Where Epidemiology Meets Biology: Primary HIV Infection and Sexual 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, the vast majority of patients are still being diagnosed after a unique and possibly crucial stage of HIV disease—primary HIV infection (PHI)—has come and gone.

Many experts continue to suggest that PHI is a window of opportunity to initiate HAART, as doing so may have positive effects on the long-term course of HIV disease (see "The Road to Eradication: Is HAART Hard Enough?" beginning on page 16). In fact, almost every issue of *The PRN Notebook* that has been published since March 2000 has featured an article highlighting the potential advantages of treatment during PHI, whether it be immunologic rescue or to preserve limited viral diversity.

As discussed in this article, which is based on academically rigorous lectures delivered in October by Dr. Christopher Pilcher of the University of North Carolina and Dr. Jim Koopman of the University of Michigan, there may also be public health advantages stemming from the rapid diagnosis and clinical management of individuals with PHI. "HIV shedding in genital secretions during the initial stage of infection is a major concern," Dr. Pilcher said during his opening remarks. "If we can step in with counseling and contact tracing, along with antiretroviral therapy, we may be able to diminish HIV shedding and, most importantly, interrupt epidemic spread in sexual networks."

PHI: Examining the Risks

Signs and Symptoms of PHI

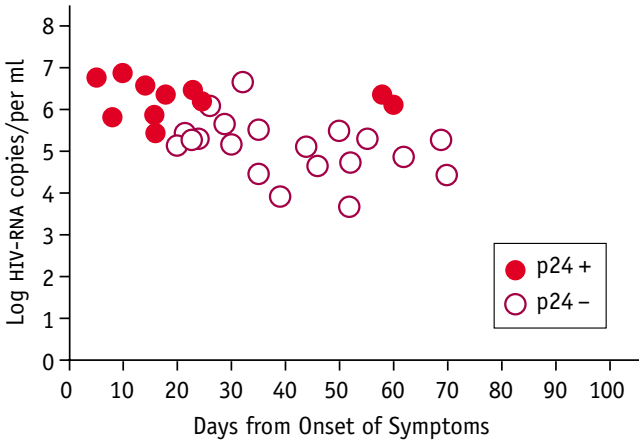
TO TAKE ADVANTAGE OF EITHER THE POSSIBLE therapeutic or public-health opportunities during PHI, clinicians face a daunting task right from the start: actually connecting with and correctly diagnosing individuals in the initial stages of acute infection. While it is true that a growing number of people are likely to seek care immediately after possible exposure, given that the stigma and general sense of pessimism surrounding HIV infection have 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.

All too often, the symptoms of PHI are chalked up to "typical" viral infections, resulting in an Rx for bed rest, liquids, and the occasional prescription for Relenza, Tamiflu, or acyclovir. But then again, the symptoms of PHI are rather nonspecific. There has, in fact, been some debate regarding the symptoms that best define PHI, although fever, fatigue, pharyngitis, weight loss, myalgias, and headaches remain among the leading constitutional symptoms to look for.

Dr. Pilcher, like Dr. Frederick Hecht before him (see "Recent Issues in Primary HIV: From Diagnosis to Oral Sex Transmission" in the December 2000 issue of *The PRN Notebook*), firmly believes that clinicians must maintain a high level of suspicion in order to really make sense of these symptoms. "It's always important to be thinking about HIV and questioning patients about the possibility of exposure," Dr. Pilcher said. "For the most part, patients don't disclose this vital piece of information without at least being asked first."

Beyond symptoms and risk-factor suspicion, clinicians should also 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,

FIGURE 1. HIV p24 Positivity Is Time Dependent



Source: Christopher Pilcher, MD

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 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). In Dr. Pilcher's experience, HIV p24 testing is best viewed as being time-sensitive. As shown in Figure 1, HIV p24 testing was accurate in the majority of his acutely infected patients who had blood drawn for analysis within three weeks after the onset of symptoms. "Thereafter," he pointed out, "we had numerous p24-negative results, even though the patients were positive for HIV-RNA. The most accurate tests to use for the diagnosis of PHI are those that measure for plasma HIV-RNA or proviral DNA."

Despite Dr. Pilcher's advice, many clinicians attending the October 2001 PRN meeting remain skeptical of their ability to figure out who, among a waiting room full of patients with nonspecific viral-like symptoms, might be in the initial throes of acute HIV infection. Perhaps only if or when RNA or DNA testing is accepted as a routine part of a patient's workup will the burden of suspicion faced by clinicians and the fears of confession faced by patients—become less of an issue.

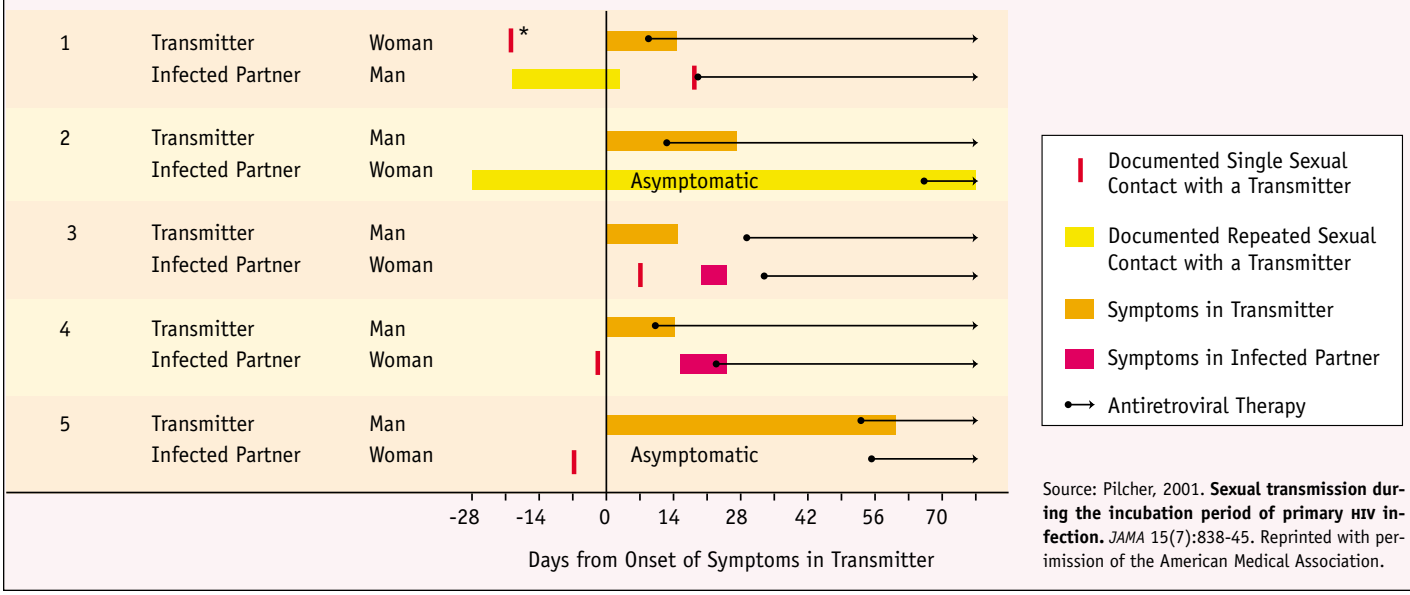
Dr. Pilcher mentioned a number of studies that speak to the potential clinical utility of routine diagnostic testing of patients with constitutional symptoms of the acute retroviral syndrome. For instance, we know that screening populations with a high prevalence of acute infection can be identified: A recent study by Dr. Eric Daar and his colleagues, published in *Annals of Internal Medicine,* diagnosed acute HIV infection in 54 (12.4%) of 436 patients referred to the authors for testing in Los Angeles and San Diego (Daar, 2001). However, Dr. Pilcher explained, there's much more work to be done to assess the utility and cost-effectiveness of routine PHI testing, not only for epidemiological purposes, but also in the development of targeted diagnostic programs. "My Christmas wish this year is to see more epidemiological data so that we can come up with clinical algorithms for the routine HIV testing in specific clinical settings," Dr. Pilcher said. "I honestly believe that routine testing might have some potential. The problem is, we still haven't seen data regarding routine testing in some of the key populations, such as those seeking care from an STD clinic, or febrile emergency department patients, or, of particular interest, the partners of patients with acute HIV infection."

PHI and HIV Transmission: Epidemiological Findings

REAMS OF EPIDEMIOLOGICAL DATA ARE NOW available to suggest that people in the acute stages of HIV are, unknowingly (one would hope!), 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.

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: The Contribution of Transmission Systems Analysis, beginning on page 25). 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,

FIGURE 2. Timing of Clinical Events Within Transmission Pairs



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

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.

additional data have surfaced to support the long-standing hypothesis that serial transmissions between acutely infected people and their sexual partners do, in fact, occur. Perhaps most chilling are data, reported earlier this year, providing hard evidence of case clustering within a cohort of patients with PHI.

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, ELISA negativity, or two or fewer bands on Western blot within 30 days of exposure. 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 2. 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 2, 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, originally reported by Professor Sabine Yerly at the 8th Conference on Retroviruses and Opportunistic Infections in Chicago (Yerly, 2001). Between 1996 and 1999, approximately 2,500 new infections were included in the cohort. One hundred ninety-seven of these cases involved patients who were diagnosed with PHI. Through nucleic acid sequence analysis of samples collected from 191 of the PHI patients, Professor Yerly's team demonstrated an astounding number of epidemiological links: 56 individuals in the neighboring cities of Geneva, Lausanne, and St. Gallen—many of them men who have sex with men—were infected with genetically similar strains within 12 months of one another. In 17 (9%) of these cases, transmission at the time of PHI was confirmed through contact tracing.

"The clusters in this analysis were really quite noticeable," remarked Dr. Pilcher. "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 singling out PHI must be contemplated 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 are 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."

Might it be individuals with high viral loads? 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-negative partner(s) than those with lower HIV-RNA levels (~40,000 copies/mL). In fact, there were no seroconversions 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.

Similarly, in a paper published recently by Professor Ronald Gray and his colleagues, also at Johns Hopkins University Medical Center and in Uganda's Rakai dis-

trict, 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.

"The close associations between viral load, STDs, and transmission, along with factors including the number of coital acts and types of sexual behavior, are very important to consider in the setting of acute HIV infection," Dr. Pilcher said. 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 definitely help explain clusters of new infections." Of equal importance are data indicating a higher rate of STDs among those with acute infection (de Loes, 1993), along with an intriguing number of papers suggesting that partner susceptibility to HIV infection may actually decrease over time because of acquired mucosal immunity (Vernazza, 2000; Mazzoli, 1999; Langlade-Demoyen, 1994; Kelker, 1992).

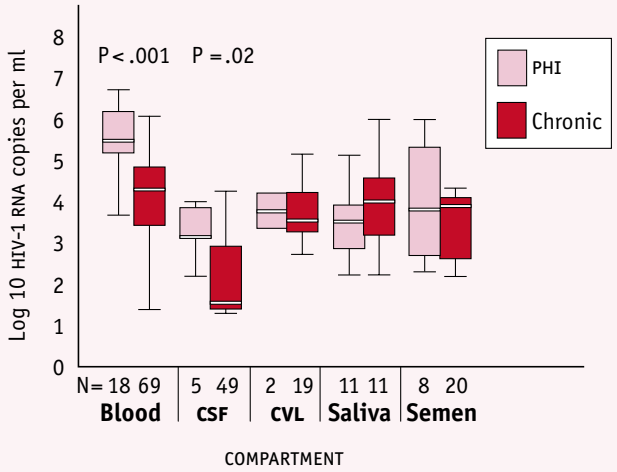
The Biological Evidence

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 likely 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 the chronically infected controls are illustrated in Figure 3. 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."

FIGURE 3. Compartmental HIV-RNA levels in Primary Versus Chronic Infection



HIV-RNA levels are shown for study subjects with primary HIV infection (PHI) prior to antiretroviral therapy (shaded boxes) and chronically infected, asymptomatic historical controls naive to antiretroviral therapy (open 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.

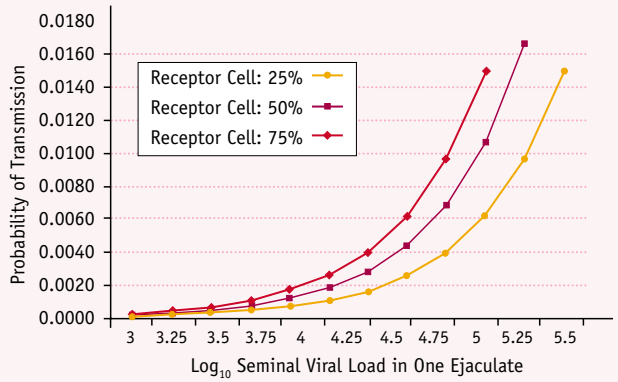
Source: Pilcher, 2001a. **HIV in body fluids during primary HIV infection: implications for pathogenesis, treatment, and public health.** *AIDS* 15(7):837-45. Reprinted with permission of Lippincott Williams and Wilkins.

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.

As clear-cut as Dr. Pilcher's statement may sound, there is still no direct evidence to show how much elevated HIV-RNA levels in genital secretions might heighten the risk of transmission during acute infection. But that is not to say that some evidence does not already exist. For this, Dr. Pilcher turned his attention to

FIGURE 4. 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.

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 yielded 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 4.

"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 set points, 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 set point 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 set point, are much less likely to transmit the virus; the probabilities of transmission in our calculations are similar to those seen in other modeling efforts." But what is really important to consider in these two patients, Dr. Pilcher pointed out, is the fold-change in HIV-RNA concentrations from the peak to set point. "What we saw was approximately a 20-fold decrease in the probability of transmission from peak to set-point. 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 set-point 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 would amount to only 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 mean much in the context of an individual patient's overall cumulative transmission probability." However, 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, "we 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."

PHI and Public Health: What Next?

The Contribution of Transmission Systems Analysis

WITHOUT A DOUBT, PUBLIC HEALTH initiatives surrounding PHI—whether it's aggressive testing and counseling of acutely infected individuals, stepped-up contact tracing efforts, or the use of HAART—need to be considered carefully in the larger context of HIV/AIDS prevention efforts. Yet our understanding of the public health consequences of "unchecked" viremia and risky sexual behavior during PHI is still in its infancy, and even less is known about the cost-effectiveness of intervention programs, particularly when pricey diagnostic tests and antiretroviral therapies are involved.

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

Skepticism surrounding the utility of expensive early intervention programs is definitely warranted, especially when one considers that only a minority of transmissions occur during PHI and that only a few of these individuals will end up being diagnosed early and treated. But as Dr. Koopman argues, taking advantage of this window of opportunity may end up having large effects on population infection levels. "In order to understand this," he says, "we need to explore transmission system analysis, especially in the process of figuring out which studies we need to conduct to assess the effectiveness of such programs."

Transmission systems involve all of the contacts that can spread infection, as well as the specific interactions between HIV and its human hosts that affect the natural history of infection. More simply put, transmission systems are what sustain the circulation of HIV and facilitate its spread to different parts of the host populations. As explained by Dr. Koopman: "these are dominant determinants of population infection levels and offer several opportunities for infection control that epidemiologists commonly miss when they use standard individual risk-based methods. Unfortunately, it has been difficult to get to transmission system analysis. But nucleotide sequence-based phylogeny data hold great promise of moving us forward."

What this all boils down to is mathematical modeling. Given that there are numerous difficulties associated with empirically measuring the impact of intervention programs as they relate to HIV—whether it be behavioral, social, or medical intervention—current impact and cost-effectiveness information is terribly limited. What information does exist generally comes from randomized controlled trials. Yet these studies are expensive and, in turn, are unlikely to be conducted in a broad range of settings.

Mathematical modeling, Dr. Koopman argues, plays a vital role in the development and implementation of epidemiological studies and infection-control programs that will likely yield the most worthwhile and cost-effective results. For example, infection-control specialists responsible for the control of infections—such as anthrax in the postal system and other "outbreaks" of bioterrorism—employ a variety of barrier techniques to prevent the spread of transmissible pathogens. These techniques are extrapolated from models that describe our understanding of the processes of transmission. "Modeling should tell us a lot about what's going on in the transmission of HIV and, more importantly, what we might be able to do about it."

Early Diagnosis and Treatment of PHI: Four Mechanisms of Indirect Transmission Benefit

UNTIL RECENTLY, THE BULK OF PHI TREATMENT research has involved two central aims: first, to understand the individual health benefits of treatment, and second, to evaluate the direct transmission benefit—that is, the reduction in a infected individual's risk of transmitting the virus to his or her sexual or drug-injecting partners while he or she is acutely infected. "The direct transmission benefit is important, but it oversimplifies things," Dr. Koopman said. "It's only a small part of the total population benefit." Dr. Koopman is particularly interested in the indirect transmission benefit of early diagnosis and treatment, which focuses on the benefits of intervention because of changed transmission dynamics. "This I think is where we'll see the majority of expected benefits."

To appreciate the potential population benefits of early intervention programs, it is necessary to step back and examine some of the mechanisms that can cause transmission occurring during PHI to amplify transmission in populations.

The first mechanism, originally discussed in a cutting-edge paper published in the *Journal of Acquired Immune Deficiency Syndromes* in 1994, involves the observation that early transmission epidemic chains grow quickly (Jacquez, 1994). Dr. Koopman, a coauthor of the paper, noted that this work "helped explain that early infection transmission best accounts for population patterns of HIV infection." For example, the pattern of high infectiousness during PHI, followed by a large drop in contagiousness, may explain the pattern of epidemic spread seen in male homosexual cohorts in the early years of the epidemic. "Some modelers remain skeptical," Dr. Koopman admitted. "At present, data to assess the role of early infection or to estimate transmission probabilities are still lacking."

The second mechanism discussed by Dr. Koopman involves fluctuating high-risk behaviors in high-risk settings that can extend or expand the transmission tree. The fluctuating risk factors, he pointed out, advance the hypothesis that indi-

viduals in an early stage of infection are more likely to transmit to those who will also have a high likelihood of transmitting during their own early stage of infection (Koopman, 1997).

Two types of fluctuations are worth mentioning: age fluctuations and transient fluctuations. Dr. Koopman suggests that most people become infected during a period of indiscretion in their lives, when they are having more sexual encounters in risky environments than during other times in their lives. There are a number of possible reasons for this: It might be a life stage when young people are coupling with other young people; it might be an even more transient life stage than youth; it might be a period of relationship instability; it might be a period of mobility with movement into unsupportive social environments that provide many sexual outlets. Such mobility might result in either adventurism or needs for relationship that lower one's guard.

It's also important to recognize that such fluctuations are almost always a "group thing"—The individuals one encounters sexually or through needle contact during these periods are also likely to be in such periods of their own lives. Consequently, the individuals to whom one transmits during this period are in turn more likely to transmit during early HIV infection than those one encounters during other life stages. "These fluctuations need to be taken into account," Dr. Koopman stated. "Most modelers don't account for such transient behavior, which may be quite significant in acutely infected individuals."

The third mechanism discussed by Dr. Koopman involves long-term contact patterns, specifically inter- and intra-risk-group mixing. The HIV epidemic depends on this mixing—that is, the extent to which high-risk individuals engage in sexual activity only with other high-risk partners (assortative mixing) or also with low-risk partners (disassortative mixing).

To examine the significance of mixing patterns, Dr. Koopman and his colleagues constructed a model with 5% of the population in a high-risk group and 95% in a low-risk group; prevalence by group was 15% and 3%, respectively. A mixing scale was included in the analysis that went from "completely assortative"—meaning no contact between the two groups—to "maximally disassortative"—in which all contacts from one group are only with individuals from the other—on opposite ends of the range.

"What we found was really quite interesting," Dr. Koopman reported. "Only a 5% reduction in contagiousness of infection in the 5% of the population in the high-risk group could decrease the total infection in the population by 28% if the mixing is not very assortative. The effect decreases as the mixing becomes more assortative, but still remains large. This shows that infection detection and treatment programs focusing on high-risk groups are indicated, which would certainly include acutely infected individuals."

A final mechanism discussed by Dr. Koopman comes about when chance raises or lowers the level of infection in a population. The models to capture such mechanisms are called "stochastic" models and are more difficult to analyze than the "deterministic" models that can be used to assess the first three mechanisms. One way these stochastic effects arise is that groups of individuals remain free of infection by chance for a prolonged period of time, when suddenly, a chance infection sets off a large tree of spreading infection. While this mechanism has the potential to be quite important for some factors spreading infection widely in a community, which was Dr. Koopman's observation during previous work involving contaminated water spreading Cryptosporidia, it is not yet known how important this mechanism might be for HIV.

The Hope of Phylogenetics

WHILE DR. KOOPMAN FIRMLY BELIEVES THAT his hypothesis that HIV transmissions during PHI are increased by transmission systems, he is also the first to point out that no studies have actually been conducted to confirm or refute any of the amplification mechanisms described above. But there is a reason for this: Because Dr. Koopman and his colleagues hope to assess the potential effects of early treatment intervention on populations of people, not just individual transmission probabilities, a vast amount of data will be needed for modeling purposes. "We don't want just a random sample of individuals and their partners," Dr. Koopman explained. "We want contact patterns. We want to see what happens in an individual and his partners and his partner's partners, connecting everyone across many links." This, he argues, will help illustrate how transmission interruption (e.g., therapeutic intervention), even in just a small percentage of patients with PHI, might have a protective ripple effect.

The problem is that data pertaining to contact patterns across links are not available and manual contact tracing would likely be incredibly laborious and expensive to conduct. A potential solution might be the use of nucleotide sequencing, such as that used in the Swiss HIV Cohort study discussed above. "We wouldn't seek to link individuals to each other, as is often done in phylogenetic analysis," Dr. Koopman said. "We only need to know the pattern of phylogenetic distances between the HIV of different classes of individuals infected at different times. Infected individuals need to be classified by their contact history. The places where partners meet is particularly useful."

Phylogenetic analysis is useful to analyze transmission because transmission is one of the "bottlenecks" that can impact viral diversity. Bottlenecks exist in both the transmission of HIV and the natural history of HIV once established in a human host. For example, the use of antiretroviral agents can narrow the variation in HIV quasispecies. These bottlenecks that fix variation in a population make the measurement of HIV phylogenetic distances particularly useful for assessing population transmission patterns. They also present a challenge, however, as they mean that more sophisticated phylogenetic analysis methods are needed. Yet Dr. Koopman remained undeterred: "We should be able to meet the challenge of identifying the right time scale for studying transmission and the right sequence changes that reflect that scale."

Mathematical Supermodel?

AS DISCUSSED ABOVE, INDIVIDUAL MATHEmatical models have their strengths and weaknesses. Deterministic models, for example, are relatively simple in their execution but almost always abstract in their results. Conversely, stochastic models account for the randomness that occurs in real life, yet they are complex and must be run a number of times to produce probability distribution of possible outcomes.

Yet both models play a role in the analysis of transmission systems.

Instead of selecting one modeling approach over another, Dr. Koopman's team is working with a new strategy called Model Transition Sensitivity Analysis (MTSA). As its name implies, MTSA calls for the adaptation of specific models so that they can be linked together. This helps to grease the wheels when shifting from easier to more complex models and increases confidence in model validity. In this particular case, Dr. Koopman will need to utilize deterministic compartmental models, stochastic compartmental models, and individual network models. Shifting between these models would be quite difficult without MTSA.

Biomedware Inc. has patented the MTSA and is developing software to implement this methodology by way of funding from a Small Business Innovative Research grant from the National Institutes of Health. "It's currently in the first phase and will be moving into the second phase of development soon," Dr. Koopman remarked. "This is very exciting for epidemiologists; shifting from one model to another can be done with a click of the mouse."

Conclusions

WHEN IT COMES TO THE SIGNIFICANCE OF acute HIV infection, multiple lines of reasoning converge to suggest that it truly is a dynamic window of opportunity, not only to achieve certain therapeutic goals, but also to curtail the continual growth of the HIV/AIDS epidemic. However, reasoning alone does 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 goals are medical, epidemiological, or a combination of both—will settle some of the complexities and controversies that continue to prevent clinicians from stepping up their efforts to more aggressively diagnose and treat 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. "There really is quite a bit of data to suggest major public health implications of primary HIV infection," commented Dr. Koopman. "Now is the time to figure out how to move forward and to design studies that will evaluate how significant it really is and the most cost-effective ways to implement control strategies."

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. As for early intervention with antiretroviral therapies, Dr. Pilcher made a point of stating that such studies are still being evaluated. "We're seeing encouraging results in terms of improving individual health and perhaps the long-term prognosis of acutely infected individuals receiving treatment," he concluded. "Perhaps this will also be good news for the epidemic." prn

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