Antibody-Negative But HIV-RNA Positive: Is PHI in Your Differential?

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Welcome to our first "special edition" of *The PRN Notebook*!

FOR MORE THAN TEN YEARS, THE PHYSICIANS' RESEARCH NETWORK HAS been providing peer support to HIV-treating clinicians through its New York City-based monthly lectures and its quarterly distribution of *The PRN Notebook*. Indeed, the past decade of research has brought a sea change in our understanding of the epidemiology, pathogenesis, and treatment of HIV infection. This has translated into a remarkably advanced standard-of-care that was barely imaginable a short while ago.

Just as the breakthroughs in basic research continue to pave the way for pharmaceutical companies and technology firms to develop novel therapeutics and laboratory tests, the advances of clinical research should serve as a reminder to all clinicians that the management of HIV disease is a work in progress and that new approaches in the diagnosis and care of HIV-positive people are always on the horizon.

This is certainly the case with primary HIV infection (PHI). Chalked up by many as a relatively inconsequential period in the overall natural history of HIV disease, PHI has now come to be recognized by some as a veritable window of opportunity for individuals fortunate enough to be diagnosed during the earliest stage of their infection. Clinicians who are alert to the risk factors, signs, symptoms, and the laboratory tools available to diagnose PHI are in an ideal situation to begin transmission risk-reduction counseling when it is most efficient and, if possible, to refer newly infected patients to research centers during this brief and fleeting stage of the disease. Unique treatment options that may offer significant immunologic benefits to individual patients and public health benefits to the larger community need to be studied further.

PHI has long been of major interest to the board members, faculty, staff, and clinician members of PRN. On a more personal note, I remember a PRN lecture delivered by Dr. David Ho back in 1995 in which he discussed the rationale for a study he was beginning to enroll, to evaluate the potency of triple-drug combinations involving the then-novel protease inhibitors in a group of subjects diagnosed with PHI. It was then that I began looking for PHI in my own patients and began referring acutely infected patients to the Aaron Diamond AIDS Research Center. The results of the study, presented by Drs. Ho and Marty Markowitz at the 1996 International AIDS conference in Vancouver, marked the true beginning of effective drug intervention in this epidemic and settled, once and for all, any doubts that this was a viral disease—and a treatable one.

Despite the relative importance of PHI in research, the diagnosis of this earliest stage of the disease has never reached the mainstream. For most people, the diagnosis of HIV disease is made later, through HIV antibody screening during the asymptomatic chronic stage of the disease, or even later, when the immune system deteriorates, resulting in AIDS-defining illnesses that make the diagnosis of HIV a formality.

In order to shed new light on the issue of early diagnosis and the potential advantages and disadvantages of treating PHI, we organized our very first "roundtable" workshop in October 2001, dedicated exclusively to this particular topic. Present at this workshop were numerous thought leaders who have been engaged in PHI-related research for many years. This special edition of *The PRN Notebook* provides a relatively detailed look at some of the milestones in PHI-focused research that have been reached over the past few years and were discussed in five presentations delivered at the workshop.

Some of the key research data discussed in these articles, along with many of the diagnostic and treatment protocols that many clinicians are beginning to experiment with, were hotly debated at the workshop and to this day at larger medical congresses and in peer-reviewed journals. To be clear, PRN does not endorse a particular diagnostic or treatment strategy for patients with PHI. PRN does, however, firmly believe that all clinicians should at least be familiar with the signs and symptoms of PHI and be more diligent in their effort to identify individuals in the early throes of HIV infection, if only to initiate transmission-reduction counseling and, when possible, refer them to academic centers involved in the study of newly infected persons.

Diagnostic Challenges in the Clinic

To effectively identify patients with PHI, clinicians need to recognize the changing demographics of the epidemic and to look beyond stereotypes about traditional risk groups. Plain and simple, anyone who is sexually active or injects drugs is at risk for infection. The first step, then, is for clinicians to increase their efforts to assess risk factors in their patients. This requires gathering detailed histories, which should include questions from the clinician regarding specific sexual behaviors. Many adolescents and adults engage in what they perceive to be low-risk activities (e.g., unprotected oral sex and anal intercourse as a way to prevent pregnancy), as well as the more commonly recognized high-risk behaviors for transmission. Such issues can be awkward to incorporate into the workup

of a syndrome with such non-specific complaints, but are important nonetheless.

Clinicians must learn to recognize the common clinical and laboratory manifestations of primary HIV infection. As explained in our article reviewing the signs and symptoms of PHI (beginning on page 6), based on judicious points raised by Dr. Rick Hecht of the University of California, San Francisco, no combination of symptoms is totally indicative of underlying HIV infection; thus screening must be broad and inclusive.

In patients with PHI, antibodies to HIV are rarely present at high enough levels to rely on standard EIA or Western blot assays. In fact, a negative HIV antibody is a hallmark feature of PHI. As a result, a correct diagnosis of PHI is dependent on two variables: a negative EIA (and, if indeterminate, a negative Western blot) and a positive virologic assay, such as p24 antigen or HIV-RNA. While p24 antigen testing has been available for many years and is highly specific for the presence of HIV infection, it has limitations in its sensitivity, given that p24 antigen levels may not be detectable during the first few days of infection and may drop again to undetectable levels just as the humoral immune response begins to form. And while highly sensitive assays that measure plasma HIV-RNA or proviral DNA are available, these tests have specificity problems and should be used with caution to avoid delivering a false-positive result to already anxious patients.

PHI and Infection Spread

The study of patients with PHI has provided epidemiologists and clinicians alike with unique opportunities to define and explore the behavioral factors and contact patterns that contribute to the ongoing HIV epidemic. Epidemiological evidence reviewed by Drs. Jim Koopman (page 8) and Christopher Pilcher (page 11) suggests that HIV-positive individuals may be most infectious during PHI, given their extraordinarily high viral loads and naiveté regarding their own infection. Thus, there are potential public health ramifications of PHI, which raise important questions regarding how aggressive clinicians should be about testing, counseling, and treatment of their acutely infected patients.

However, preliminary epidemiological data alone do not justify sweeping changes in clinical care guidelines, especially when costly diagnostic tools and antiretroviral agents are involved. Only data from well-designed clinical trials—whether the intended beneficiary is the infected individual or the larger community—will settle some of the complexities and controversies that continue to prevent clinicians from more aggressively diagnosing and treating individuals in this earliest stage of HIV disease.

As illustrated by Drs. Pilcher and Koopman, a great deal of foundational work has been completed, which certainly paves the way for future efforts, both in research and in the clinic. Yet, even without more concrete answers, a take-home message stemming from what has been determined is possible. Preliminary case-clustering data, modeling predictions, and other biological and epidemiological findings justify efforts to step up certain intervention methods, including more aggressive and rapid contact tracing.

The Rationale for Treatment

If viral eradication or remission is possible, it will likely be documented in patients treated earliest, particularly during PHI. The reason for this can be found in the plethora of pathogenesis research that has been documented over the past decade.

First, if started early enough, HAART may limit the pool size of long-lived HIV-infected cells, such as memory CD4+ cells. Because these cells are rapidly seeded within days of infection, therapy must be initiated promptly and effectively to slow this process. Second, initiating therapy during PHI appears to protect the function of HIV-specific CD4+ cells and, consequently, HIV-specific cytotoxic T-lymphocytes. Protecting these key immune responses to HIV may translate into a low viral setpoint—which has been shown to translate into long-term clinical benefit—once therapy is halted. This has certainly been the experience of researchers, including Drs. Bruce Walker and Eric Rosenberg at Massachusetts General Hospital (MGH) in Boston (page 20). Third, HIV is generally quite homogenous immediately after transmission, but the virus then diversifies, limiting the ability of the immune system and antiretroviral treatments to control HIV-RNA levels.

There is also the lingering question of whether or not HIV eradication is truly feasible. As reviewed by Dr. Martin Markowitz (page 16), the original eradication time frame—one and a half to three years of triple-drug antiretroviral therapy—has proved to be improbable. We now know that HIV infection is widely disseminated during PHI and persists for an extended period of time in certain cellular reservoirs. We've also learned that HAART as we know it is not potent enough to completely halt viral replication. But as Dr. Markowitz suggests, these two obstacles may not necessarily be insurmountable.

The fact is, the eradication of HIV or the long-term control of infection without life-long treatment remains a worthwhile goal. While many of us are currently locked into the debate regarding when to start treatment and which drugs to start with, the end result is still the same: the long-term use of antiretroviral drug combinations, none of which are risk-free. If ongoing research is able to demonstrate with certainty that the short-term use of potent antiretroviral therapy initiated during PHI is associated with either eradication or remission, then we will have achieved a breakthrough unsurpassed by treatment at any other later stage of disease.

At the present time, the United States Department of Health and Human Services and the International AIDS Society-USA recommend the initiation of potent antiretroviral therapy in PHI. However, both sets of recommendations are quick to point out that the true risks and benefits of treatment during PHI have not been defined. There is also the risk of developing drug resistance early in HIV disease that would preclude effective treatment during the later stages of illness and potentially expose patients to toxicities at a much earlier time. In turn, we at PRN firmly believe that clinicians should refer their acutely infected patients to research centers where they may participate in studies to assess the role of antiretroviral and immune-based therapies during this fascinating but brief and often forgotten stage of HIV infection. prn

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