PHI and Transmission Risk (Part 2): Epidemiology and Infectivity

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Reams of epidemiological and biological data are now available to suggest that people in the primary stages of HIV are, unknowingly, significant contributors to the spread of HIV and, consequently, the proliferation of the AIDS epidemic. However, the precise extent to which individuals with PHI play into this unfortunate scenario remains unclear. To help make sense of the data that have emerged thus far—and to comment on its relevancy within the realm of public health—Dr. Christopher Pilcher shared his ongoing experiences and thoughts with PRN.

Complex mathematical models, constructed by teams of calculus-savvy epidemiological groups, have suggested that individuals with PHI are one of the most important populations to target therapeutically—even though they constitute a time-limited minority population in the much larger HIV community (see: "PHI and Transmission Risk (Part 1): The Contribution of Mathematical Modeling," beginning on page 8). There are also epidemiological data indicating an increased incidence of infection in partners of recent seroconverters, compared to partners of chronically infected men and women (Leynaert, 1998). In recent days, chilling data have surfaced to support the long-standing hypothesis that acutely infected people can infect their sexual partners in turn. These new data suggest that HIV infection can be passed on serially from one acutely infected individual to uninfected partners within a matter of days, and also that such events may be quite common.

PHI and the Serial Transmission of HIV

To address the issue of serial transmission, Dr. Pilcher referred to one of his own studies—conducted at the University of North Carolina in collaboration with several prominent researchers scattered throughout Switzerland—involving five patients drawn from four university-based hospital clinics in whom sexual transmission was suspected to have occurred between an individual with documented PHI and a sexual partner who later developed documented PHI (Pilcher, 2001). For the sake of this study, PHI was defined as HIV p24 positivity, HIV-RNA or HIV-DNA positivity, together with EIA negativity or two or fewer bands on Western blot. Each transmission pair was confirmed by phylogenetic analysis of HIV reverse transcriptase sequences.

The results of this analysis, published in an October 2001 issue of the *Journal of the American Medical Association* (*JAMA*), are illustrated in Figure 1 (on the next page). Three of the couples consisted of men who transmitted HIV to female sex partners (couples 2, 3, and 4); couple 1 involved a woman who infected a male partner, and couple 5 involved a male who transmitted the virus to his male partner. Couples 1 and 2 reported frequent, regular sexual intercourse during periods of possible exposure, whereas couples 3, 4, and 5 recalled only single sexual contacts during the time of possible transmission. In couples 1 through 4, transmitters infected a steady sexual partner via penile-vaginal intercourse; in couple 5, transmission was via insertive anal and oral sex.

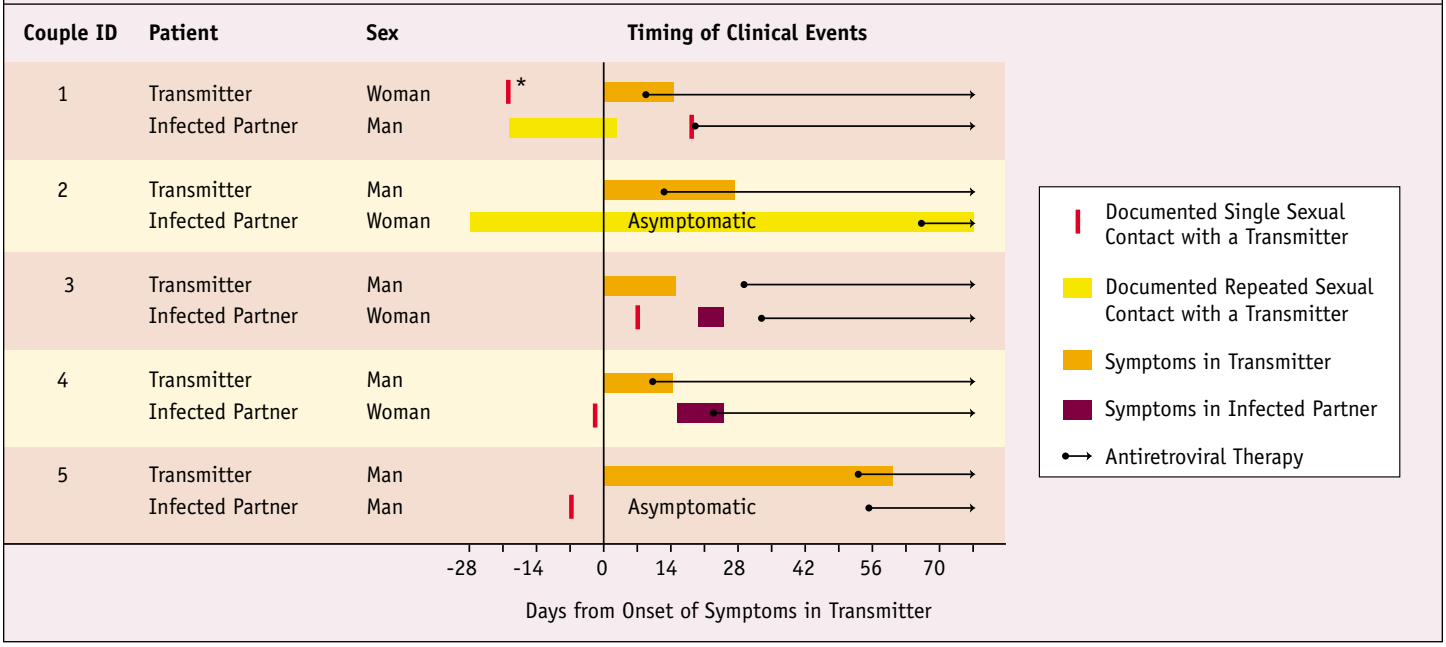
As shown in Figure 1, the single reported exposure occurred before the transmitter's onset of symptoms for couples 4 (day –2) and 5 (day –7). Couple 1 had multiple sexual exposures, but all occurred prior to day +2 after the transmitter's onset of symptoms. A single exposure occurred on day +7 after symptom onset in couple 3. Observed incubation periods for transmitter 1, infected partner 3, and infected partner 4 were 20, 12, and 17 days, respectively, consistent with previously published observations (Schacker, 1996).

"The conclusions we came to are basic, yet very important," Dr. Pilcher said. "We can't say that sexual transmission is more likely to occur during PHI; this five-couple study can't tell us that. What we were able to confirm is that HIV is readily transmitted during the acute stages of infection, as early as seven days before the onset of symptoms. This is definitely something to bear in mind when contemplating public health initiatives, especially when you consider that the majority of acutely infected patients don't present until symptoms have developed."

Moving on to some recent case-clustering data, Dr. Pilcher reviewed the preliminary results of a Swiss HIV Cohort study, reported by Professor Sabine Yerly and colleagues in *AIDS* (Yerly, 2001). The study included all individuals with documented PHI identified in six AIDS centers of university hospitals in Switzerland and two AIDS centers of a hospital close to Geneva. Among the total of 197 individuals infected between January 1996 and January 2000, PHI was documented by evolving HIV antibody response and/or symptoms consistent with acute retroviral syndrome within three months in 70% of individuals and by seroconversion within 12 months of presentation in 30%. Sequence analyses were performed on plasma samples where plasma had been collected before the initiation of HAART (available for 193 of 197 subjects); a phylogenetic tree was constructed using a neighbor-joining method on available reverse transcriptase sequences.

The phylogenetic analysis revealed significant "clustering" for 56 (29%) of 193 individuals, indicating that the viruses from patients in each cluster were genetically related. The eighteen clusters in this study

FIGURE 1. Timing of Clinical Events Within Transmission Pairs



ID indicates identification number; asterisk (*) indicates that sexual contact shown for the transmitter in couple 1 represents a sexual assault on her by an HIV-positive individual. Seminal HIV-RNA concentrations, collected from couple 5 only, were higher than commonly seen in chronic infection for both the transmitter and infected partner (5.7 and 5.9 log, respectively). Other sexually transmitted infections were found in couple 1 (genital herpes and chlamydia) and in couple 5 (genital herpes and early syphilis); in couple 4 the transmitter had a sterile inguinal abscess.

Source: Pilcher, 2001. **Sexual transmission during the incubation period of primary HIV infection.** *JAMA* 15(7):838-45. Reprinted with perimission of the American Medical Association.

ranged in size from two to 11 PHI individuals per cluster and involved intravenous drug use, homosexual, and heterosexual modes of transmission. Retrospective contact tracing firmly established the chain of transmission to explain 17 (9%) of the 56 clustered infections.

"The clusters in this analysis were really quite noticeable," remarked Dr. Pilcher. "Approximately one-third of individuals with recent transmission harbored variants that were genetically linked to variants from other individuals with recent HIV transmission. Unfortunately, this doesn't tell us if the clustering was a result of rapid, serial transmissions or the result of multiple, parallel infections by core transmitters. Either way, we cannot underestimate the importance of rapid contact tracing during this window of opportunity. In the event of serial transmissions, contact tracing will allow for the infected partners to receive an early diagnosis and possibly begin treatment. If it's core transmitters, contact tracing may aid in their identification and permit intervention to curb the spread of infection by these individuals."

PHI in Context

Dr. Pilcher was careful to point out that data concerning transmission risk during PHI must be considered in the context of transmission rates and risk factors among chronically infected HIV-positive people. Drawing upon the results of seven studies that followed chronically infected individuals engaging in penile-vaginal intercourse—which, Dr. Pilcher added, is the route of transmission for approximately 75% of all people now being infected with HIV worldwide—the probability of HIV transmission was quite low. Taken together, these studies estimate HIV transmission risk, per coital act, to be 1 in 500 to 1000 (0.001, ranging from 0.0008 to 0.002). "If these numbers were accurate," Dr. Pilcher said, "I don't think we'd have much of an epidemic. Clearly, there are some individuals who are more likely to transmit HIV than others. The question is: is it people with acute infection, or is it some other population?"

Dr. Pilcher went on to review a number of features of PHI that might make transmission especially likely. The most obvious factor is viral load, which is at its highest during the acute retroviral syndrome and is a strong risk factor for transmission by individuals with chronic infection. This connection is logical inasmuch as high viral loads in blood might be indicative of high viral loads in other infectious body fluids, such as semen and vaginal fluid.

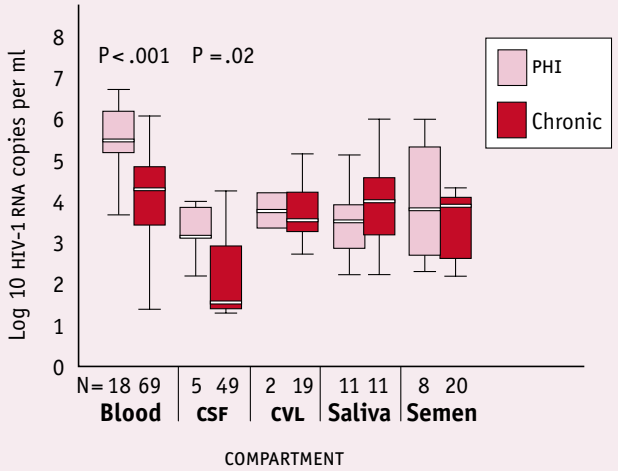
According to a study spearheaded by Dr. Thomas Quinn of Johns Hopkins University School of Medicine—conducted as part of a larger community-based STD intervention study conducted in the Rakai district of Uganda—415 couples discordant for HIV were followed for an average period of 22.5 months (Quinn, 2000). The male partner was infected with HIV in 228/415 (55%) couples, and the female partner was infected in 187/415 (45%) couples. Collateral seroconversions occurred in 90/415 (22%) couples studied during the 30-month period. Interestingly, there was no difference in the male-to-female and the female-to-male transmission rates: Both were 12%.

The viral load of the HIV-positive member of a serodiscordant couple turned out to be a major factor in collateral transmission. According to Dr. Quinn's team's report, which is summarized in the December 2000 issue of *The PRN Notebook*, HIV-positive men and women with HIV-RNA levels around 90,000 copies/mL were more likely to transmit the virus to their

HIV-RNA levels are shown for study subjects with primary HIV infection (PHI) prior to antiretroviral therapy (darker boxes) and chronically infected, asymptomatic historical controls naive to antiretroviral therapy (lighter boxes). Upper and lower fences represent the range, boxes represent the 25th to 75th interquartile range, and horizontal lines represent median values. CVL = cervicovaginal lavage.

Source: Pilcher, 2001a. **HIV in body fluids during primary HIV infection: implications for pathogenesis, treatment, and public health.** *AIDS* 15(7):837-45. Reprinted with permission of Lippincott Williams and Wilkins.

FIGURE 2. Compartmental HIV-RNA Levels in Primary Versus Chronic Infection



HIV-negative partner(s) than those with lower HIV-RNA levels (~40,000 copies/mL). In fact, there were no transmissions among couples in which the HIV-positive partner had a viral load less than 1,500 copies/mL. Among HIV-positive partners with viral loads greater than 50,000 copies/mL, the risk of transmitting HIV was approximately 23% per year. And with each log increase in viral load, the risk of transmission increased 2.45-fold.

However, Dr. Pilcher noted, it may not simply be differences in viral load powering apparent differences between acute and chronic infection transmission risk. For instance, partner susceptibility to HIV infection within stable partnerships may actually decrease over time because of acquired mucosal immunity (Vernazza, 2000; Mazzoli, 1999; Langlade-Demoyen, 1994; Kelker, 1992).

The association between PHI and other acute STDs may also be important in augmenting transmission in this group. In a paper published recently by Professor Ronald Gray and his colleagues, also at Johns Hopkins University Medical Center and in Uganda's Rakai district, STDs were once again shown to significantly increase the risk of HIV transmission among heterosexuals (Gray, 2001). In this analysis involving 174 monogamous serodiscordant couples, the overall per-coital-act of HIV transmission was 0.0011. In the setting of an STD associated with genital ulceration, the probability of transmission jumped to 0.0041, compared to a rate of 0.0011 among couples in which neither partner had an ulcerative STD.

Behavioral factors could contribute to high rates of HIV transmission as well. Two studies reviewed by Dr. Pilcher suggest that individuals with acute infection may have a higher number of sexual partners than their chronically infected peers (Colfax, 2000; Sey, 2001). "If individuals with PHI are engaging in risky behavior with a number of different partners," he added, "this would further explain clusters of new infections."

The Biological Evidence

While there is no shortage of data concluding that HIV-RNA levels in peripheral blood are exceedingly high during PHI, there is very little in the way of data regarding HIV-RNA concentrations in the genital fluids and other peripheral compartments of acutely infected individuals. "One thing we really wanted to find out was the correlation between HIV levels in the blood and those in other compartments, including semen and cervicovaginal lavage, during PHI," Dr. Pilcher explained. "High HIV-RNA levels in these fluids would be very likely to increase the risk of transmission; thus we wanted to confirm this and also take a look at the effects of antiretroviral therapy on viral seeding and shedding in the compartments."

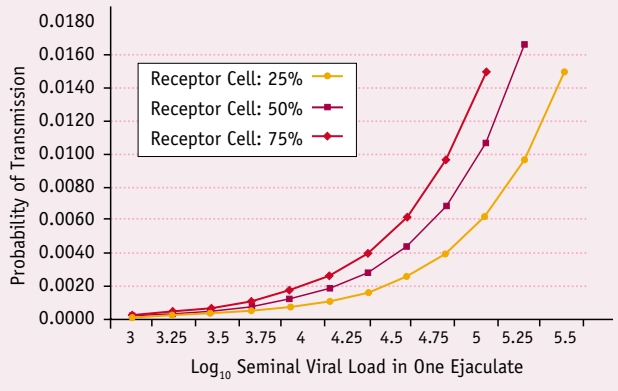
A decidedly tall order to fill: Together with colleagues at the Duke-UNC-Emory Acute HIV Consortium, Dr. Pilcher helped conduct an observational cohort study in which 17 individuals with PHI provided various laboratory specimens, including blood plasma, cerebrospinal fluid (CSF), seminal fluid, cervicovaginal lavage, and/or saliva (Pilcher, 2001a). Once the samples were collected and processed, the viral load of each fluid was compared to a corresponding sample collected from a handful of chronically infected, antiretroviral-naive HIV-positive patients serving as historical controls. With the baseline assessment completed, the PHI subjects were treated for six months with an antiretroviral regimen consisting of didanosine (Videx), stavudine (Zerit), and nevirapine (Viramune)—either with or without hydroxyurea (Hydrea)—and then provided follow-up samples for analysis.

The results of the pretreatment comparisons between the subjects with PHI and a group of chronically infected controls are illustrated in Figure 2. Interestingly, HIV-RNA levels in semen were variable among the PHI subjects but were not significantly higher overall (3.96 log) than for the chronically infected controls (3.61 log). However, a correlation was significant between semen and blood viral loads for individuals. In addition, Dr. Pilcher noted that two subjects—so-called "hyperexcretors"—had seminal HIV-RNA levels that consistently exceeded concurrent blood plasma levels on repeated measures. "Interestingly, these two hyperexcretors had STDs, which is certainly consistent with earlier studies showing that STDs increase viral load in blood and semen. As for treatment, we were successful in our ability to reduce viral levels in all of the compartments, which is certainly good news."

Genital HIV Shedding and Increased Transmission: Is There a Link?

"We were actually quite disappointed at our inability to demonstrate that seminal HIV-RNA levels in our PHI subjects were significantly higher than our historical controls of chronically infected patients," commented Dr. Pilcher. "In fact, the numbers were all over the place. We had our hyperexcretors, but we also had acutely infected individuals with moderate and low viral levels in semen." But it's important to keep in mind that in this study, like other studies in humans and animal models, Dr. Pilcher's team demonstrated that HIV-RNA levels in genital secretions really do mimic those in peripheral blood. It is therefore likely that peak shedding, perhaps very early in PHI, increases the risk of transmission.

FIGURE 3. Estimated Male-to-Female Per-Sexual-Contact HIV Transmission



Estimated male-to-female per-sexual-contact HIV transmission probability for different seminal viral loads and for different receptor cell counts when 100% of the isolates in the semen are NSI. The horizontal axis represents $\log_{10}$ seminal viral load in one ejaculate, and the vertical axis represents the male-to-female per-sexual-contact HIV transmission probability. The three lines represent different receptor cells/mm^2 counts: 25th percentile, 50th percentile, and 75th percentile.

Source: Chakraborty, 2001. **Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model.** *AIDS* 15(5):621-7. Reprinted with permission of Lippincott Williams and Wilkins.

But to what extent might fluctuations in seminal viral load, for instance, affect transmission risk during PHI? For this, Dr. Pilcher turned his attention to the work of Dr. Hrishikesh Chakraborty and his colleagues, working with Drs. Joe Eron and Myron Cohen at the University of North Carolina (Chakraborty, 2001).

Dr. Chakraborty's team set out to describe a mathematical model to help predict HIV transmission, in this case between men and women. As reiterated by Dr. Pilcher, this model estimates sexual transmission as a function of both the infectiousness of the transmitter and the susceptibility of the uninfected partner. By studying the concentration and genotype (syncytium-inducing [SI] or non-syncytium-inducing [NSI]) of HIV in male genital secretions and the number of receptors (CCR5) for HIV in the endocervix of women, Dr. Chakraborty's team amassed biological data that could be made to square with existing epidemiological data.

Enrolled in this study were 86 men—none of whom were receiving antiretroviral therapy—in whom CD4+ cell counts and quantifiable semen samples were available, and 24 women in whom the number of endocervical CCR5 receptors was determined. The outcome of the study was a final model equation allowing one to predict the probability of HIV transmission from men to women, per coital act, based on the absolute burden of NSI-HIV in a given man's ejaculate (volume x HIV-RNA copies/mL seminal plasma) and a given woman's receptor-cell density.

With the data collected and the applicable numbers plugged into the model, the resulting equation yields a number of concise predictions. For example, when semen contains 100,000 copies/mL of NSI HIV-RNA, the probability of HIV transmission is 1 per 100 episodes of intercourse. Conversely, with 1,000 copies/mL of NSI HIV-RNA in semen, the probability of transmission falls to 3 per 10,000 coital acts. More specific findings are illustrated in Figure 3.

"We liked this model and wanted to plug in our own numbers of genital HIV-RNA levels seen during PHI," Dr. Pilcher explained. "More specifically, we wanted to calculate how the change in genital HIV-RNA levels, from their peak concentrations to their setpoints, would affect the probabilities of transmission over time for different individuals."

Dr. Pilcher's observations are reported in Table 1. In order to determine hypothetical transmission probabilities over time for individuals with low, moderate, and high peak and steady state HIV-RNA levels in semen, Dr. Pilcher assumed that changes in the genital tract paralleled those that have been well described in the blood compartment. For instance, an individual with a very high setpoint seminal viral load of 7 log may have a peak seminal viral load of 8.85 log during PHI. "For that individual," Dr. Pilcher commented, "the per-coital-act probability of transmission is 1.0—he's bound to transmit the virus to almost everyone he has unprotected intercourse with. The individuals with low and moderate HIV-RNA levels, both during peak and at setpoint, are much less likely to transmit the virus." But what is really important to consider in these patients with low and moderate viral loads, Dr. Pilcher pointed out, is the fold-change in HIV-RNA concentrations from the peak to setpoint. "What we saw was approximately a 20-fold decrease in the probability of transmission from peak to setpoint. Looking at this another way, what we end up seeing is a 20-fold increase in the probability of transmission when viral shedding in semen is at its peak."

Another key variable discussed by Dr. Pilcher was what the model may predict about the contribution of PHI to an individual's total cumulative individual HIV transmission probability. For example, in an individual who has peak seminal viral load of 5.43 log, a setpoint seminal viral load of 3.85, and a duration of chronic infection of ten years—numbers, Dr. Pilcher reckons, that are representative of a large percentage of HIV-positive people—the probability of transmission during PHI

TABLE 1. Predictions of Combined Model for Three Hypothetical Individuals

Seminal Viral Load (log)		Per-Act Transmission Probability			% Total Cumulative Individual Transmission Probability	
Peak (day 23)	Setpoint (day 120)	Peak (day 23)	Setpoint (day 120)	Fold-Change	Acute (day 0–120)	Chronic (day 120–10 years)*
3.75	2.17	.0015	.0001	22.2	0.07	0.93
5.43	3.85	.0308	.0018	19.7	0.06	0.94
8.85	7.27	1.000	.8484	1.4	0.02	0.98

*Observed values from chronically infected cohort.

Source: Christopher Pilcher, MD

would amount to roughly 7% of the total cumulative probability over the duration of that individual's infection. "In other words," Dr. Pilcher elucidated, "the 20-fold increase in transmission probability during PHI may not dominate an individual patient's overall cumulative transmission probability." However, he emphasized, transmission to a sexual partner is still much more likely to occur sometime over the ten-year span of chronic HIV infection if the infected individual remains undiagnosed and untreated.

Dr. Pilcher cautioned clinicians against interpreting these data as downplaying the importance of diagnosing PHI. "Actually," Dr. Pilcher postulated, "those interested in PHI as a potential public health opportunity should find these data energizing. What this means is that much of an individual's cumulative transmission risk rests during the period of chronic infection, and can be prevented by early diagnosis. That is, even if the window of hyperinfectiousness associated with PHI has come and gone by the time patients are diagnosed, we can still make a profound difference by identifying these individuals and by being aggressive about counseling and contact tracing. It's never too late to interrupt the spread of the epidemic."

KEY POINTS

- Biological and epidemiological evidence converge on the hypothesis that partners of individuals with PHI are likely to be at very high risk for infection.
- Proof of ready transmission by individuals with early acute infection, and of extensive case clustering in PHI cohorts, justify efforts to perform rapid contact tracing.
- Future directions include the improvement in strategies to expand screening, taking into account both feasibility and cost effectiveness, and the study of short-course antiretroviral therapy on genital shedding of HIV and its impact on serial transmissions.

References

Chakraborty H, Sen PK, Helms RW, et al. **Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model.** *AIDS* 15(5):621-7, 2001.

Colfax G, Mansergh G, Vittinghoff E, et al. **Drug use and high-risk sexual behavior among circuit party participants** [Abstract TuPeC3422]. XIII International Conference on AIDS, Durban, 2000.

Gray RH, Wawer MJ, Brookmeyer R, et al. **Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda.** *Lancet* 357(9263):1149-53, 2001.

Kelker HC, Seidlin M, Vogler M, et al. **Lymphocytes from some long-term seronegative heterosexual partners of HIV-infected individuals proliferate in response to HIV antigens.** *AIDS Res Hum Retroviruses* 8(8):1355-9, 1992.

Langlade-Demoyen P, Ngo-Giang-Huong N, et al. **Human immunodeficiency virus (HIV) nef-specific cytotoxic T lymphocytes in noninfected heterosexual contact of HIV-infected patients.** *J Clin Invest* 93(3):1293-7, 1994.

Leynaert B, Downs AM, de Vincenzi I. **Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. European Study Group on Heterosexual Transmission of HIV.** *Am J Epidemiol* 148(1):88-96, 1998.

Mazzoli S, Lopalco L, Salvi A, et al. **Human immunodeficiency virus (HIV)-specific IgA and HIV neutralizing activity in the serum of exposed seronegative partners of HIV seropositive persons.** *J Infect Dis* 180(3):871-5, 1999.

Pilcher CD, Eron JJ Jr., Vernazza PL, et al. **Sexual transmission during the incubation period of primary HIV infection.** *JAMA* 286(14): 1713-4, 2001

Pilcher CD, Shugars DC, Fiscus SA, et al. **HIV in body fluids during primary HIV infection: implications for pathogenesis, treatment and public health.** *AIDS* 15(7):837-45, 2001a.

Quinn TC, Wawer MJ, Sewankambo N, et al. **Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group.** *N Engl J Med* 342(13): 921-9, 2000.

Schacker T, Collier AC, Hughes J, et al. **Clinical and epidemiologic features of primary HIV infection.** *Ann Intern Med* 125(4):257-64, 1996.

Sey K and Harawa N. **High-risk behavior among individuals diagnosed with acute/primary or recent HIV infection** [Abstract 216]. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 2001.

Vernazza PL, Kahlert C, Fierz W. **Sensitization to human immunodeficiency virus in seronegative exposed partners.** *J Infect Dis* 182(6):1810-2, 2000.

Yerly S, Vora S, Rizzardi P, et al. **Acute HIV infection: impact on the spread of HIV and transmission of drug resistance.** *AIDS* 15:2287-92, 2001.