Primary HIV Infection

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Primary HIV infection is a critical and highly dynamic time period in the course of HIV infection. The initial pathologic processes are important in determining long-term disease progression. In the absence of our ability to eradicate the virus, identifying individuals during primary HIV infection and performing interventions that optimize outcome are important to provide adequate care to a newly infected patient and, from a public health perspective, to identify sexual networks and provide a platform to reduce HIV exposures during a time of high viremia.

Introduction

The term "primary HIV infection" refers to the period from initial infection with HIV to complete seroconversion. It is a period of extreme infectiousness and dynamic viral and immunologic activity. The diagnosis should be considered in all at-risk patients experiencing a primary infection-like illness, and they should be offered HIV antibody and HIV RNA testing as well as counseling. The occurrence and severity of symptoms during primary HIV infection correlate with the rapidity of clinical and immunologic decline. Treatment of patients during primary infection may improve immune preservation and reconstitution. The current approach to management of primary HIV infection is based more on expert opinion than on clinical trial results, although ongoing clinical trials should provide more information about the management of this syndrome. A key development from primary HIV infection research is determining the epidemiologic spread of resistant HIV.

Epidemiology

The Joint United Nations Program on HIV/AIDS estimates that there are 42 million persons worldwide living with HIV/AIDS, 18.5 million (44%) of whom are women, and 3.2 million (7.1%) of whom are children [1•]. The hardest hit area in the world is sub-Saharan Africa, with almost 30 million infections. Southeast Asia also is an area of high infection rates, with 6 million cases of HIV/AIDS. Areas of growing concern and increasing incidence of infection are China, India, and Eastern Europe. With more than 1 million infections each estimated for China and the former Soviet Union, infection rates in these areas are predicted to increase, fueled by rampant intravenous drug use, increasing prevalence of other sexually transmitted diseases, and health care systems that are not equipped to deal with an epidemic of HIV. In the areas of highest prevalence, such as Botswana and Zimbabwe, rates of HIV infection may exceed 30% in the general population and 50% among selected groups, such as pregnant women, male patients at sexually transmitted infection clinics, and female sex workers. Worldwide, there are an estimated 16,000 new infections daily.

In the United States, there are 900,000 people living with HIV/AIDS, 180,000 (20%) of whom are women and 10,000 (1.1%) of whom are children. Ethnic and racial minorities in the United States comprise a disproportionate number of incident AIDS cases—the incidence rate per 100,000 population among blacks is 58.1, 22.5 among Hispanics, and 6.6 among whites. Young homosexual men also continue to be heavily affected. In a sample of 15- to 22-year-old men who have sex with men in seven urban areas, 7% were already infected with HIV. Higher percentages of blacks (14%) and Hispanics (7%) were infected than were whites (3%) or Asians (2%) [2]. In 2000, 59% of reported HIV infections among adolescent males aged 13 to 19 years and 53% of cases among men aged 20 to 24 years were attributed to male-to-male sexual contact.

Worldwide, heterosexual transmission is the most common mode for spreading HIV. Other common modes of transmission include homosexual sex, intravenous drug use, occupational exposure through needlesticks and mucosal exposure to blood and body fluids, transfusion of contaminated blood products, and mother-to-child transmission. Understanding the epidemiology and risk factors for HIV infection will help the astute clinician assess a patient's risk for HIV infection and, therefore, identify cases of HIV infection when patients present with typical signs and symptoms of primary HIV infection.

Clinical Syndrome and Diagnosis

With careful prospective evaluation of HIV-at-risk populations, up to 87% of individuals who acquire HIV may experience some symptoms of primary HIV infection [3]. The clinical syndrome of primary HIV infection was first

Table 1. Signs, symptoms, and laboratory values of primary HIV infection [6•]

Signs, symptoms, laboratory values	Frequency, %
Fevers	>90
Fatigue	>90
Rash	>70
Headache	32–70
Lymphadenopathy	40–70
Pharyngitis	50–70
Myalgia, arthralgia	50–70
Nausea, vomiting, or diarrhea	30–60
Night sweats	50
Oral ulcers	10–20
Genital ulcers	5–15
Thrombocytopenia	45
Leukopenia	40
Elevated hepatic enzymes	21

reported in 1985 and resembles a mononucleosis-like illness, appearing within days to weeks of exposure [4]. The most common symptom is fever, present in more than 75% of patients [5]. Other commonly reported symptoms include fatigue, lymphadenopathy, headache, pharyngitis, and rash (Table 1) [6•]. The rash, which is present in 40% to 80% of cases, may be evanescent, is typically maculopapular, and involves the trunk [5]. The two symptoms that most effectively diagnose primary HIV infection among individuals with risk factors are rash and fever [7••]. Symptoms such as thrush and ulceration of genital or oral mucosa, although not common in primary HIV infection, are sufficiently unusual as to suggest the diagnosis. Symptoms in cohorts from other areas of the world suggest a different range of presenting symptoms in nonwhite individuals. Symptoms may be mild or severe and may last from a few days to several weeks; the average duration is 14 days. A more severe clinical syndrome with primary HIV infection has been associated with a more rapid clinical course [8].

The nonspecific symptoms of primary HIV infection make diagnosis a challenge. Even among high-risk individuals with symptoms consistent with primary HIV infection, only 25% may be diagnosed during their initial presentation [3].

Diagnosis of primary HIV infection requires high clinical suspicion and special testing considerations. Routine serologic test results may be negative during a window period of 22 to 27 days after exposure [9], although newer third-generation antibody tests may shorten this window. For patients in whom primary HIV infection is clinically suspected, a direct virologic test, in addition to HIV antibody testing, is warranted.

The optimal virologic test for diagnosing primary infection has not been defined. Serum testing for p24 antigen is 79% sensitive and 99% specific in antibody-negative patients, whereas quantitative assays for plasma HIV RNA (by branched-chain DNA or polymerase chain reaction) have more than 99% sensitivity but occasionally result in false-positives. False-positive test results usually report HIV-1 RNA levels of less than 3000 copies per mL, in contrast to the very high levels typically seen in true primary HIV infection [7••]. By examining stored samples from HIV-infected plasma donors, it can be estimated that an HIV RNA test with a sensitivity of 50 copies per mL would detect HIV infection 7 days before a p24 antigen test and 12 days before a routine HIV antibody test would [10].

Direct HIV viral assays (p24 antigen and RNA testing) are not licensed for the diagnosis of HIV infection, and positive RNA or p24 antigen tests during acute infection must be confirmed with subsequent HIV antibody positivity. A diagnostic algorithm for primary HIV infection is presented in Tables 2 and 3.

Identification of recent infections is important for individual treatment, education, and public health surveillance. By altering the testing characteristics of the routine enzyme immunoassay (EIA) to make it is less sensitive, the combination of routine EIA and less sensitive EIA can distinguish between recent and chronic infection [11]. The Serologic Testing Algorithm for Recent HIV Seroconversion incorporates this algorithm for use in measuring HIV seroincidence, and similar strategies can be used to help estimate the date of individual infections.

Immunopathogenesis

In animal models of sexual HIV infection, virus is detectable inside mucosal cells within 1 hour of inoculation, in the regional lymph nodes within 2 days of infection, and can be cultured from the blood after 5 days of infection [12]. Infection in humans is followed within days to weeks by extremely high levels of viremia, peaking at an average of 6 to 15 days after the onset of symptoms [13], with serum HIV RNA often present in the range of 1 to 10 million copies per mL. In the early phases of infection, the HIV replication rate is 0.35 log copies per mL per day, corresponding to a doubling time of 20.5 hours [10]. The initial proliferation and dissemination of HIV in the newly infected host involves a relatively clonal virus population, which becomes more diverse during chronic infection [14].

Such high levels of viremia likely correlate with a period of high infectivity and potential spread of infection. However, these high levels of viremia are short-lived as the generation of the host immune response brings the viremia somewhat under control.

During primary HIV infection, there is a profound oligoclonal expansion of HIV-specific cytotoxic lymphocytes (CTL), which express high levels of activation markers such as CD38, CD27, and HLA-DR [15]. The breadth and strength of this CTL response is correlated with the degree of viral control and rapidity of clinical progression [16,17]. In addition, CTL responses act through lytic and nonlytic mechanisms to potently inhibit HIV viral replication [18]. T-helper cell (CD4 cell) responses also are necessary for control of HIV viremia.

Table 2. Algorithm for the workup of patients with suspected primary HIV infection: evaluation

History	Evaluate for risk of HIV exposure/infection
Examination	Search for signs or symptoms of primary HIV infection
Lab studies	HIV RNA* (or p24 antigen) and ELISA/EIA antibody

*Not licensed for HIV diagnosis and requires antibody confirmation.
ELISA/EIA—enzyme-linked immunosorbent assay/enzyme immunoassay.

Table 3. Algorithm for the workup of patients with suspected primary HIV infection: serologic interpretation and management

ELISA/EIA	Negative	Negative	Negative	Positive
HIV RNA*	Negative	Positive (< 3000 copies/mL)	Positive (> 3000 copies/mL)	Positive
Interpretation	Possible exposure, infection not confirmed	Possible false positive	Primary HIV infection	Established (chronic) HIV infection
Management	Consider PEP based on history; follow-up in 4 weeks, follow-up in 12 weeks	Repeat ELISA/EIA and HIV RNA in 1 week	Manage as primary HIV infection; repeat ELISA/EIA in 4 weeks to confirm HIV infection	Initiate routine HIV care

*Not licensed for HIV diagnosis and requires antibody confirmation.
ELISA/EIA—enzyme-linked immunosorbent assay/enzyme immunoassay. PEP—postexposure prophylaxis (antiretroviral treatment).

CD4 cell counts typically decrease during primary HIV infection, occasionally to levels that allow opportunistic infections to develop. Activated CD4 cells provide excellent targets for infection by HIV virions. Thus, HIV-specific CD4 cells, the cells activated to protect an individual during primary HIV infection, are preferentially infected and destroyed by the virus. In addition to decreased numbers of CD4 cells, the function of these cells also is impaired [19]. Absolute CD4 cell count often rebounds after the primary infection but may not return to a normal baseline.

Although cellular responses to HIV often precede the decrease in viral load and are thought to be responsible for the decline, neutralizing antibody production may not be detectable until after the reduction in viral load [20].

After the initial reduction of viremia, a viral "set-point" is established 12 to 18 months after infection, the level of which is closely related to the ultimate clinical outcome of HIV disease [21]. Predictors of the viral or immunologic set-point are unknown.

High levels of detectable virus also may be found in genital secretions during primary HIV infection, indicating a possibly highly infectious period. Investigators have demonstrated higher levels of HIV in semen samples obtained during primary HIV infection, compared to untreated individuals with chronic infection. With these high levels of seminal fluid HIV viral load, transmission probabilities during primary HIV infection are 4.2 times those of latent chronic infection [22].

Drug-resistant Virus in Primary HIV Infection

An important development in understanding primary HIV infection is the awareness of the transmission of drug-resistant virus. Resistance to single drugs [23] and multiple classes of antiretrovirals [24] has been reported. In most areas where treatment is widely available, 10% to 25% acquisition rates of drug-resistant HIV have been reported (Table 4), and those figures have been generally increasing. In most areas, resistance to nucleoside reverse transcriptase inhibitors emerged first, followed by resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors, reflecting the availability of those classes of agents on the market.

Certain specific mutations may not be as efficiently transmitted as other mutations or wild-type virus. Reductions in relative viremia and viral fitness of populations of viruses with specific mutations, such as the M184V mutation in the reverse transcriptase gene, may reduce the transmissibility of viruses with this mutation [39].

Drug resistance in primary HIV infection has implications for antiretroviral therapy (ART) beyond simply limiting the choice of active agents. For patients with drug-resistant virus before initiation of ART, the time to full viral suppression is longer and time to virologic failure is shorter [29••].

The persistence of drug resistance in primary HIV infection is somewhat different than in drug-experienced patients. In patients who develop drug resistance while on therapy and subsequently discontinue ART, wild-type (nonresistant) HIV begins to re-emerge at a mean of 6 weeks after ART discontinuation [40]. This is thought to represent reactivation of archived wild-type virus from latently infected reservoirs, which has a fitness advantage over drug-resistant virus in the absence of drug pressure. In contrast, drug resistance in primary HIV infection, in which there is no latent reservoir of wild-type virus, is likely to persist for many years

Table 4. Prevalence of drug resistance in acute or recent HIV infection

Location	*n*	Definition	Year	Prevalence, %	Notes
United States [25•]	141	< 1 year	1989–1998	2	—
Italy [26]	38	< 1 year	1994–1997	21	—
United Kingdom [27]	69	< 1 year	1994–2000	14	—
United States (New York City, Los Angeles) [28]	80	< 5 months	1995–1999	16	MDR in 4%
United States [29••]	264	< 1 year	1995–1998	8	MDR increased from
	113	< 1 year	1999–2000	22.7	3.8% to 10.2%
Switzerland [30]	35	< 1 year	1996	8.6	Resistance in IDU = 13%,
	41	< 1 year	1997	14.6	homosexual = 11%,
	60	< 1 year	1998	8.8	heterosexual = 6%
	61	< 1 year	1999	5	
San Francisco [31••]	40	< 1 year	1996–1997	25	MDR increased from 2.5%
	94	< 1 year	1998–1999	18	(1996–1997) to 13.2%
	91	< 1 year	2000–2001	27	(2000–2001), NNRTI resistance increased from 0% (1996–1997) to 13.2% (2000–2001), PI resistance increased from 2.5% (1996–1997) to 7.7% (2000–2001)
Europe and Israel (CATCH) [32]	596	< 1 year	1996–2002	10	—
Montreal [33]	170	< 1 year	1996–2003	12	—
United Kingdom [34]	157	< 18 months	1996–2003	17	—
United States (STAHRS) [35]	182	STAHRS	1997–2001	12	Increase
Canada (STAHRS) [36]	144	STAHRS	1997–2001	10	—
San Francisco [37]	180	< 1 year	2000–2002	26	Decrease
France [38]	296	< 6 months	2001–2002	11	Decrease

CATCH—Combined Analysis of Resistance Transmission Over Time of Chronically and Acutely Infected HIV Patients in Europe; IDU—intravenous drug use; MDR—multidrug resistance (defined as resistance to at least two different classes of drugs); NNRTI—non-nucleoside reverse transcriptase inhibitor; PI—protease inhibitor; STAHRS—Serological Testing Algorithm for Determining Recent HIV Seroconversion.

[41], which will influence ART treatment response in these patients and may allow for secondary transmission of this drug-resistant variant.

Because of the implications of drug-resistant virus on treatment of ART-naïve patients, HIV resistance testing in recently infected individuals is recommended [42•].

Clinical Interventions During Primary HIV Infection

Antiretroviral therapy

There are many theoretic rationales for treating patients during primary HIV infection with ART. ART has been shown to be safe and tolerable when administered during primary HIV infection, and to demonstrate virologic and immunologic effect [43]. ART may block viral dissemination and preserve HIV-specific immune responses. Recovery of certain CD4 cell subsets is more complete and more rapid when ART is administered early in the course of HIV infection [44]. However, there has been no randomized trial of ART to support this therapeutic approach.

Interleukin-2

Interleukin-2 (IL-2) is a cytokine that has many effects on the cellular immune system, including the stimulation of CD4+ and CD8+ T-cell proliferation and the promotion of CD8+ cell maturation. When administered with ART during early HIV infection, IL-2 treatment results in large, sustained increases in CD4 cell counts of naïve and memory phenotypes [45]. Any clinical benefit of these increases is yet to be demonstrated.

Cyclosporine A

As a suppressor of the cellular immune response, cyclosporine A (CsA) may prevent T-cell activation and subsequent destruction during primary HIV infection. In addition, CsA administered during primary HIV infection may limit the size of the latently infected pool of T cells that have proven to be a barrier to viral eradication. In the only trial of CsA during primary HIV infection, nine patients were selected to add CsA to a regimen of highly active ART for 8 weeks. After 1 year, patients administered CsA had statistically larger CD4 cell increases and no difference in serum HIV RNA or cell-associated HIV RNA or DNA [46].

Vaccines

Therapeutic vaccination during a period of viral suppression may induce HIV-specific immune responses without the danger of increased CD4 cell infection and destruction. In 16 patients successfully treated during primary HIV infection (11 of whom were administered vaccines during viral

suppression), HIV viral rebound was uniformly demonstrated after cessation of ART [47]. No differences between vaccinated and unvaccinated patients were seen in terms of viral dynamics during rebound, although transient suppression of viremia immediately after ART discontinuation and subsequent decline in viremia of 0.3 to 3.1 $\log_{10}$ copies per mL after the initial burst of viremia argue for further study of this intervention.

Treatment interruption

The cessation of treatment with an improvement in virologic control is the ultimate goal of the initiation of treatment during primary HIV infection. Strategies examining the effect of sequential treatment interruptions on control of viral replication have demonstrated improved HIV-specific immune responses but have not seen a demonstrable clinical benefit. Additional studies are ongoing.

Partner Notification in Primary HIV Infection

The issue of contact tracing and partner notification (PN) in HIV is contentious. Using models similar to PN in other sexually transmitted diseases such as syphilis, 33 states have enacted HIV/AIDS-specific PN laws, and many others have general communicable disease reporting laws that may be applied to HIV [48]. In addition, states receiving Ryan White funding are required to show "good faith efforts" to notify spouses of HIV-positive individuals.

Early in the HIV epidemic, opponents to PN cited concerns about HIV stigmatization, the high cost and questionable benefit of PN, the potential for PN to decrease HIV testing, and the lack of effective HIV treatment as barriers to its widespread implementation [49]. Legal scholars and ethicists cite the implicit breach in provider-patient confidentiality that ensues from PN.

Although some of those issues remain, the balance has shifted somewhat. Experience with PN programs has shown that they do not have a dramatic decrease on testing volume and have proven to be cost effective [50•]. Also, given the success in prevention of perinatal transmission of HIV, and the potential reduction of spread of HIV by persons who are unaware of their infection status through education and treatment, PN can reduce additional spread of HIV. However, most importantly, individuals identified as HIV-infected through PN programs may take advantage of the effective treatments for HIV that now exist.

Studies of the effect of PN are conflicting. Several studies have indicated that PN is less effective among homosexual men than heterosexuals [50•]. In areas of the United States where HIV infection rates are the highest, most patients diagnosed with HIV do not receive public health PN services [51]. Concerns about HIV PN leading to partnership dissolution, new partner acquisition, or domestic violence have not borne out [52,53]. Increased condom use after PN has been demonstrated [52,53]. PN is more effective when implemented by trained public health counselors than by the newly diagnosed patients themselves [54] and may allow the public health counselors to offer education, counseling, and testing to potentially exposed individuals.

Because of the relatively short time period of possible exposure among patients diagnosed with primary HIV infection and the potential for high rates of spread during primary infection, PN may be more efficient and more effective during this time period. In the context of primary HIV infection, PN is a potentially important public health intervention and warrants more consideration and evaluation.

Conclusions

Early diagnosis and appropriate management of primary HIV infection may significantly alter the long-term course of the disease and help reduce further transmission. The diagnosis should be considered in all at-risk patients experiencing a primary infection-like illness, and they should be offered HIV antibody and HIV RNA testing. The decision to evaluate a patient for primary infection presents clinicians with a unique opportunity to merge medical intervention with a comprehensive education program, including counseling for subsequent exposure risk reduction in patients who are subsequently determined to be HIV uninfected, counseling to prevent further HIV transmission, and evaluation for potential therapeutic interventions for patients who are determined to be experiencing primary HIV infection. Thus, considering and testing for primary HIV infection in the correct clinical situation allows early treatment for patients truly infected and provides an opportunity for patients who are HIV exposed but not infected to reduce subsequent exposure risks. Once the diagnosis is established, early treatment with combination ART should be considered, and awareness of local epidemiology of transmitted drug resistance should influence the empiric choice of ART, if it is started. Resistance testing during primary HIV infection is indicated whether or not ART is initiated. Public health interventions such as PN may be particularly effective during the relatively brief and highly infectious period of primary HIV infection. Whenever possible, patients experiencing primary infection should be referred to natural history or intervention studies in order to enhance our understanding of the immunopathogenesis and clinical management of HIV disease.

Acknowledgments

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