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Thomas Parran Award Lecture: Transmission and Prevention of Transmission of HIV-1

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Let me begin this Award Lecture with several heartfelt thanks and an historical perspective. I want to acknowledge the many students, postdoctoral fellows, and faculty collaborators with whom I have worked over the past 30 years. I want to thank my wife, Gail Henderson (my collaborator on all projects in China), and my children, Jessie and Michael, who over their childhoods heard more about sexually transmitted diseases (STDs), HIV, and genital secretions than is appropriate by any standard. I want to thank 3 mentors who had great influence on my career: Dr. Stuart Levin (Rush Medical School) who nurtured my interest in infectious diseases, Dr. Richard Root (my advisor at Yale University), and P. Frederick Sparling (my friend and colleague during my entire career at the University of North Carolina) who helped me to move from granulocyte research to work on gonorrhea, bacteriology, and molecular biology. I was recruited to UNC to work on gonococcal host interactions, which I did for many years. However, the global spread of HIV led me to studies of HIV–STD interactions in the genital tract, which is the subject of my work over the past 20 years. I want to thank the National Institutes of Health (the National Institute of Allergy and Infectious Diseases and the National Institute of Diabetes and Kidney Diseases) and many wonderful program officers for 25 years of intellectual and financial support that permitted me to do research. I especially want to thank the hundreds of study subjects in many countries whose selfless generosity allowed us to make the observations summarized in this report.

The Biology of HIV Transmission

Transmission of HIV requires a sufficiently infectious HIV carrier and a susceptible host.[1,2] The parameter most closely associated with the sexual transmission of HIV is the viral concentration generally measured in serum or plasma as a surrogate for genital tract secretions. In their landmark study, investigators working in the Rakai District of Uganda demonstrated that HIV transmission was very unlikely to occur when the concentration in blood fell below 3000 copies/mL blood.[3] We developed assays to detect HIV in semen[4,5] and collected a large number of specimens so as to accurately model the relationship between the concentration of HIV in semen and transmission probability.[6] Shown in Figure 1 are the results of a probabilistic model built on measurement of HIV concentration in semen and the number of endocervical CCR5 receptors. The results of this model agree quite closely with empiric data available.[6]

The most contagious subjects would be expected to have the greatest concentration of HIV in genital secretions.[6,7] Increased viremia is observed under 3 circumstances: 1) during the first days of infection when "ramp up viremia" is observed before host defenses such as antibodies and cell-mediated immunity can reduce viral replication[7]; 2) when patients with acute or established HIV harbor concomitant "classic" STD pathogens; and 3) in the last stages of HIV disease when AIDS develops but people remain sexually active.

Acute HIV Infection

Early modeling papers suggested that subjects with acute HIV infection might be particularly important to the spread of HIV.[8–10] This hypothesis has received powerful support from recent further interpretation of the studies from the Rakai District of Uganda.[11] In retrospective analysis of discordant couples assembled from research records, Wawer et al. found that 43.2% of all transmission events in this cohort could be ascribed to index (infected) subjects with acute and early infection. In addition, subjects with advanced disease were also more likely to transmit HIV, consistent with increased viral burdens during these windows of time. These ideas are summarized in Figure 2.[12,13] Data obtained from studies of blood and semen obtained from subjects at different stages of disease allow even more precise calculation of the risk of HIV transmission per episode of intercourse, confirming a very high risk of subjects with acute infection.[14,15]

It should be noted that despite these empiric data, there remains considerable debate among mathematical modelers.[16–18] For example, investigators at Imperial College argue that the long duration of lower-level viremia is of far greater

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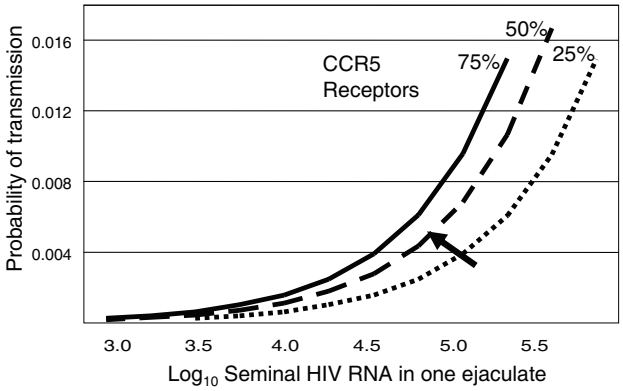

Fig. 1. The probability of HIV transmission from a man to a female sexual partner through heterosexual intercourse based on the concentration of HIV in semen (adapted from[6]). Numbers in parentheses represent the density of endocervical CCR5 receptors required for HIV acquisition.

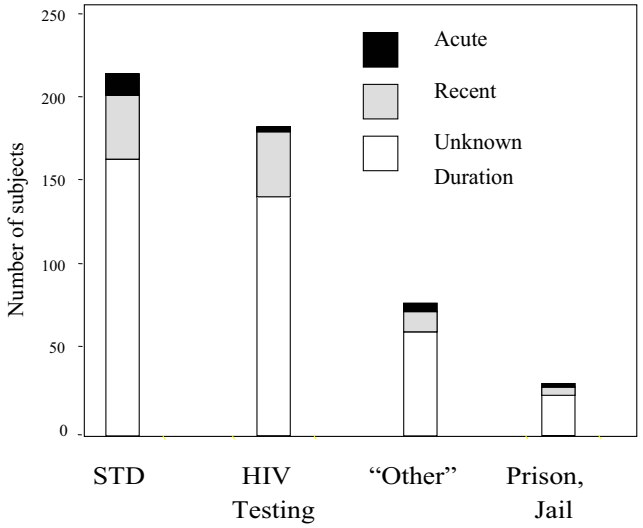

Fig. 3. The location of subjects with newly detected HIV infections through screening in public testing sites in North Carolina over 9 months (adapted from[25]).

importance to the overall epidemic than the "supershedding" among subjects with acute HIV infection (AHI).[17,18] Indeed, Fraser et al. suggest that the greatest spread of HIV stems from infected, untreated subjects with 4.68 logs HIV in blood viral load, the exact concentration of HIV we observed in blood collected from subjects in Malawi with established infection.[14]

Cross-Sectional Detection of Acute HIV Infection

To further dissect these hypotheses, we set out to find a large number of subjects with AHI. Heretofore, only 2 strategies have been used for this purpose. First, investigators have tried to find at-risk patients with a "monolike illness."[19] Second, very-high-risk subjects have been enrolled in observational cohorts in which a small percentage of subjects can be expected to acquire HIV each year.[20] Neither of these approaches has proven efficient, and they often lead to detection of subjects only weeks after infection, too late for biologic studies of HIV transmission and maximal prevention efforts.

Bollinger et al. conducted a retrospective analysis of subjects in STD clinics in India[21] with detection of p24 antigen in HIV antibody-negative subjects consistent with undiscovered AHI. Quinn et al. used a pooling strategy to simplify detection of HIV RNA in large numbers of HIV antibody-negative specimens.[22] Recognizing the importance of this strategy, Pilcher et al. conducted a series of studies designed to detect HIV RNA in HIV negative blood samples.[23–25] The results of a large-scale study conducted in North Carolina are shown in Figure 3.[25] More than 100,000 serum samples were examined in "real time" over 12 months. Twenty-three subjects with acute HIV infection were identified, demonstrating that very contagious subjects were being missed by routine screening. In addition, the majority of subjects with AHI in this study were identified in STD clinic settings.

To further examine the relationship between STD clinics and HIV transmission, we conducted several studies in HIV epidemic "hot spots" in sub-Saharan Africa. Through retrospective analysis of samples from an STD Clinic in Lilongwe, Malawi, we noted AHI in 2.1% of HIV antibody-negative subjects.[24] In a more recent prospective study of 1441 men and women in the same clinic, 20 subjects with AHI were identified.[26] We observed a very large difference in HIV in blood and genital secretions comparing samples from subjects with AHI and established HIV infection. To demonstrate that the extreme prevalence of AHI was not unique to Malawi, we collaborated with investigators at the University of Wittswatersrand in Johannesberg, South Africa.[27] Among 1906 subjects screened, established HIV infection was detected in 672 (35%); among HIV antibody-negative subjects, 12 with AHI were detected.

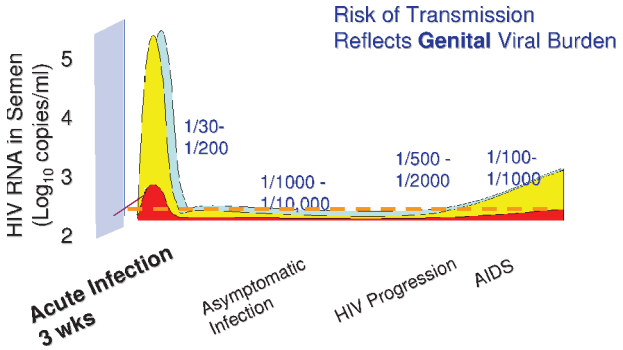

Fig. 2. The probability of the sexual transmission of HIV at different stages of diseases based on the concentration HIV in semen (adapted from[12,13]).

Further Consideration of Sexually Transmitted Diseases

Finding AHI in STD clinics should not be surprising. The results support the well-established synergy between STDs and HIV.[1,28] STDs greatly increase the concentration of HIV in genital secretions (Fig. 4)[29] as well as the diversity of the viral swarm.[30] STDs cause mucosal disruption and inflammation that would be expected to facilitate HIV acquisition.[1] Recent findings emphasize the importance of genital ulcers and suggest the possibility of cotransmission of HIV and other STD pathogens. Genital ulcers caused by herpes simplex virus appear to be a particularly powerful risk factor for HIV acquisition.[31,32] Treatment of STDs reduces the genital tract excretion of HIV.[29,33] However, clinical trials designed to use treatment of STDs to reduce incidence of HIV in a general population have had mixed results, almost certainly because of limitations in study design and approach.[34]

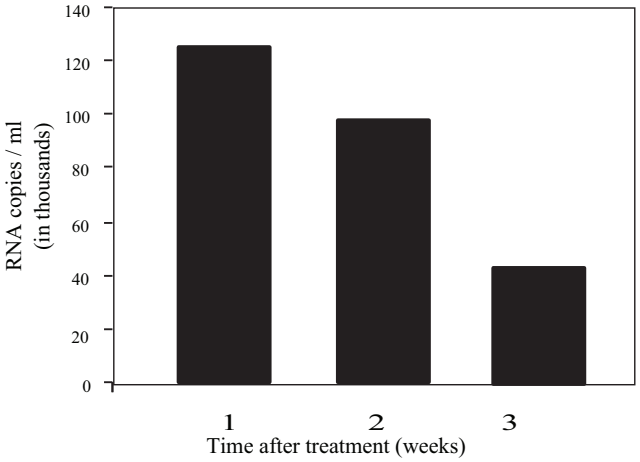

Fig. 4. Effects of treatment of urethritis on excretion of HIV in semen in 87 subjects in Malawi. Bars represent the median values (adapted from[29]).

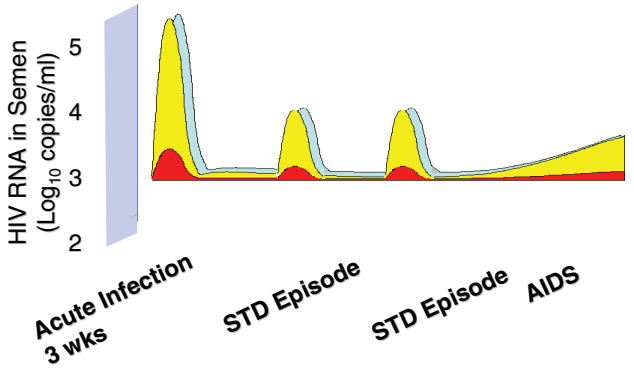

Fig. 5. The effects of intermittent sexually transmitted disease infections on the probability of the sexual transmission of HIV (adapted from[12,13]).

Strategies to Prevent the Sexual Transmission of HIV: Focus on Antiviral Agents

Table 1 summarizes strategies designed to prevent the sexual transmission of HIV-1.[35] There has been some success with the traditional strategy of condoms, STD control, and behavioral intervention. Additional strategies are in different stages of development.

We have focused on the use of antiviral agents for HIV prevention.[35,36] Antiretroviral therapy (ART) can be used before exposure (PREP), after sexual exposure as nonoccupational postexposure prophylaxis (nPEP), and to prevent spread of HIV from an infected person to his or her sexual partners(s). The 3 most critical questions to be addressed are 1) does ART reduce HIV excretion in the genital tract; 2) do some ART drugs work better than others; and 3) can the prevention benefits of ART be demonstrated at the individual or population level?

We conducted a series of studies to determine the effects of ART on HIV in semen.[37,38] ART can lead to sustained reduction of live virus, HIV RNA in seminal plasma, and HIV DNA in seminal cells. Similar but less complete reduction in HIV in female secretions with ART has been reported.[39,40]

These effects of antiviral agents can be ascribed to their ability to concentrate in genital secretions[41]; however, antiviral agents differ greatly in this capacity. The penetration of antiviral agents depends on pKa, influx and efflux pumps, protein binding, p-glycoprotein concentration, and other factors.[41] We have recently shown that FTC, 3TC, and tenofovir concentrate in the male and female genital secretions.[42] Zidovudine, DDI, and D4T achieve similar concentration in blood and genital secretions, whereas most protease inhibitors are excluded from the genital tract.[39] Perhaps not surprisingly, protease-resistant HIV variants in seminal plasma of men receiving such therapy have been detected[43] consistent with exposure of HIV to subtherapeutic drug concentrations. In addition, nonnucleoside reverse transcriptase inhibitors require phosphorylation to exert their antiviral activity, and we have demonstrated phosphorylation of 3TC and tenofovir recovered from seminal cells.[44]

These results are of more than passing interest. It seems obvious that agents that concentrate in the genital tract would have a substantial prevention advantage. Animal experiments have demonstrated success with PREP and nPEP with tenofovir (reviewed in[36]). More recently, complete protection from simian immunodeficiency virus (SIV) rectal exposure was demonstrated with oral truvada.[45] We believe that nPEP demands selection of agents expected to concentrate in the genital tract.

It should be emphasized that suppression of HIV in the genital tract by ART is incomplete. Sadiq et al. reported detection of HIV in semen of subjects suppressed by ART when they acquired STDs; the variants they recovered were resistant to antiviral agents administered.[46] Given that many people with HIV acquire STDs, such "breakthrough" viremia can represent a significant risk for HIV transmission (Fig. 5 adapted from[13]).

TABLE 1. Prevention of HIV

1. Sexually transmitted disease control, behavior change, condoms
2. Vaccines (trials ongoing)
3. Treatment of bacterial vaginosis
4. Topical microbicides (trials ongoing)
5. The diaphragm (trials ongoing)
6. Male circumcision (trials ongoing)
7. Antiviral therapy (trials ongoing)
8. Societal (structural) change: incentives for safer sex?

Conclusions

We have developed an ever better understanding of the requirements for HIV transmission. It seems clear that considerable HIV transmission occurs at the extremes of the infection (during acute infection and as the disease progresses and viral burden increases), but HIV prevention strategies to date have all but ignored such people. In addition, STDs help to drive HIV transmission, and STD clinics are sites where unrecognized infections can be readily detected. Success in HIV prevention demands that we focus on those who are most susceptible and those who are most contagious so as to maximize utilization of resources.

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