RECOGNITION AND TREATMENT OF PRIMARY HIV INFECTION

In the first decade of the AIDS epidemic, studies of the pathogenesis of HIV infection focused on the later stages of HIV disease. More recently, significant progress has been made in understanding the virologic and clinical events that occur immediately after the initial HIV infection, called primary HIV infection. At the San Francisco course James O. Kahn, MD, discussed this phase of HIV infection. He reviewed the definition of primary infection, how to recognize it clinically, and findings from studies evaluating treatment of this phase of the disease.

Definition of Primary HIV Infection

As with all infectious processes, infection with HIV starts when the uninfected and susceptible host receives an exposure to the pathogen sufficient to result in independent replication of the pathogen in the host tissues. Dr Kahn presented a definition for primary HIV infection incorporating two phases—phase I, or acute HIV infection, and phase II, or early HIV infection.

The distinction between primary infection and chronic infection, and between the two phases of primary infection (acute and early HIV infection), is based on the pathogenesis of HIV and the timing of the host immune response. Immediately after infection, rapid viral replication occurs in the tissues with a burst of viremia, measured as plasma viral RNA, that usually peaks within the first month (Figure 1). After this peak of virus replication the viremia decreases and then stabilizes. The peak in viremia coincides with the first appearance of an immune response, both humoral and cellular. There is delay of weeks to months between the ability to first detect virus in blood and tissues and the subsequent ability to detect antibodies. The time between the appearance of viral RNA and the appearance of antibodies is the period of acute HIV infection. Of note, neutralizing antibodies often do not appear for 6 months.
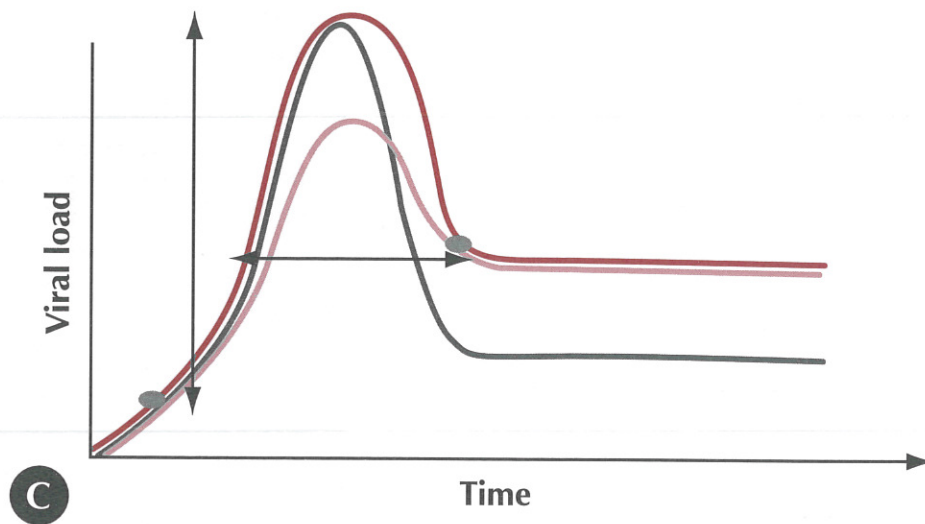

Figure 1. Model for the viral dynamics during primary HIV infection (see text).

Acute HIV Infection

The first phase of primary HIV infection, called acute HIV infection, constitutes approximately the first 30 days after the initial infection. According to Dr Kahn, acute infection can be further subdivided into three categories: A, B, and C (Table 1). In category A of acute infection the patient has evidence of viral replication (detectable HIV RNA by reverse transcriptase polymerase chain reaction [RT-PCR] or by branched DNA [bDNA]

assays) but there is no antibody measured by enzyme immunoassay (EIA) or by western blot analysis. In category B there is detection of viral RNA, the EIA assay can be positive or negative, and the western blot is indeterminate. Since about 5% of non-HIV infected individuals have an indeterminate western blot, the viral load measure may be able to distinguish true HIV infection from a false-positive serology. Category C acute infection is characterized by detectable HIV RNA in

Table 1. Defining and Characterizing Primary HIV Infection

Phase	Category	EIA	Western blot	Plasma HIV RNA
Acute HIV	A*	–	–	+
	B	+/–	Indeterm.	+
	C**	+/–	+	+
Early HIV†		+	+	+

* With evolution of antibody response or confirmation of HIV RNA.

** With a negative EIA or negative/indeterminant western blot in the previous 30 days.

† Within 12 months of a documented negative EIA.

plasma and evidence of antibodies by western blot, usually with an evolving pattern, but a known negative EIA or a negative or indeterminate western blot when tested within the prior 30 days.

Early HIV Infection

This subdivision of primary infection is similar to category C of acute infection, in that there is evidence of viral replication (detectable plasma HIV RNA) and antibodies by western blot, but the EIA serol-

> *The acute HIV syndrome mimics other, more benign viral infections, and is often not recognized as HIV in the primary care setting.*

ogy has been negative within the prior 12 months. Detection of this category of infection follows the classic seroconversion technique used in diagnosing many viral diseases by obtaining two serum specimens, one collected before or during the onset of symptoms of acute infection, and one collected after the resolution of acute symptoms (the convalescent phase).

One caveat in using quantitative tests for viral RNA is that false-positive results occur in about 3% of cases. However, most false-positive values are low level, typically at or below 1,000 copies/mL, and such results should lead to a repeat test if serologic and clinical data are not definitive.

Recognition of Primary HIV Infection

In order to intervene in primary HIV infection, the clinician first must recognize the event that leads to the necessary laboratory tests. Currently there is inconsistent recognition and diagnosis of the clinical syndrome associated with primary infection, which occurs in approximately 80% of primary infections. In one evaluation of 23 laboratory-confirmed cases of acute infection, 20 patients (87%) had signs or symptoms at the time of infection. Of

these, 19 (95%) sought medical evaluation, but acute HIV infection was considered in only 5 of the 19 patients.

Table 2 shows the most common signs and symptoms associated with acute HIV infection, in order of frequency. Symptoms typically appear 1 to 4 weeks after the exposure to HIV. The acute retroviral syndrome mimics many other viral syndromes, except the common cold, since there are no rhinitis and coryza with acute HIV. Taking a detailed history, including recent sexual and injection drug practices, is an important part of the evaluation. A history of higher-risk behavior raises the index of suspicion and helps distinguish clinically other common viral infections from acute HIV infection.

Rationale for Treatment of Primary Infection

Theoretical Basis for Treatment of Primary Infection

Following the initial burst of viral replication and the peak of viremia, the plasma HIV RNA level decreases and then stabilizes to a level called the viral set point (light gray circle in Figure 1). The set point is the result of a number of factors, including the maximum or peak viral load, the duration of the viral burst, the viral replicative half-life, and the host immune response. Antiretroviral intervention could have several effects on the kinetics of the acute phase of infection. The peak viral load may be reduced without affecting the set point, as shown by the red curve, or, the peak viral load might not be affected, but the duration of the viral burst might be shortened, which would reduce the set point (pink curve).

The amount of replicating virus to which a person is exposed, conceptually the area-under-the-curve in Figure 1, may determine the damage done to the immune system and the later steady state viral load indicated by the set point. Theoretically with a lowered peak viral load there would be less seeding of the virus to the lymphoid and other tissues during the viral burst, which might reduce the overall body burden of HIV during the chronic infection. This might have important implications for "sanctuary sites" of HIV infection, such as the central nervous system. Additionally, the extent of the initial immune system damage may

Table 2. Signs and Symptoms of Acute HIV Infection

Sign or Symptom	Percent of Patients
Fever	87
Rash	68
Lymphadenopathy	55
Sore throat	48
Myalgia	42
Oral ulcers	40
Headache	39
Diarrhea	32
Genital ulcers	23
Perleche	6

Percentages are based on 30 patients with acute HIV infection.

From Kinloch-de Loës. Clin Infect Dis. 1993.

be lessened, reducing the level of immunocompromise during the chronic phase.

Lastly, according to Dr Kahn, the viral quasispecies (the spectrum of genetic variants) during the acute phase of infection is likely to be relatively more homogeneous than later in the infection. This is because virus produced during the early replicative cycles will be the progeny of a relatively limited genotypic repertoire of the small number of viral particles that initiated the infection. The rate at which HIV develops mutations that are resistant to antiretroviral drugs is proportional to

> *Treatment of primary HIV infection may be less likely to result in HIV resistance.*

the genotypic heterogeneity of the viral population being treated. The more heterogeneous the genotypes the more likely that resistant mutants already exist in the population. Theoretically, patients with a more homogeneous infection would be less likely to develop resistance mutations, and there would be a better chance to eliminate all HIV replication with early treatment.

Primary Infection Studies

The NIAID announced the funding of an ambitious new program that focuses on innovative ways to study how HIV-1 causes disease in adults. Scientists at six research units will use interventions, such as highly active antiretroviral therapy given in the acute and early phases of infection, to increase the understanding of the mechanisms and course of HIV disease. They will also directly study the outcomes of these interventions.

The six *Acute Infection and Early Disease Research Program* principal investigators and their proposed research plans are:

- Lawrence Corey, MD, of the Fred Hutchinson Cancer Center in Seattle, will define the role of cytotoxic T-lymphocytes in controlling early infection and determine whether initial HIV-1 specific CD8+ T-cell responses are predictive of subsequent disease progression.

- David Ho, MD, of the Aaron Diamond AIDS Research Center in New York, will examine the effect of antiretroviral therapy on virus in the blood and lymphoid tissue on CTL response. His team also proposes to monitor B and T-cell responses.

- Jay Levy, MD, of the University of California San Francisco, will evaluate the effect of therapy on viral load, the rate at which the virus is produced, immune activation and CD8+ T-cell function.

- Joe Margolick, MD, of the Johns Hopkins University School of Medicine, will explore how the virus adapts to the host during early infection and determine whether treatment during acute infection allows the immune system to recover its function.

- Robert T. Schooley, MD, of the University of Colorado Health Sciences Center in Denver, proposes to examine the differences among virus in the lymph tissue and blood, and to determine the types of cells that are involved in active versus latent infection.

- George Shaw, MD, PhD, of the University of Alabama at Birmingham, will study where HIV is distributed and sequestered in the body and its form in various reservoirs, the dynamics of virus reproduction and the host immunogenetic profile.

NIAID press releases, fact sheets and other materials are available on the Internet via the NIAID home page at:

http://www.niaid.nih.gov.

Laboratory Data Supporting Treatment of Primary Infection

Dr Kahn reviewed a study performed at the University of Washington in Seattle in monkeys challenged with simian immunodeficiency virus (SIV). The monkeys were administered PMPA, an antiviral compound related to adefovir, 48 hours before and 4 hours or 24 hours after challenge inoculation. In the control group of 10 monkeys all developed infection as determined by detection of viral RNA in plasma, SIV DNA in peripheral blood mononuclear cells (PBMC), development of SIV-specific antibodies, and SIV in lymph node tissue. None of the treated monkeys developed any evidence of SIV infection, including those treated 24 hours after the challenge inoculation.

Clinical Data Supporting Treatment of Primary Infection

Dr Kahn presented summaries from several epidemiologic or clinical studies in other settings of HIV infection (eg, post-exposure prophylaxis and maternal-fetal transmission) providing indirect pathogenetic support for the concept of early treatment in the setting of primary infection. The Centers for Disease Control and Prevention (CDC) conducted a multinational, case control study of healthcare workers exposed to HIV. Among 31 healthcare workers who had an occupational exposure to HIV, the use of zidovudine monotherapy soon after the exposure reduced the risk of HIV infection (odds ratio of 8.5). In the placebo-controlled ACTG 076 trial, zidovudine monotherapy given during both the prenatal and postnatal period (presumably during the time that primary infection of the child occurs) reduced the rate of infection in the infants at 18 months of age from 25.5% to 8.3% (P <0.001). These data indirectly suggest that treatment during the time of initial HIV infection is likely to have clinical benefit and provides a rationale for treating people with primary HIV-infection.

Cautions About Early Treatment

According to Dr Kahn, there are also theoretical risks associated with early treatment. Modulating the infection early, before the development of a full immunologic response to the virus, might result in an overall weaker immune response, manifested as lower levels of antibodies, or lower affinity antibodies, or a less vigorous cellular immune response. This may result in more rapid HIV progression later if the treatment is discontinued or if viral resistance develops. There are anecdotal reports of a clinical syndrome similar to that with acute HIV infection that occurs in some patients who discontinue treatment for primary HIV. As with any unproven therapy, the benefit to risk ratio may be lower for antiretroviral intervention during primary infection since the long-term benefits are not known but the toxicities of the drugs may still be considerable.

Preliminary Data on Treatment of Primary Infection

Reported Early Treatment Studies

Dr Kahn summarized a multicenter, double-blind, placebo-controlled study of zidovudine monotherapy 250 mg bid. A total of 77 patients with primary HIV infection were treated for 6 months, with a mean follow-up of 15 months. Among the 39 patients randomized to zidovudine, 1 patient had an early opportunistic infection (OI), and 7 of 38 patients on placebo had an OI, including herpes simplex infection, oral hairy leukoplakia, and candidiasis. Compared with the placebo group, the treated group experienced a rise in CD4+ cell counts that persisted for about 6 months, after which time the decline paralleled that of the placebo group, perhaps due to the fact that zidovudine was discontinued at that point.

In another report reviewed by Dr Kahn, a Vancouver group studied a combination of zidovudine/didanosine in patients who were HIV p24-antigen positive but HIV-antibody negative, or who had evidence of seroconversion within the prior 6 months. This was not a randomized study, as treatment was determined by patient choice. Seven of eight gay men and one of ten injection drug users accepted treatment. The 10 patients who declined treatment were followed as the control group. The

mean plasma HIV RNA level among all patients at entry was 350,000 copies/mL. Compared with the control group, combination treatment resulted in approximately a two log drop in HIV RNA, and

Preliminary clinical data show a marked reduction in HIV RNA following treatment of acute HIV infection.

by week 12 four of six treated patients had plasma HIV RNA levels less than 500 copies/mL.

Dr Kahn also summarized a study in which 12 patients were treated with zidovudine/lamivudine/ritonavir within 65 days of the onset of symptoms of acute HIV infection. At entry all patients had detectable plasma HIV RNA (mean 91,000 copies/mL), and the mean CD4+ cell count was 633/µL. Three patients reportedly withdrew, leaving nine who were followed up long term. From the first month of treatment, at least 75% of the patients had plasma HIV RNA levels below 500 copies/mL by bDNA assay (Figure 2). This antiviral effect appeared to have persisted for at least 9 months.

Initiation of treatment with antiretroviral drugs during primary infection results in marked decreases in HIV viral load. Based on the rationale for early treatment that Dr Kahn outlined above, these reductions in HIV load may translate into immunologic and clinical benefit, and clinical studies are under way to evaluate this possibility. However, at present there is no direct clinical evidence that early treatment provides long-term benefit.

Summary

Primary HIV infection is underdiagnosed, but can be confirmed by recognition of the acute HIV clinical syndrome followed by appropriate laboratory testing. There are compelling preliminary laboratory and clinical data to suggest that antiretroviral intervention during primary HIV infection may alter the long-term outcome of the infection. Key to the laboratory diagnosis of primary infection is a combination of EIA and western blot serology and testing for plasma HIV RNA (or alternatively HIV p24 antigen). Early intervention should consist of combination antiretroviral treatment, preferably with potent antiretroviral drug regimens that include at least one protease inhibitor. There are risks associated with treatment during the primary phase of infection. Until well-designed clinical studies of early intervention are completed, the potential benefits and risks must be evaluated on an individual patient basis, or patients may be referred into one of these clinical trials.

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Suggested Readings

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