-de Loes *et al.* [32] demonstrated that zidovudine taken during primary HIV-1 infection resulted in short-term immunologic and clinical benefits. Other small noncontrolled studies have also suggested potential benefits associated with early treatment. Berrey *et al.* [33] reported on 47 subjects randomized to receive placebo or lamivudine, zidovudine, and indinavir who were followed for 78 weeks. They showed a reduced frequency of opportunistic infections and progression to AIDS in the treated group. Nevertheless, they also found that there was prompt viral rebound after discontinuation of therapy.

In the current era, the principal rationale for treatment during primary HIV-1 infection has been to preserve immune responses in order to enhance virologic control at the time of treatment discontinuation. Anecdotal reports have described variable outcomes associated with treatment during primary HIV-1 infection followed by withdrawal of therapy [34,35]. Consequently, investigators have pursued novel strategies for withdrawing therapy started during primary HIV-1 infection. A notable example was the early success in a small number of subjects treated during primary HIV-1 infection who demonstrated excellent virologic control after serial treatment interruptions [36]. However, followup of larger numbers of subjects from the same group has been less promising [37••]. Others have studied the use of novel immune modifiers such as hydroxyurea, interleukin 2, cyclosporine A, and even HIV-1–specific immunogens with variable but less than overwhelming results [38–41]. While there remains substantial interest in this area of research, concerns have been raised about the potential for drug toxicities and the emergence of drug resistant mutations if treatment is instituted during primary HIV-1 infection [42••]. Therefore, the potential benefits of antiretroviral therapy must be balanced by the known risks of treatment (Table 1).

Since data remains inconclusive regarding the potential benefits of early therapy, clinicians must share what is currently known of the risks and theoretical benefits of treatment with newly infected individuals. Recommendations from guideline panels have evolved in the face of the available data, with the most recent US Department of Health and Human Services (DHHS) guidelines published in 2004 suggesting that treatment of primary HIV-1 infection be considered optional at this time. This panel recommended that these subjects should be coun-

seled and if treatment is started, the goal should be to achieve undetectable levels of plasma HIV-1 RNA. Moreover, treated subjects should be closely monitored for immunologic and virologic response as well as for drug-related toxicities. The optimal regimen for these subjects has not been defined; however, in light of the high prevalence of transmitted drug resistant virus, it is advisable to do resistance testing when possible. Since there is currently insufficient data regarding the optimal drug combination(s) to be used in those with primary HIV-1 infection, it is reasonable to use combinations similar to those recommended for the treatment of chronically infected people [30]. Recent trends reported from the French PRIMO multicenter cohort showing a move away from treating subjects identified with primary HIV-1 infection are probably in keeping with the lack of definitive data as to its potential benefits [43].

HIV-1 Superinfection

A novel observation that has emerged from cohorts of subjects identified during primary HIV-1 infection is that of superinfection. Distinct from the previously reported cases of dual infection, where an uninfected person acquires infection from two different individuals at the time of primary infection, these subjects have established chronic infection and are then thought to acquire a second strain from a new source partner. Until recently, this event was mostly a theoretical concern, but recent case reports provide increasing evidence that superinfection does occur. Moreover, these cases provide additional insight into the immunopathogenesis of disease and raise new concerns for HIV-1-infected individuals and vaccine development.

One case of superinfection described an individual initially infected with HIV-1 clade AE clone from South Asia who was successfully treated with antiretroviral therapy, stopped treatment and then was reinfected by a subtype B strain with an associated increase in plasma HIV-1 RNA and decline in CD4+ T cells. This report raised early concerns that the immunity offered by natural HIV-1 infection might not provide protection against superinfection [44]. Several other probable cases of superinfection have since been reported, including that of Altfeld *et al*. [45] in which a patient who had excellent viral control after treatment during primary infection was discontinued then experienced a sudden rebound in plasma HIV-1 RNA with a strain that was distinct from the original infecting virus [45]. Of note, this patient had strong cellular immune responses to both the original and the presumed superinfecting strain, despite which he was unable to control the second virus, once again raising serious concerns regarding the extent of protective immunity associated with natural infection. Another recent case report by Yang *et al*. [46] described a patient who acquired a multi-drug-resistant strain of HIV-1 that was initially controlled for 5 months without treatment, followed by a progressive increase in viremia associated with the detection of a drug-susceptible, phylogenetically distinct superinfecting strain that was poorly recognized by host immune responses.

Preliminary studies have been performed to further define the frequency and clinical relevance of superinfection. Smith *et al*. [47] reported a superinfection rate of approximately 5% (95% confidence intervals: 1.7%–13.3%) per year in a cohort of subjects followed from the time of primary HIV-1 infection. Of note, those with suspected superinfection experienced an increase in plasma HIV-1 RNA and a decline in CD4+ T cells associated with the emergence of the superinfecting strain. In another cohort, Gottlieb *et al*. [48] found that five of 64 subjects were dually infected and all five were noted to experience rapid progression to AIDS. These studies suggest that superinfection may not be a rare event and when it occurs it can be associated with disease progression. Interestingly, other studies of chronically infected individuals screened for evidence of superinfection have failed to demonstrate any cases. This includes a study of 37 active drug users with 215 person years of followup [49], and another group of chronically infected individuals in medical care [50]. The latter studies suggest that superinfection may be a phenomenon that is more likely to occur in those during the first months of infection, or that for technical reasons it may be difficult to identify superinfection in chronically infected individuals. Regardless, the possibility that superinfection is a real phenomenon calls for renewed efforts to reinforce risk reduction strategies among HIV-1–infected individuals both in order to prevent transmission to uninfected partners and to protect the infected person from potential superinfection and subsequent virologic and immunologic progression.

Conclusions

The acute retroviral syndrome is often present at the time of initial HIV–1 infection and if recognized provides an opportunity for early identification of newly infected individuals. These subjects are of tremendous public health interest because of their potential to transmit to others if not counseled regarding their status. Moreover, they provide a unique opportunity for studies of the natural history of disease. The definition of primary HIV-1 infection is variable and the diagnosis requires a complete understanding of the timeline in which various virologic and immunologic tests first become positive after infection. Once the diagnosis is made, the person must be counseled regarding how to prevent transmission to others, and the theoretical benefits and real risks associated with early antiretroviral therapy. In addition, whenever possible these subjects should be referred to a research study to further define the natural history of disease and to study novel strategies to optimize clinical outcomes.

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