Primary Human Immunodeficiency Virus Type 1 Infection

Malini Soogoor, MD, and Eric S. Daar, MD*

Address
*Division of HIV Medicine, Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, 1124 W Carson Street, Torrance, CA 90502, USA. E-mail: edaar@labiomed.org

Current Science Inc. ISSN 1548-3568
Copyright © 2005 by Current Science Inc.

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. 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.

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 meningoencephalitis 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 homogeneous population of CCR5-tropic viruses [14]; however, some data suggests 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]. 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]