The Diagnosis of PHI: Is There Consensus?

Frederick M. Hecht, MD
Associate Professor of Medicine, UCSF Positive Health Program
San Francisco General Hospital, San Francisco, California

A number of experts suggest that PHI is a unique window of opportunity with respect to treatment, since it may be the optimal time to initiate HAART to alter the long-term course of HIV disease. On a public-health level, correct diagnosis and medical intervention during PHI—a period in which viral load is exceptionally high—may be useful in halting the unintentional spread of the virus when someone is hypothesized to be most infectious.

But, to take advantage of either the possible therapeutic or public-health opportunities during PHI, clinicians face a daunting task right from the start: actually connecting with and correctly diagnosing individuals in the initial throes of acute infection. While it is true that a growing number of people are likely to seek care immediately after possible exposure, given that the stigma and general sense of pessimism surrounding HIV infection has lessened, the most likely scenario involves patients who appear in the clinic only after symptoms of PHI have surfaced—not necessarily aware that they may be connected to acute retroviral syndrome.

The Options Project, developed and run by the University of California, San Francisco (ucsf) ANS Program at San Francisco General Hospital, is dedicated to the study of PHI clinical management. This program, along with other cohort-based projects across the country, have made headway in elucidating the symptoms of PHI and in deciphering the validity of various diagnostic tools currently available to clinicians. “Clinicians need to know what signs and symptoms to look for and what tests to order if they’re suspicious,” commented Dr. Hecht, director of the project. “These are definitely the first steps in dealing appropriately with PHI.”

The Options Project
The Options Project, which began enrollment at San Francisco General Hospital in April 1996, actually contains three distinct groups of patients: 1) patients who present with symptoms of acute HIV infection and a recent history of potential exposure; 2) patients with symptoms of acute HIV disease referred by other physicians in the San Francisco Bay area; and 3) patients who had been infected and seroconverted within 12 months prior to entering the study. As of December 2001, the Options Project team had screened 648 patients. Of these, 267 were documented to be experiencing PHI upon entry; the remaining 381 volunteers screened either were found to be HIV-negative or had been infected with HIV for longer than a year.

For Dr. Hecht and his colleagues, ferreting out newly infected patients among HIV-positive study volunteers required both sleuth work and reliance on a new detuned HIV-antibody test. “One thing we can do is look at a study volunteer’s HIV-antibody testing history,” explained Dr. Hecht. “We can couple his or her new positive-antibody test result with recent sexual or IV drug use and weigh it against a previous antibody-negative result within 12 months prior to entering the study. Chances are, we’re dealing with someone who was infected within six months before entering our study.” However, researchers have wanted additional confirmation of recent infection in persons without documentation of a recent negative-antibody test, which is where the detuned HIV-antibody test has come in.

The detuned (or less sensitive) HIV-antibody assay is the main ingredient of an HIV testing strategy known as the Serologic Testing Algorithm for Recent HIV Seroreconversions (STASHER). The detuned assay was developed at San Francisco’s Blood Centers of the Pacific in connection with the U.S. Centers for Disease Control (CDC). It is less sensitive to HIV antibodies than standard ELA tests and, in most cases, takes approximately four months longer than conventional antibody tests to become reactive. Pairing a negative detuned-assay result with a positive result using a standard assay—which can usually detect antibodies within four to six weeks post-infection—would indicate an infection less than six months old.

Making Sense of Symptoms
Of the estimated 40,000 people in the United States who become infected with HIV each year, the rate of people who will actually experience symptoms of PHI probably ranges from 50% to 90%. Even then, it is still not known how many people with symptomatic PHI actively seek out medical care or are correctly diagnosed upon doing so. “We do know that a relatively large percentage of patients do, in fact, experience symptoms related to PHI,” explained Dr. Hecht. “In some cases where we are considering PHI, we’re dealing with patients who contact us soon after a high-risk activity, such as sex without a condom, condom breakage, or even intravenous drug use. Otherwise, we’re usually dealing with patients who come to us with symptoms.”

The time from exposure to the onset of symptoms is usually two to four weeks, but the incubation may be as long as 10 months in some cases (Ridzon, 1997). “One of the issues we’ve been looking at is which symptoms best distinguish patients with PHI among patients in whom the diagnosis is considered,” Dr. Hecht explained. “In comparing various symptoms of disease experienced by the patients with...
TABLE 1. Symptoms Results: UCSF Options Project

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sensitivity/Specificity</th>
<th>Odds</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>51%/82%</td>
<td>4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oral Ulcers</td>
<td>37%/85%</td>
<td>3.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>54%/68%</td>
<td>1.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Weight Loss (&lt;5lbs)</td>
<td>32%/86%</td>
<td>2.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>54%/68%</td>
<td>2.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Malaise</td>
<td>68%/51%</td>
<td>2.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Myalgias</td>
<td>49%/69%</td>
<td>2.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Fever and Rash</td>
<td>46%/91%</td>
<td>8.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Source: Frederick M. Hecht, MD; modified from data presented at the 6th Conference on Retroviruses and Opportunistic Infections, January 1999 (Abstract 178).

PHI and uninfected patients in the Options Project cohort, Dr. Hecht and his colleagues were able to determine the sensitivity and specificity of various symptoms. At the time this analysis was originally presented, at the 6th Conference on Retroviruses and Opportunistic Infections in Chicago in 1999, 227 patients were screened for PHI through the Options Project; 30 had PHI and 197 were either HIV-negative or had been infected with HIV for at least a year. “We looked at 20 different symptoms,” he said. “The key symptoms were rash and fevers, followed by loss of appetite, arthralgias, and pharyngitis.” These findings are reported in Table 1.

Using logistic-regression models, Dr. Hecht and his colleagues were able to determine which symptoms were the best independent predictors of PHI. The odds of rash predicting PHI were 4.0 (p=0.002); the odds of fevers predicting PHI were 3.4 (p=0.009). “In other viral infections, we don’t often see fevers and we rarely see rash,” he explained. “These two symptoms, especially if accompanied by some of the other symptoms frequently seen in PHI, should heighten the level of suspicion.”

In another evaluation conducted by researchers in Los Angeles and San Diego, 436 patients who had symptoms consistent with PHI were evaluated; primary infection was diagnosed in 54 (12.4%) of them (Daar, 2001). According to the report published in 2001 in *Annals of Internal Medicine*, fever, myalgia, rash, night sweats, arthralgia, and lack of nasal congestion occurred more frequently in patients with PHI, compared to those with other infections. However, the authors cautioned that the symptoms of PHI do not appear to be specific enough to “allow targeted screening for primary infection.”

Because many of the symptoms of PHI are really quite nonspecific, compounded by the fact that many patients fail to disclose HIV risk factors upon seeking medical care, many patients with PHI are not diagnosed correctly. “In this sense,” Dr. Hecht argues, “the diagnosis of PHI requires a high index of suspicion. Clinicians should always consider HIV risk factors, even if they are not voluntarily disclosed by the patient, particularly in the presence of symptoms of an acute febrile illness.”

Making the Diagnosis: p24 or HIV-RNA?

Beyond symptoms and risk-factor suspicion, clinicians should be familiar with the appropriate diagnostic tests to perform. During the first one to two weeks of infection, humoral (antibody) responses to HIV are virtually nonexistent and, thus, cannot be detected using even the most sensitive ELISA assay. An assay to detect HIV p24 antigen is widely available and relatively cheap. However, it may miss cases of HIV infection because of limitations in its sensitivity. “The main problem with sensitivity of p24 antigen testing,” Dr. Hecht remarked, “appears to be that it can decline below detectable levels due to early immune responses that standard ELISA are not sensitive enough to detect.” According to one report published several years ago, HIV p24 was found to be undetectable in as many as 20% of patients with symptomatic PHI (Kinloch-de Loes, 1993). More sensitive tests are those that measure for plasma HIV-RNA or proviral DNA.

Dr. Hecht and his colleagues have done their own analyses of viral-based assays for the diagnosis of PHI. To do so, the Options Project team compared blood samples collected from patients who were definitively in the primary stages of HIV infection (n=22) and those who were definitely not infected with the virus upon entering the program (n=193). Results of HIV-RNA testing using Chiron’s branched DNA (bDNA) assay are provided in Table 2a.

“What we saw when using the bDNA was excellent sensitivity,” explained Dr. Hecht. “However, we also appear to be dealing with a slight risk when it comes to specificity; 4% of our volunteers who were definitely HIV-negative upon entering the program had a positive bDNA test result. Branched DNA testing, like polymerase chain reaction (PCR), is meant to be used for diagnostic, not diagnostic, purposes in the setting of HIV. False positives were much more likely to be present in patients reported to have low viral loads, generally no higher than 2,000 copies/mL, whereas those with high viral loads proved to have actual infection.” As for a take-home message, Dr. Hecht suggests that “an HIV-RNA level that is less than 5,000 copies/mL should be considered an indeterminate PHI test result and should be repeated immediately; an HIV-RNA level less than 2,000 copies/mL is probably a false positive.”

With respect to HIV p24 antigen testing, Dr. Hecht commented that “we hoped
to be able to substitute this cheaper assay for the more expensive HIV-1 RNA testing for 
PHI diagnosis.” An analysis of data from the Options Project using an HIV p24 assay is 
reported in Table 2b. “While the specificity using this assay was better than what we 
chose using the bDNA assay, we obviously had a problem with sensitivity,” com-
mented Dr. Hecht. “Almost one-quarter of our patients who were not antibody-positive 
could not be diagnosed using p24 antigen testing alone. The five patients who 
had false-negative p24 readings were actually in the early stages of antibody 
conversion and had indeterminate antibody tests. The fifth patient, who appeared 
to be completely antibody-negative, had an HIV-RNA level of 6,000 copies/mL. 

“What we’re seeing with the p24 assay is a limited window of opportunity. Our five 
patients who had false-negative p24 antigen tests had probably already experi-
enced their p24 antigenemia peak. Antibodies were probably being produced and 
and binding with antigen in peripheral blood. At the same time, antibody levels 
were too low to pick up using standard EIA tests.” It’s during this time, Dr. Hecht ar-
gues, that HIV-RNA testing may be the most useful. “HIV-RNA assays detect infection 
before p24 antigen is detectable, and remain positive toward the end of the symp-
tomatic stage of PHI, when the humoral immune responses that can clear p24 antigen 
are beginning to form.” 

Pairing a p24 assay with an EIA test 
that can detect IgM antibodies present in 
the early stages of seroconversion is an 
opportunity to increase sensitivity. “But again,” warns Dr. Hecht, “we may run into the 
issue of limited specificity. Some of our data suggest that third-generation EIA anti-
body tests that can detect IgM as well as IgG antibodies may have an elevated 
false-positive rate when other infections that may look like PHI are present. “ 

In summing up his discussion regarding 
the diagnosis of patients with PHI, Dr. 
Hecht attempted to underscore the fine 
line that separates the need to be diag-
nostically aggressive and the need to pro-
tect patients from unnecessary anxiety. “There most certainly are potential bene-
fits to diagnosing patients in the primary 
stage of HIV infection. However, these bene-
fits are not lifesaving unless we’re aiming 
at an immediate intervention like post-
exposure prophylaxis. There are negative 
consequences in telling a patient that he or 
she has low detectable HIV-RNA or a con-

K E Y  P O I N T S

• “Primary HIV infection” (PHI) is defined using biological determinants, such as symptoms of 
acute retroviral syndrome and high levels of viremia that precede antibody seroconversion, 
during the initial stage of infection. The duration of PHI can vary, ranging from several weeks 
in some individuals to several months in others. “New HIV infection” is defined using a time 
determinant, usually an infection that has been established for less than one year. Biological 

determinants of PHI, not the duration of infection, are of greatest concern to those exploring 
the pathogenesis and management of HIV infection during the earliest stage of infection. 

• To take advantage of the unique windows of opportunity during PHI, clinicians must 
quickly and effectively identify potentially infected individuals and employ rapid and 
accurate laboratory testing to yield a diagnosis. 

• Fever and rash may be the symptoms most strongly associated with primary HIV infection. 
Myalgias, arthralgias, night sweats, oral ulcers, weight loss and loss of appetite should also 
increase likelihood of PHI. 

• Because many of the symptoms of PHI are really quite nonspecific, compounded by the 
fact that many patients fail to disclose HIV risk factors upon seeking medical care, the 
diagnosis of PHI requires a high index of suspicion. Clinicians should always consider 
HIV risk factors, even if the patient who presents with symptoms does not voluntarily 
disclose them. 

• Diagnostic testing involving p24 antigen is less sensitive than HIV-RNA tests for diagnosing 
PHI. It is likely to be most sensitive within the first week after the onset of PHI symptoms. 
Pairing a p24 assay with a third-generation EIA antigen “sandwich” test that can detect IgM 
antibodies present in the early stages of seroconversion is an option to increase sensitivity, 
but third-generation EIA antibody tests are not available in many clinical settings. 

• PCR or bDNA tests are highly sensitive PHI diagnostic tools, but have a lower specificity 
than p24 antigen tests. Repeat HIV-RNA testing is recommended to confirm results. 
Patients with an HIV-RNA level between 50 and 5,000 HIV copies/mL without a positive 
antibody test should be regarded as having an “indeterminate” result that is likely to 
represent a false positive. These testing results are especially important to repeat.

References
Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County 

Kinloch-de Loe S, de Saussure P, Saurat JH, et al. Symptomatic primary infection due to 
human immunodeficiency virus type 1: review of 31 cases. Clin Infect Dis 17(1):59-65, 
1993. 

Ridzon R, Gallagher K, Ciesielski C, et al. Simultaneous transmission of human immuno-

Roland ME, Elbeik TA, Martin JN, et al. HIV-1 RNA testing by bDNA and PCR in asympto-
matic patients after sexual exposure to HIV [Abstract 776]. 7th Conference on Retrovirus-