Primary HIV Infection: Recognition and Management

At the Los Angeles course, Eric S. Daar, MD, discussed scientific, clinical, and social issues concerning primary HIV infection. Dr Daar presented an overview of diagnosis and management given the current understanding of the biology of HIV disease and of this initial stage of infection.

Primary HIV infection offers unique insights into the pathogenesis of HIV disease and the immune response to HIV. The management of primary HIV infection requires consideration of almost every factor operating in HIV disease: virology, immunopathogenesis, transmission, treatment, and medication adherence. Unfortunately, primary HIV infection is often not identified, and thus, may represent a lost opportunity to impact the patient's disease at a crucial time. Furthermore, this under-identification has meant that the available data for primary infection are largely based on small nonrandomized studies, and often associations and anecdotes. Dr Daar stressed that there is a great need for state and national priorities to increase the recognition of primary HIV infection, to gain further knowledge about the immunopathogenesis of this disease state, and to define the optimal treatment.

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Virologic and Immunologic Aspects of Primary Infection

Primary infection refers to the period surrounding the time at which HIV first enters the body. During the first few weeks of infection (generally 3-6 weeks after exposure to the virus), a burst of viremia accompanies the acute syndrome and may go unnoticed. From 1 week to 3 months following infection, an HIV-specific immune response develops. Dr Daar noted that physicians commonly look for a humoral immune response in individuals suspected of recent HIV infection, but the cellular immune response may be a more important controlling factor in early viremia. As data from prospective studies accumulate on primary HIV infection (ie, from following individuals from the first few weeks after exposure), several relationships emerge:

- Individuals who are most symptomatic during primary infection have the highest plasma HIV RNA levels.
- Persons who are symptomatic during the primary infection period have more rapid disease progression than those who are asymptomatic during this time.
- The viral set point parallels clinical outcome, such that individuals with high plasma viral load set points (eg, >10,000 copies/mL), at approximately 6 months after seroconversion, are more likely to progress to AIDS in the first 5 years than individuals with lower plasma viral load set points (eg, <10,000 copies/mL).
- Primary infection results in seeding of virus into the lymphoid tissue and central nervous system (CNS).
- Potent CD8+ cytotoxic lymphocyte (CTL) responses after seroconversion are associated with greater decreases in viremia (after the initial burst) and slower CD4+ cell declines over a 2- to 3-year period.

The composition of the virus population is an important variable to consider during primary infection. According to Dr Daar, evidence suggests that the virus population at this time is relatively homogeneous; apparently there is preferential transmission of the nonsyncytium-inducing viral phenotype, now called R5 viruses (referring to the utilization of the chemokine receptor CCR5). With regard to the virus's resistance phenotype or genotype, the acquisition of resistant strains of HIV have been recognized with increasing frequency.

The immunology of primary HIV infection is also gradually being characterized. It has been shown that early immune damage does occur. Several factors negatively affect the immune responses to HIV infection, and other factors produce responses that are important for controlling HIV replication (Table 1).

Recognizing Primary HIV Infection

Of the estimated 40,000 people in the United States who become infected with HIV each year, a poorly defined 30% to 80% may develop symptoms of primary infection, called the acute retroviral syndrome. The majority of these patients will not be diagnosed for several reasons. First, the patients themselves are often not aware of their exposure risk or the

Table 1. Immunology of Primary HIV Infection

- **Possible immune damage**
  - Decline in lymphoproliferative responses to mitogens
  - Immune activation
  - Decline in CD4+ T-lymphocyte number
  - Decline in HIV-specific CD4+ cell responses
- **Potentially beneficial immune responses**
  - CD8+ cytotoxic T-lymphocytes
  - CD4+ helper cell responses
  - Humoral immune response

symptoms associated with the acute retroviral syndrome, and therefore do not seek medical care. When patients do present for care, HIV risk factors are often not disclosed and, in turn, the classic signs and symptoms of primary infection are not recognized and the appropriate evaluation is not performed.

Fever, adenopathy, and sore throat are the most frequent but very nonspecific signs and symptoms of primary HIV infection (Table 2). Thus, the original description of the syndrome was of an acute mononucleosis-like or flu-like illness. Rash is a more specific finding, but it can still be associated with several other illnesses. The presence of a rash often leads to diagnostic tests for syphilis; but suspecting syphilis should raise the index of suspicion for primary HIV infection as well. In addition to rash, patients with oral ulcerations resembling herpes or aphthous stomatitis should also be evaluated for primary HIV infection.

Diagnosing primary HIV infection requires a high index of suspicion for the clinical syndrome and a sound knowledge of the appropriate diagnostic tests to perform. Evidence of an immunologic response can be identified during the first few weeks after exposure. As the screening antibody tests have become more sensitive, the seronegative window period has narrowed. Virologic tests narrow this window further, as plasma viremia can be detected within days of infection. Dr Daar recommended that the diagnosis of primary HIV infection be made on the basis of HIV viremia rather than antibody testing alone, since early infection is characterized by low levels or the absence of antibodies to HIV. Determination of HIV p24 core antigen levels has been considered an insensitive assay for established HIV infection, but the test is often positive during symptomatic primary infection. The more commonly used tests (because they are more sensitive) are those that measure for plasma HIV RNA. Unfortunately, false-positive plasma HIV RNA results occasionally occur. However, Dr Daar noted that in this setting plasma HIV RNA levels are generally below 10,000 copies/mL, while those with primary HIV infection typically have levels in the range of 100,000 to greater than 1 million copies/mL.

Common laboratory abnormalities include leukopenia, anemia, thrombocytopenia, elevated transaminases, and atypical lymphocytosis. These signs, symptoms, and laboratory abnormalities should lead to a differential diagnosis that includes Epstein-Barr virus or cytomegalovirus mononucleosis, toxoplasmosis, secondary syphilis, rubella, viral hepatitis (in the presence of elevated transaminases), group A streptococcus infection or herpes simplex and other viral infections. All of these need to be addressed and evaluated for at the same time that the HIV tests (virologic and immunologic) are being performed.

Table 2. Signs and Symptoms of Primary HIV Infection Among 365 Patients

Sign or Symptom	Number of Patients (%)
Fever	342 (94)
Adenopathy	253 (69)
Sore throat	241 (66)
Rash	197 (54)
Myalgia/arthralgia	175 (48)
Headache	140 (39)
Diarrhea	115 (32)
Nausea/vomiting	105 (29)

Adapted from Katsufrakis PJ and Daar ES. In: *Primary Care*. 1997.

Clinical Issues Specific to Primary Infection

Patients who present with suspected primary HIV infection require a considerable amount of education and counseling. The risk of a false-negative or a false-positive result needs to be explained during the pre-test counseling. When the test results become available, appropriate post-test counseling will then be necessary. It is important to recognize that patients with primary infection are often quite ill and may think that being symptomatic with HIV disease means having AIDS, particularly given the prolonged duration of the syndrome (several weeks). The counseling after positive test results presents an opportunity to clarify the difference in these stages of HIV disease.

Individuals who are ill with primary infection are often asked to make immediate decisions related to complex aspects of treatment that often have long-range consequences. It is the clinician's responsibility to help the patient understand the rationale for and the goal of therapy, as well as the importance of medication adherence, before they initiate treatment. Physicians can play a critical role at this stage by spending time with patients upfront, thereby improving the odds that patients will continue on therapy and avoid creating an environment favorable to the development of drug-resistant virus.

Therapy During Primary Infection

The question of when to initiate therapy for primary HIV infection remains an important one, but has yet to be answered. This issue is being addressed in several research programs, including a collaborative state project in California. In the interim, based on scientific rationale, Dr Daar believes it is reasonable to initiate antiretroviral therapy as early as possible in patients who are prepared to commit to the complex therapy required. Education and counseling about the various drugs and regimens and the requirements of antiretroviral therapy should be provided, after which time patients should be offered a potent antiretroviral regimen. It is not known which drug regimen is the most effective in this setting, but many

open label studies have resulted in maximal viral suppression with several different 3-drug regimens. The best antiretroviral regimen will be one that is most likely to be adhered to. Importantly, it must be explained to the patient that the therapy will most likely need to be continued for an extended period of time, and possibly for life.

In the context of therapy, the biologic and physiologic difference between the first few days and the first few months after exposure to HIV is just beginning to be studied. New research is being implemented to examine the virologic and immunologic status of primary infection in patients treated within days versus months of acquisition of HIV infection.

As with most issues surrounding antiretroviral therapy today there are potential advantages and disadvantages associated with treating primary HIV infection (Table 3). Treating primary infection as early as possible may have clinical, virologic, and immunologic effects. Two placebo-controlled clinical trials have demonstrated the benefits of early therapy during primary infection, although both utilized zidovudine monotherapy, which would not be considered today. In both trials, patients did better when treatment was instituted during primary HIV infection. In one study, the mean monthly change in CD4+ cell count was better and the development of HIV symptoms was less common in treated patients.

The potential virologic benefits associated with treatment of primary HIV infection include a reduction in plasma HIV RNA levels and a reduction in the seeding of virus to the lymphoid and CNS tissues. In addition, early treatment might decrease the long-lived viral reservoirs. A study by Finzi and colleagues evaluated patients with primary and chronic infection and suggested that HIV reservoirs are established extremely quickly, perhaps within the first days or weeks of infection.

The immunologic benefits are unknown at this time, although data from studies by Walker and coworkers suggest that early treatment is associated with persistent HIV-specific CD4+ cell responses, such as a lymphoproliferative response to HIV p24 antigen. Patients who received antiretroviral therapy during primary infection retained these proliferative responses, a benefit which is usually lost in chronically infected patients. More research is being devoted to the CTL response, and although scant, available data do suggest that an initially robust CTL response appears to wane in patients treated during primary infection. Thus, strategies to maintain or even bolster the immune response in patients treated during this stage of HIV disease seems to be an important approach for the future. Primary infection may also be the best stage at which to attempt to purge HIV reservoirs by cellular activation with cytokines. Several groups are designing trials that include immunomodulatory therapies in primary HIV infection for long-term control of viremia.

No antiretroviral therapies or regimens are specific for primary infection; the same HIV-suppressive regimens that are used for chronic infection (ie, those containing a protease inhibitor) are believed to be appropriate for primary infection. Eventually, phenotypic or genotypic analysis for drug resistance of an individual patient's viral isolates may help determine the best regimen for initial therapy. For now, epidemiologic surveys and clinical research need to be completed to determine the precise role of resistance testing in the treatment of primary infection. This is emphasized by the recent reports of increasingly resistant virus being acquired by newly infected individuals.

One trial (reported by Hoen and colleagues from France) studied the effects of zidovudine/lamivudine/ritonavir in 40 patients with primary infection. Among the 18 adherent patients, 17 (94%) had plasma HIV RNA levels below 50 copies/mL after 6 months of therapy. Although the reduction of plasma HIV RNA to below detectable levels in the adherent patients is hopeful, the number of patients lost to follow-up and the number of patients who could not maintain adherence to the complex regimen is worrisome.

ACTG 371 is evaluating a four-drug combination (zidovudine and lamivudine along with the investigational drugs abacavir and amprenavir) in primary infection. A substudy of ACTG 371, a collaborative effort by universities in California, will seek to address the following:

- The effect of early therapy on development and decay of HIV reservoirs in latently infected cells.
- The effect of timing of therapy during primary infection on development and maintenance of HIV-specific cellular immune responses (to determine whether initiating therapy within days versus weeks versus months of the acute syndrome affects virologic and immunologic parameters).

Table 3. Rationale and Concerns in Treatment During Primary HIV Infection

Rationale (possible advantages)	Concerns (possible disadvantages)
Therapy could blunt dissemination	Therapy could decrease the magnitude and potency of the initial immune response
Therapy could blunt early immune damage	Risk of long- and short-term adverse effects
Narrow target for therapy because of homogeneous viral population	Cost
Therapy could decrease viral set point	Adherence
Therapy could decrease viral reservoirs	Effect of therapy in body compartments outside of blood

- The virologic determinants important to HIV transmission during the primary infection period.

Adherence is of central importance to the success of treatment for primary HIV infection. A patient's plasma viral load will gradually or abruptly rebound when therapy is interrupted. This observation alone underscores the fact that long-term therapy is crucial. Thus, patients who start antiretroviral therapy during primary infection need to understand that they are going to be on some form of therapy for an exceedingly long time, and possibly for life.

Although there are compelling reasons and an emerging scientific rationale for initiating antiretroviral therapy as early as possible in primary infection, there are also potential risks and many unanswered questions. The risks of adverse effects, for example, are important considerations. Individuals who are relatively healthy will be embarking on long-term treatment, and only now are some long-term toxic effects being recognized. These long-term abnormalities being reported in association with protease inhibitor use include glucose intolerance, fat redistribution, and hyperlipidemias. These alterations are added to the already well-known, short-term side effects. Additionally, the emergence of drug resistance possibly due to poor adherence or the transmission of resistant viruses is a key factor that will continue to influence the timing and choice of the initial therapeutic regimen. Epidemiologic monitoring of the prevalence of drug-resistant viruses in specific populations of newly infected individuals is essential to understanding the patterns of primary HIV resistance.

Summary

Clearly, more prospective and long-term data are needed to provide both scientific and clinical rationales for initiating treatment for primary HIV infection as early as possible, and for continuing suppressive treatment indefinitely. As these data accumulate, information about the immunopathogenesis of HIV infection immediately following exposure may provide insights into immunologic strategies for controlling HIV.

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Suggested Readings

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