Recent Issues in Primary HIV: From Diagnosis to Oral Sex Transmission

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Thanks to sweeping improvements in the identification and clinical management of HIV among virtually all risk groups in the United States, HIV-infected people are now being diagnosed and receiving care earlier than their counterparts a decade earlier. However, most patients are still being diagnosed after one of the most unique and clinically crucial stages of HIV disease—primary HIV infection (PHI)—has come and gone.

Unlike the relatively slow progression rate associated with chronic HIV infection, PHI—loosely defined as the brief period after HIV first enters the body—invokes an awesome display of immune activity, high viral levels, and, in some cases, symptomatic disease. At the same time, many 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 (see sidebar on page 13). 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 at his or her most “infectious.”

The Options Project, developed and run by the University of California, San Francisco (UCSF) AIDS Program at San Francisco General Hospital, is dedicated to the study of PHI clinical management. Dr. Frederick Hecht, a codirector of the program, and his colleagues have made significant headway in addressing three thorny PHI-related issues: the risk of HIV transmission through oral sex; the diagnosis of PHI in patients who have not yet seroconverted; and the transmission of drug-resistant HIV strains.

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 have been infected and seroconverted within 12 months prior to entering the study. As of April 2000, the Options Project team had screened 444 patients.

For Dr. Hecht and his colleagues, ferreting out newly infected patients from the general population of 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 risk and weight 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 6 to 12 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 Serocoversion (starsh). The detuned assay was developed at San Francisco’s Irwin Memorial Blood Bank in connection with the U.S. Centers for Disease Control (CDC). It is less sensitive to HIV antibodies than standard ELISA tests and, in most cases, takes approximately three 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 three to four weeks post-infection—would indicate an infection less than four to six months old.

Diagnosing PHI in Clinical Practice

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 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, 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 the most distinguishable symptoms among patients with PHI.” In comparing various symptoms of disease experienced by the patients with 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. “We looked at 20 different symptoms,” he said. “The key symptoms were rash and fevers, followed by loss of appetite, arthralgias, and pharyngitis.”

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 3.7 (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.”

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.”

Beyond symptoms and risk-factor suspicion, clinicians should be familiar with the appropriate diagnostic tests to perform. During the first few weeks of infection, humoral (antibody) responses to HIV are virtually nonexistent and, thus, cannot be detected using even the most sensitive ELISA or Western blot 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. According to one report published several years ago, HIV p24 was found to be undetectable in as many as 20% of people 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 UCSF team compared blood samples collected from patients who were definitely 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 bDNA assay are provided in Table 1a. “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 PCR, is meant to be used for prognostic, not diagnostic, purposes in the setting of HIV. False positives were much more likely to occur in patients with low viral loads, generally no higher than 2,000 copies/mL, whereas those with high viral loads proved to have much more specific results.”

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 diagnostically aggressive and the need to protect patients from unnecessary anxiety. “There most certainly are potential benefits to diagnosing patients in the primary stage of HIV infection. However, these benefits are not lifesaving unless we’re hinting 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 conflicting p24 and ELISA result.”

<table>
<thead>
<tr>
<th>1a. Laboratory Diagnosis of Primary HIV Infection with HIV-RNA</th>
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<tr>
<td><strong>Acute HIV (n=22)</strong></td>
</tr>
<tr>
<td>HIV-RNA (bDNA) +</td>
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<tr>
<td>HIV-RNA (bDNA) -</td>
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<tr>
<td>HIV Uninfected (n=193)</td>
</tr>
<tr>
<td>96% (n=185)</td>
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<table>
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<tr>
<th>1b. Laboratory Diagnosis of Primary HIV Infection with p24 Antigen</th>
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<tr>
<td><strong>Acute HIV (n=22)</strong></td>
</tr>
<tr>
<td>HIV-RNA (bDNA) +</td>
</tr>
<tr>
<td>HIV-RNA (bDNA) -</td>
</tr>
<tr>
<td>HIV Uninfected (n=193)</td>
</tr>
<tr>
<td>99.5% (n=192)</td>
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Source: Grant. 2000. 13th International Conference on AIDS (Abstract WePpB1304). Adapted and printed with permission of Frederick Hecht, MD.
The Transmission of Drug-Resistant HIV Variants

As discussed in the March 1999 issue of The PRN Notebook, Dr. Hecht and his colleagues made international headlines during the 12th World AIDS Conference for being the first research team to document the transmission of a multiple-drug-resistant HIV strain from one person to another. Much of the information and data initially presented in Geneva in June 1998 were published in the New England Journal of Medicine later that summer (Hecht, 1998).

Dr. Hecht and his colleagues have since gone on to analyze HIV drug-resistance patterns in the Options Project cohort. Blood samples collected from patients experiencing pH1 are subjected to a battery of genotypic and phenotypic tests. Using Affymetrix genotypic technology, the UCSF team have been sequencing the first 250 codons of the reverse transcriptase gene and the entire protease gene. Using ViroLogic’s PhenoSense hrv assay, they have also been able to test hrv’s in vitro ability to replicate in the presence or absence of antiviral drugs.

Data thus far are available from 118 patients. According to Dr. Hecht, genotypic-resistance patterns to nucleoside reverse transcriptase inhibitors (nrtis) were seen in 15.4% of samples collected from pH1 patients in 1996, 17.9% of samples collected in 1997, followed by a sharp decrease to 2.2% of samples in 1998 and 6.3% of samples in 1999. As for genotypic resistance to non-nucleoside reverse transcriptase inhibitors (nnrtis) and protease inhibitors (rns), there were identical—and gradual—increases in resistance rates to these two newer classes of drugs between 1996 (0%) and 1999 (6.3%). Resistance rates to nrtis, nnrtis, and rns are illustrated in Figure 1.

Interestingly, phenotypic resistance data from the Options Project have yielded slightly different results from those produced using genotypic testing. In 1996, the rates of resistance to pIs, nnrtis, and rntis were 0%, 17%, and 16.7%, respectively, in patients with pH1. In 1997, the rate of rnt resistance jumped to 10.7%, followed by a decrease to 4.8% in 1998 and a slight rebound to 7.7% in 1999. Similarly, resistance to nnrtis was reported in 10.7% in 1997, 4.8% in 1998, and 11.5% in 1999. As for resistance to rntis, a downward trend was reported in 1997 and 1998—from 3.6% to 0%, respectively—followed by a 3.8% prevalence rate in 1999.

### Table 2. Oral Transmission Classification

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Level 1</td>
<td>Only oral sex, partner corroboration</td>
<td>12.5% (n=1)</td>
</tr>
<tr>
<td>Level 2-A</td>
<td>Only oral sex, no partner corroboration</td>
<td>12.5% (n=1)</td>
</tr>
<tr>
<td>Level 2-B</td>
<td>Protected anal sex, partner corroboration</td>
<td>0% (n=0)</td>
</tr>
<tr>
<td>Level 2-C</td>
<td>Protected anal sex, no partner corroboration</td>
<td>50% (n=4)</td>
</tr>
<tr>
<td>Level 2-D</td>
<td>Only unprotected anal sex with documented hrv-negative partner (verified)</td>
<td>25% (n=2)</td>
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Source: Dillon, 2000. 7th Conference on Retroviruses and Opportunistic Infections (Abstract 473). Adapted and printed with permission of Frederick Hecht, MD.

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**Oral Sex: A Risk To Be Reckoned With?**

While few experts would argue that HIV cannot be spread through oral sex, the actual level of risk has yet to be defined. Fueling the debate have been the results of several studies conducted since 1984—more than 65 of them in total—demonstrating the risk of oral transmission to be almost nonexistent to small, at worst. According to Dr. Richard Rothenberg of Emory University School of Medicine, who delivered a detailed analysis of several oral hrv transmission studies at a ccc conference in August 1999, the estimated per-contact transmission risk has varied from 1 in 600,000 to more recent estimates of 1 in 100.

A possible reason for this disparity can be found in the studies themselves. Most studies contained too few patients to yield truly convincing data. Moreover, studies were rarely designed to consider the actual time of hrv infection. Without this information, researchers faced the daunting task of evaluating the risk of a single sexual act in the context of an individual’s entire sexual history.

Taking both of these factors into consideration, the Options Project investigators hoped to paint a more conclusive picture. Using the STARHS technology discussed above, Dr. Hecht and his colleagues isolated 102 men who had had sex with men who had been infected with hrv for six months or less. The men studied were approximately 34 years of age; 75% were white, 10% were Latino, and 2% were African-American.

After the first round of questioning, most of the men—83 (82%) in total—reported at least one episode of unprotected anal sex or condom breakage during intercourse. Interest was then placed on the remaining 19 (18%) men surveyed, all of whom reported oral sex as their only form of sexual activity during the preceding six months. After a second round of questioning, 11 of the men failed to provide convincing evidence that oral sex was, in fact, their only risk factor. The remaining

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**Figure 1. Genotypic Resistance 1996–1999**

![Figure 1. Genotypic Resistance 1996–1999](image-url)

Source: Grant, 2000. 13th International Conference on Aids (Abstract WePpR1304). Adapted and printed with permission of Frederick Hecht, MD.
8 men—7.8% of the overall study population—were stratified using an oral-transmission classification system produced by the UCSF team. Classification system data were reported by Dr. Hecht and are illustrated in Table 2.

In essence, unprotected oral sex accounted for 7.8% of the HIV infections followed in this study. These data suggest that nearly one in 12 HIV infections is attributable to oral sex—one of the highest estimates provided to date.

Dr. Hecht mentioned that three of the eight men who reported oral sex as their only risk factor had active gum disease. What’s more, of the eight suspected oral sex transmission cases, seven continued oral sex through ejaculation. When questioned about the reliability of patient self-reports, Dr. Hecht commented that falsified accounts of sexual activity might have occurred by some but not all of the eight patients during the study. “We can quibble about the numbers and honesty reflected in this small cohort all we want,” offered Dr. Hecht in his closing remarks. “Our data, however, are consistent with the concept that lower risk behavior such as unprotected oral sex, if experienced often enough by people who are avoiding higher risk behavior such as unprotected anal sex, may lead to a significant number of new infections.” The fact is, oral sex is a risk and that many of our study participants reported having unprotected oral sex as a safer alternative to unprotected anal sex. Yes, the risk is lower, but it’s still there.

References


The virus and that in the way the immune system handles antiviral treatment as early as possible can eventually cease therapy and maintain low steady-state HIV-RNA levels. The study, reported in the September 28 issue of Nature, involved a group of eight PHI patients taking part in a structured treatment interruption (STI) study at MGH (Rosenberg, 2000). While the course for each participant has varied, all participants achieved at least temporary suppression of the virus for several months.

Currently five of the eight participants are still off drug treatment after 8 to 11 months, maintaining viral levels below the level at which treatment would be recommended (<10,000 HIV-RNA copies/mL). Of the three who resumed taking medication, two participants chose to restart and only one was required to reinstate treatment because of rising HIV-RNA levels.

“This is the first time that anyone has shown that the immune system can successfully be manipulated to keep HIV under control,” said Dr. Walker in a press release prepared by MGH. “We want to deliver two messages with this report: that diagnosing HIV infection and beginning antiviral treatment as early as possible can make a fundamental difference in the way the immune system handles the virus and that HIV treatment strategies based on the immune system—including vaccines—appear to have great potential. We also want to stress that persons currently taking HAART should continue taking their drugs.”

Dr. Walker and his colleagues note that, at this time, only those who began antiviral treatment during PHI and show signs of HIV-specific immune activity have been able to go on to control virus without drugs.

The current findings are an extension of a 1997 report in Science from the same team (Rosenberg, 1997). That study found that starting HIV-infected individuals on antiviral treatment when they exhibit signs of symptomatic PHI acute infection can lead to a significant reduction in HIV-RNA levels and induction of HIV-specific CD4+ cells.

The 1997 study left open the question of whether early treatment could duplicate the immune responses seen in long-term non-progressors (LTNP), a phenomenon discussed in several past issues of The PRN Notebook and elsewhere. To test that hypothesis, Drs. Rosenberg, Walker, and their colleagues first conducted a pilot study involving a single patient with a strong HIV-specific CD4+ and CD8+ cell responses after treatment was halted as part of an STI. The patient’s HIV-RNA level soon rose above 10,000 copies/mL—the point at which the study protocol required reinstatement of treatment—and his viral load was again reduced to undetectable levels upon resuming therapy. However, when the patient had to discontinue treatment again because of an unrelated infection, his virus levels first increased to approximately 40,000 copies/mL. The patient resumed therapy after recovery from his illness, but once again discontinued several months later. This time the increase in virus levels was less than in the earlier treatment interruptions and was followed by a rapid drop to less than 5,000 copies/mL. The patient maintained a low HIV-RNA level—with one transient increase associated with pharyngitis—for 130 days until he chose to resume therapy.

Based on this result, the MGH team enrolled eight patients in a revised study protocol, which required reinstatement of therapy if HIV-RNA levels either stayed above 5,000 copies/mL for three weeks or rose to 50,000 copies/mL at any point. HIV-RNA levels in all patients increased within 17 days, but levels in three patients soon dropped below 5,000 copies/mL. Two of those patients have stayed off therapy and currently have viral levels below 200 copies/mL after 9 to 11 months off therapy. The third patient chose to resume therapy after three months, even though his viral load never exceeded 5,000 copies/mL. He discontinued again about three months later and currently has a viral load below 300 copies/mL, more than nine months into the second discontinuation.

In the remaining five patients, viral levels exceeded the established limits during the initial discontinuation, and treatment resumed. Levels of cytotoxic T-lymphocytes (CTLs) increased in all five following reinstatement of therapy, so they each elected to stop drugs a second time. Their viral loads rose again but soon dropped below 5,000 copies/mL. Two of those patients remain off treatment with current viral levels between 200 copies/mL and 300 copies/mL after eight and nine months. Two other patients in this group chose to restart therapy after four and five months, although their viral levels did not require resumption.

Only one patient was required to resume therapy when his viral level exceeded 5,000 copies/mL for three weeks after about five months off therapy.

Several key questions remain to be addressed in future studies: how long antiviral therapy should continue before discontinuation is attempted, how long the viral suppression might be expected to continue, and whether any factors might predict who would or would not be successful with this treatment strategy. And beyond those questions lies the larger one of how this or other immune-system-based approaches can be applied to those treated during the chronic stages of HIV infection.

References