

# STDs, Viral Load, Circumcision, and the Transmission of HIV

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**I**N THE WAKE OF THE 13TH INTERNATIONAL AIDS Conference, held this past summer in Durban, there has been no avoiding the harrowing reports of AIDS in Africa. UNAIDS estimates that a total of 33.4 million people are living with HIV globally and 95% of them are in the developing world. Sub-Saharan Africa has suffered a disproportionate toll, with 67% of the world's AIDS cases estimated to be in this region—a total of 24.5 million cases—according to data published in June 2000. The World Health Organization says that the disease is now the leading cause of death in Africa, and the cause of one fifth of all the continent's deaths.

In Uganda, the sub-Saharan focus of Dr. Quinn's work, some 838,000 people have died of AIDS since it was first diagnosed there in 1982 (Agence France-Presse, 2000). According to a report by the country's Ministry of Health, released in early October of this year, up to 1,438,000 people in Uganda—more than 8% of Uganda's population—are infected with HIV, the majority of them women of childbearing years.

While some efforts to provide access to antiretroviral therapies for Africans living with HIV and AIDS are currently under way, the primary response to the epidemic in Africa has been to reduce the number of new HIV infections. "The number of sub-Saharan Africans living with HIV is frighteningly high," opined Dr. Quinn. "The number is almost meaningless, it's so high. We wanted to take some of the lessons we learned early in the United States, such as condom use and safer sex education, and see if we could make them work over there."

The lessons learned from Dr. Quinn's work are hardly limited to those working to fight the epidemic within Uganda's borders. "We've gathered a lot of information regarding risk factors and the risk of infection," he explained. "Much of what we've learned about viral load and sexually transmitted diseases, as they related to

HIV transmission, has implications both here in the United States, in Uganda, and in other nations."

Compared to sub-Saharan Africa, where the route of HIV transmission is almost exclusively heterosexual sex, the epidemiology of HIV infection in the United States is much more diverse. However, when considering the various behavioral and biological risk factors associated with transmission risk, it becomes clear that heterosexuals in Africa have a great deal in common with heterosexuals—and, to some extent, other risk groups—in the industrialized world.

Whether in Africa or the United States, the behavioral and biological risk factors associated with HIV transmission include the frequency and types of sexual contact, the use or nonuse of condoms, a diagnosis of AIDS, immunologic status, and the presence or absence of chemokine receptors. Other factors studied by Dr. Quinn and his colleagues—which served as the foundation for Dr. Quinn's June 2000 PRN lecture and the basis of this summary—include the presence or absence of sexually transmitted diseases (STDs), circumcision, and viral load.

## The Rakai STD Control for AIDS Prevention Study

THE STD CONTROL FOR AIDS PREVENTION Study, a community-based randomized trial, was conducted in Rakai between November 1994 and October 1998. The study—results of which were published last year in *The Lancet*—was originally designed as an efficacy trial to test the hypothesis that STD control would result in a lower incidence of HIV infection (Wawer, 1999). Additional data regarding the effects of viral load and circumcision on HIV transmission were reported earlier this year in the *New England Journal of Medicine* (Quinn, 2000).



Photo: Denise McNair, Johns Hopkins University School of Medicine

**A cluster of Rakai homes in southwestern Uganda.** Rakai is a place of beauty and tragic history. In 1979, when the Tanzanian and rebel Ugandan armies were marching on the forces of Uganda's former dictator Idi Amin, the first major battles of the war were fought there. Not only might soldiers in the area have contributed to the rapid spread of HIV, the war itself placed incredible strain on the already frail health-care infrastructure, which, as a result, was virtually unprepared to deal with the onslaught of AIDS a few years later.

Fifty-six communities in Rakai, a rural district in southwestern Uganda, were selected from among numerous trading villages on secondary roads in the south and central regions of the district. Inclusion criteria required that villages have year-round road access, population stability, and data suggesting a high incidence and prevalence of STDs and HIV infection. Communities were aggregated into ten groups, or clusters, of four to seven contiguous villages and were designed to encompass social networks—including sexual networks—to keep to a minimum the reintroduction of STDs and outside sources of HIV.

Eligible persons, who included any villager between the ages of 15 and 59, were read a consent form that explained the

study and its potential risks and benefits. Potential volunteers were also informed of their rights to decline all or part of the study activities without loss of access to clinical and educational services.

The trial was approved by the AIDS Research Subcommittee of the Uganda National Council for Science and Technology, along with the institutional review boards (IRBs) of Columbia University and Johns Hopkins University, and the National Institutes of Health Office for Protection from Research Risk. Safety was assessed by an independent data safety and monitoring board, composed of U.S.-based and Ugandan participants, established by, but independent from, the National Institutes of Health.

### STD Treatment Randomization

THE CLUSTERS WERE RANDOMLY ASSIGNED to receive mass STD treatment or mass antihelminthic, vitamin, and iron-folate treatment. The study was single blinded, and participants were told that their community would be assigned either regimen by chance. Although participants were not informed of their community's randomization assignment, intervention and control regimens could not be concealed from project personnel.

All households in both study groups were visited every 10 months. During the visits, consenting participants underwent a sociodemographic, behavioral, health, and treatment-seeking interview in the home. Biological samples were collected in the home immediately after the interview. Blood samples were collected and tested for HIV (see below), syphilis, and herpes simplex virus type 2 (HSV-2); urine samples were tested for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. In addition, women were asked to self-collect vaginal swabs for *Trichomonas vaginalis*, bacterial vaginosis, and *Candida albicans*. Participants who reported genital ulcers were asked to permit study personnel to collect a swab to test for HSV-2, *Treponema pallidum*, and *Haemophilus ducreyi*. Ulcer swabs were the only samples for which collection depended on self-reporting of symptoms.

Mass antimicrobial STD treatment or antihelminthic-vitamin-iron-folate therapies were offered to all consenting individuals at each survey round, immediately after interview/sample collection, whether or not

they had symptoms. Single-dose oral regimens were selected for all infections except syphilis and were given over a period of two days. For those randomized to the intervention group, broad-spectrum antibiotics were used (e.g., azithromycin, ciprofloxacin, and metronidazole). For those randomized to the control group, mebendazole (an antihelminthic drug), an iron-folate tablet, and a single low-dose multivitamin were given. For ethical reasons, control participants who reported current STD symptoms at interview were referred for free treatment to a Rakai Project mobile clinic or a government medical post.

### HIV Education, Testing, and Viral Load

ALL SUBJECTS IN BOTH GROUPS RECEIVED INTENSIVE instruction from trained project personnel on the prevention of HIV and condom use. Subjects were also offered free condoms and voluntary, confidential serologic testing for HIV and counseling by trained project counselors. Since this was a community-based trial that enrolled all consenting adults, the identification of couples within the general population was done only retrospectively. Counseling for individuals and couples was continually offered to all subjects—all of whom were strongly encouraged to make use of this service—as recommended by the AIDS Control Program of the Ugandan Ministry of Health.

Participants were also strongly encouraged to obtain the results of their tests for HIV and to share the results with their partners, in accordance with the testing policy of the AIDS Control Program. "Between 85% and 90% of the entire community was tested for HIV and learned of their serostatus," explained Dr. Quinn. "Nearly all of those who were tested shared the results with their partners."

There has been some controversy surrounding the Rakai Project's reluctance to divulge a participant's HIV serostatus to his or her sexual partner(s) (Angel, 2000). Dr. Quinn has been quick to refute arguments in favor of breaking confidentiality in the face of public health concerns. "I believe in confidentiality," he said. "We lacked the resources for anonymous contact tracing and, according to Ugandan law, we were expressly forbidden from making any efforts to divulge such information without a participant's explicit consent."

Ugandan law states that "it is the right of the patient to decide who to inform about the results" and thus precludes "revealing results to sexual partners or spouses." The policy also specifies that "medical personnel and anybody who has, during the course of their work, access to confidential information about the patient, does not divulge this information to third parties who are not directly involved in the care of the patient" and that, "because of the stigma and discrimination arising from HIV infection and AIDS, it is more important that everybody adheres strictly to this principle."

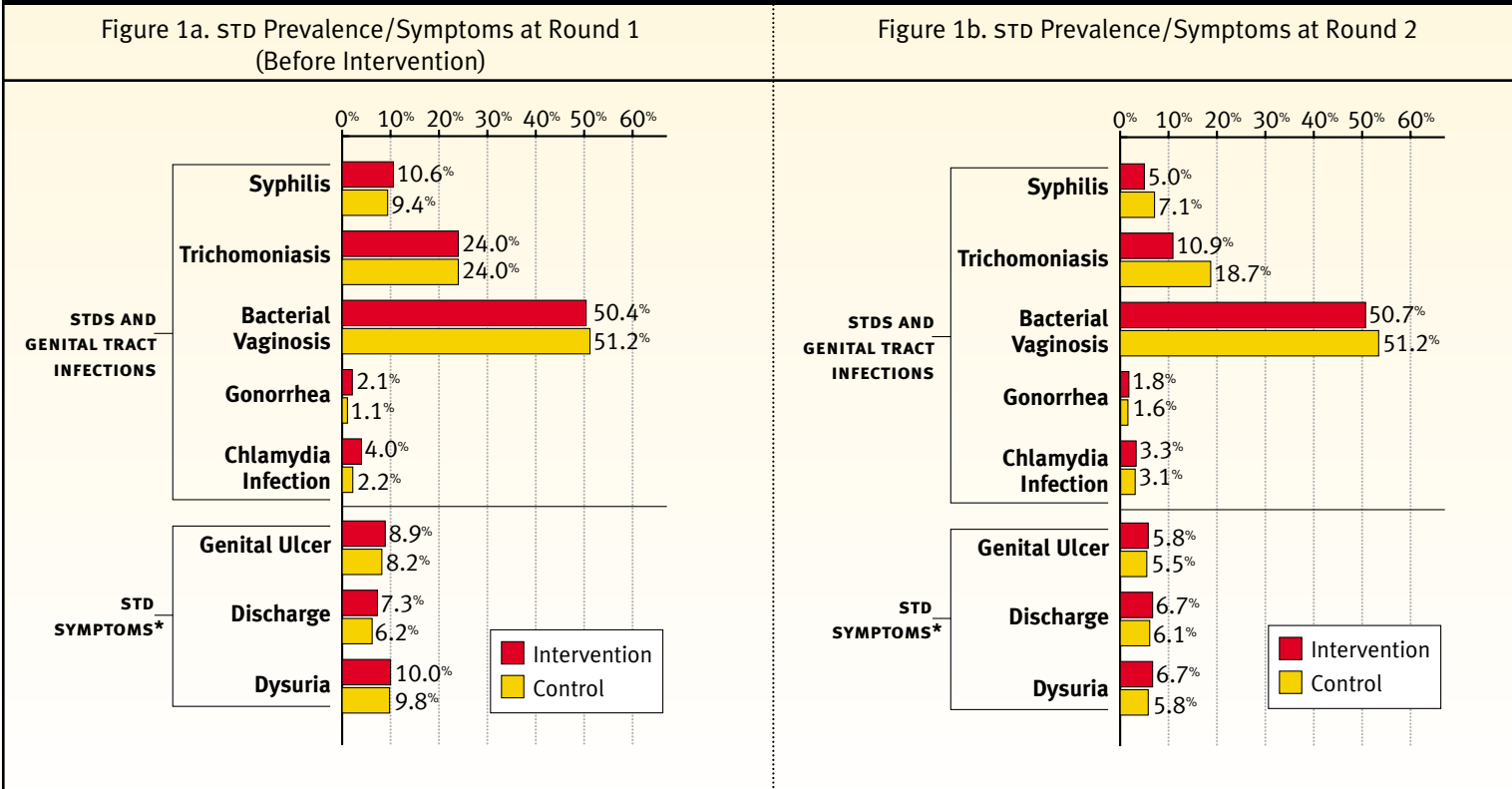
"We were criticized for not breaking the Ugandan law," argued Dr. Quinn. "It's important to keep in mind, however, that it was Ugandans, not us, who were really conducting this study. For us, as Western researchers, to challenge this policy is nonsensical. As a result of this policy against involuntary disclosure, Uganda has the highest voluntary counseling and testing rate in Africa. Furthermore, couple counseling was always available and most couples utilized the service."

Free condoms were made continuously available to the entire community. Subjects who were legally married or in consensual union, defined as a culturally accepted long-term sexual relationship, were asked to provide the name and address of the spouse or consensual partner. Such information was obtained for 75 percent of all eligible couples. At the end of the studies, Dr. Quinn and his colleagues were able to identify 415 couples that were discordant for HIV (see below).

Blood samples were collected and analyzed for syphilis, and treatment was provided immediately to all positive individuals. Archived serum samples from the couples were tested in batches approximately one year after the completion of the trial when viral load assays became available. Roche's Amplicor HIV-1 PCR Monitor version 1.5 was used, as it has been shown to categorize reliably all subtypes of HIV-1, including subtypes A and D, which are present in Uganda.

Among couples in which the HIV-negative partner seroconverted, HIV-RNA testing was performed on the serum sample obtained from the HIV-positive index partner at the study visit before the 10-month interval at which the first positive test in the partner was noted (i.e., an average of 4 to 5 months before probable serocon-

**Figure 1. STD Prevalence/Symptoms at Round 1 (Before Intervention) and Rounds 2 and 3**



Source: Adaptation of data reported in *The Lancet* (Wawer, 1999).

\*Symptoms in previous year for round 1 and in previous 10 months for rounds 2 and 3.

version). Couples with no seroconversion were matched to couples with seroconversion according to the sex and age (within five years) of the HIV-positive and HIV-negative partners and the timing of the follow-up visit. For the couples that remained discordant, researchers selected from the HIV-positive partner the serum sample that was obtained closest in time to that of the matched seroconverting couple. Thus, the assays were frequency-matched according to sex, age, and the time at which samples were obtained both in the case of HIV-positive partners who transmitted the virus and those who did not.

Antiretroviral drugs are not available in rural Uganda. Consequently, the HIV-RNA levels were not influenced by the use of antiretroviral drugs. "We were also criticized for not providing antiretroviral therapy to Ugandans we knew were HIV-positive, especially those in serodiscordant relationships," Dr. Quinn said, responding to an editorial and various correspondences published in *NEJM* (Angel, 2000). "But it's important to think back; HAART wasn't a standard of care anywhere in 1994 when we started the study. We also didn't know that they were serodiscordant until we analyzed the data in 1999; by then the study

had been stopped one year previously. So, in essence, it was almost impossible for us to have implemented any kind of treatment program. Besides, we did not have access to the drugs and HAART was and is still not the treatment standard in Africa."

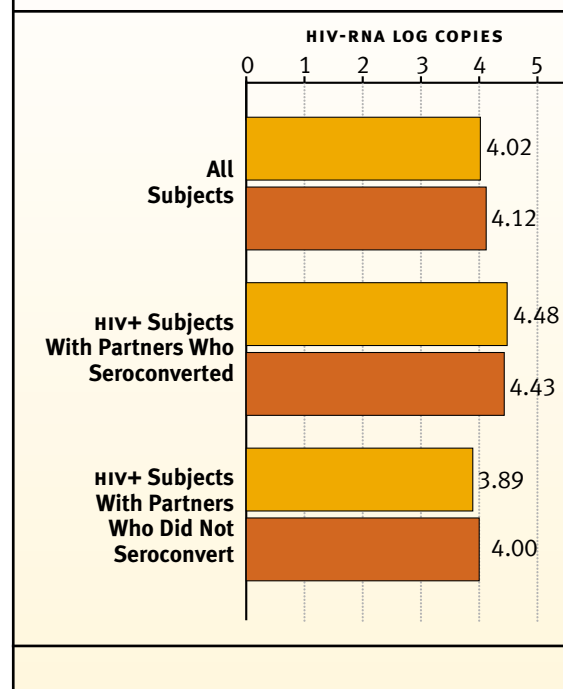
**STDs and HIV Transmission**

THE STD CONTROL FOR AIDS PREVENTION Study was actually one of two randomized clinical trials conducted in sub-Saharan Africa. Results from the first study, conducted in the rural Mwanza region of Tanzania, were published in a 1995 issue of *The Lancet* (Grosskurth, 1995). The study compared the HIV incidence in six STD-intervention clusters and six control communities. In a nutshell, the study authors reported that improved STD treatment reduced HIV incidence by about 40% in this rural population.

Interestingly, the STD Control for AIDS Prevention Study failed to duplicate these findings (Wawer, 1999). According to Dr. Quinn, the baseline prevalence of HIV infection in the Rakai cohort was 15.9%. Six thousand two HIV-negative individuals were enrolled in the intervention group and 6124

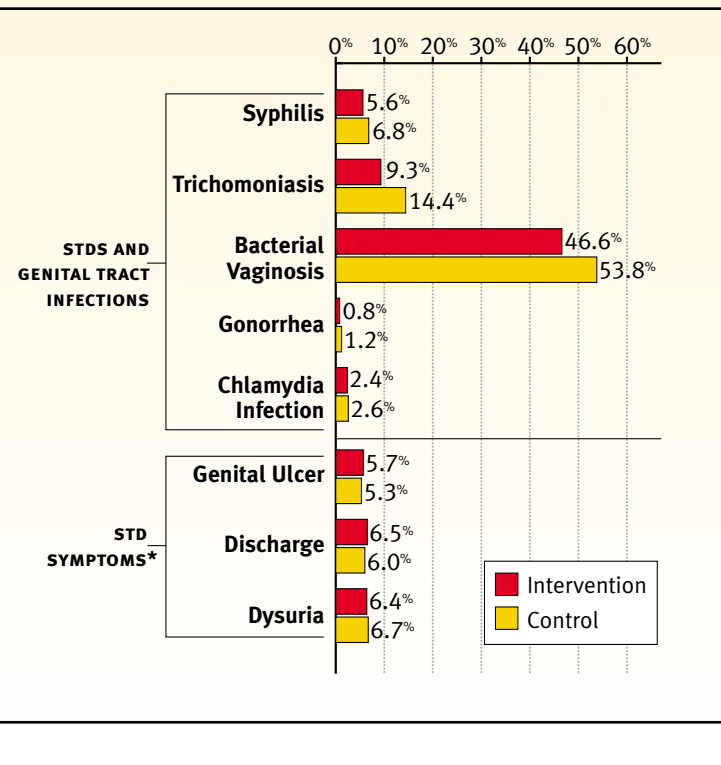
were enrolled in the control group. As demonstrated in Figures 1a, b, and c, treatment intervention resulted in significant

**Figure 2a. Collateral Seroconversions Among All Subjects**



## (Follow-Up): Intent-to-Treat Cohort

Figure 1c. STD Prevalence/Symptoms at Round 3



differences from the control group in the prevalence and incidence of some STDs, particularly in pregnant women, and de-

the same in our Ugandan clusters. Unfortunately, this did not turn out to be the case.”

clines in STDs over time. Much to Dr. Quinn’s dismay, however, the investigators found no differences in the incidence of HIV infection between the study groups—the incidence was 1.5 per 100 person-years in both groups. Also, the seroconversion rate was the same in pregnant women as in the group overall. “The HIV infection prevalence was 16% when we started and 16% when we finished the study,” Dr. Quinn said.

“We were all really quite disappointed with the results,” he said. “Even though we were able to reduce the number of STDs, what we really wanted was to have an impact on the incidence of HIV in the Rakai district. It was encouraging to see the positive results of the Tanzania study, and we really thought that we could do

Looking for explanations, Dr. Quinn and his colleagues went back and reviewed the data, leaning heavily on the surveys collected from those participating in the study. “What we found,” he said, “was really quite surprising and startling.”

### Viral Load, Circumcision, and Transmission

OF PARTICULAR INTEREST TO DR. QUINN AND his colleagues were the serodiscordant couples participating in the Rakai district study. “For the most part,” Dr. Quinn said, “a large percentage of new HIV infections reported during the study were seen in couples consisting of one partner who was HIV-positive and one partner who was HIV-negative at baseline. We called these couples serodiscordant couples and they offered a great deal of information regarding the risk of HIV transmission.”

As explained in their *NEJM* report, as part of the community-based study, 415 couples discordant for HIV were enrolled between the first and the fourth home visits (Quinn, 2000). These couples were followed for an average period of 22.5 months. The male partner was infected with HIV in 228/415 (55%) couples and the female partner was infected in

## Figure 2. HIV-RNA Levels and Collateral Seroconversions

Figure 2b. Collateral Seroconversions Among All Female Subjects

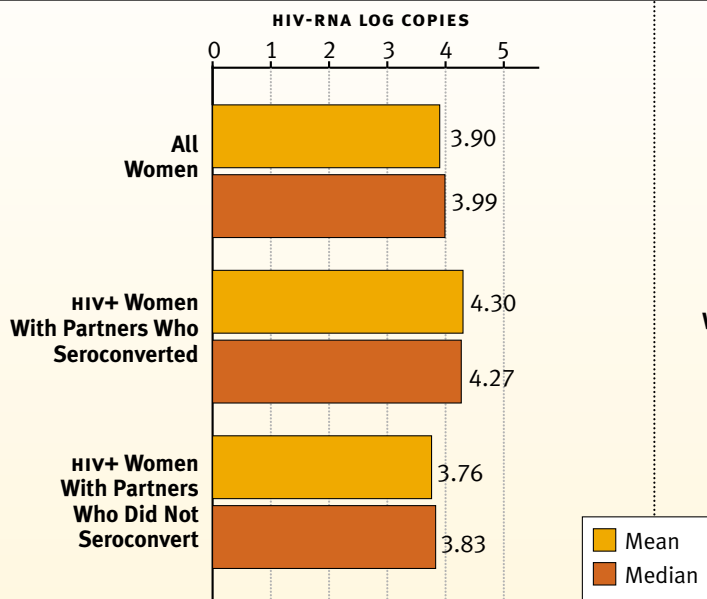
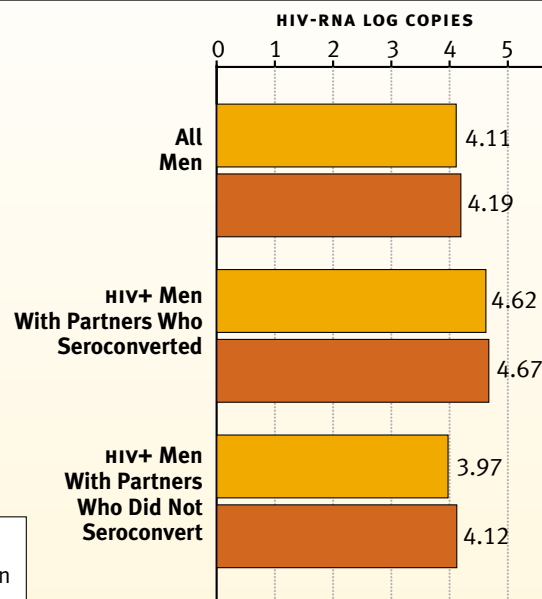


Figure 2c. Collateral Seroconversions Among All Male Subjects



Source: Adaptation of data reported in the *New England Journal of Medicine* (Quinn, 2000).

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 highest rate of seroconversion was among couples in the age group 15 to 19 years. The incidence declined with the age of both HIV-negative and HIV-positive partners, but these trends were not statistically significant.

The viral load of the HIV-positive member of a serodiscordant couple turned out to be a major factor in collateral transmission. Of the 415 seropositive partners, 364 (88%) had detectable HIV-RNA levels at baseline. The mean viral load among the 228 HIV-positive men was 59,591 copies/mL and was significantly higher than the mean level of 36,875 HIV-RNA copies/mL among the 187 HIV-positive women.

As demonstrated in Figures 2a, b, and c, HIV-positive men and women with HIV-RNA levels around 90,000 copies/mL were more likely to transmit HIV to their HIV-negative partner 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.

Of particular interest was the “dose-dependent” effect with respect to both male-to-female and female-to-male transmission. The rate of transmission was zero among the 51 couples in which the HIV-positive partner had an undetectable viral load or less than 1500 HIV-RNA copies/mL. Among HIV-positive partners with HIV-RNA levels less than 3500 copies/mL, the rate of transmission was 2.2 per 100 person-years, and the rate progressively increased with increasing viral loads, to a maximum of 23.0 per 100 person-years at a level of 50,000 or more copies/mL.

There was no significant difference between male-to-female and female-to-male transmission rates after the results were adjusted for viral load, and there were no consistent differences between male-to-female or female-to-male transmission rates within strata of viral load. “This is very different from what we see in the

United States and other similarly situated countries. But this probably has less to do with socioeconomics than it does with something else—circumcision.”

## Circumcision and Transmission

THE ISSUE OF CIRCUMCISION AS IT RELATES TO HIV transmission is hardly trivial. In 1989, Dr. Bill Cameron and his colleagues published the results of a prospective study demonstrating a greater than eightfold increased risk of HIV infection among uncircumcised men (Cameron, 1989). There have also been a number of reports illustrating that the foreskin provides a vulnerable portal of entry to HIV and other pathogens.


As summarized in an editorial authored by Dr. Daniel Halperin of the University of California, San Francisco, and Dr. Robert Bailey of the University of Illinois at Chicago in a recent issue of *The Lancet*, the highly vascularized prepuce contains a higher density of Langerhans cells—the primary target cells for sexual transmission of HIV—than cervical, vaginal, or rectal mucosa (Halperin, 1999). They also note research finding the foreskin is more susceptible to traumatic epithelial disruptions during intercourse, which allows additional vulnerability to ulcerative STDs and HIV.

Circumcision was clearly associated with a lower incidence of HIV transmission among men in the Rakai district. There were no seroconversions among 50 circumcised men, as compared with 40 infections among 137 HIV-negative uncircumcised men with HIV-positive sexual partners. With respect to the “infectiousness” of circumcised and uncircumcised HIV-positive men, uncircumcised male subjects had a higher rate of transmission to the female partner than circumcised male subjects (13.2 per 100 person-years vs. 5.2 per 100 person-years), but this difference was not statistically significant.

As explained by Dr. Quinn, this association between male circumcision and a decreased risk of infection with HIV may partially explain the low frequency of female-to-male transmission in U.S. studies of HIV-discordant couples, since over 70% of men in the United States are circumcised. “I don’t think this is coincidental,” he said. “Rates of female-to-male transmission are low in almost all coun-

tries where circumcision is the norm, not the exception.”

## Conclusion

IN CONCLUSION, DR. QUINN REITERATED THAT heterosexual transmission of HIV—much like all transmission risks—involves a complex interaction between biologic and behavioral factors. Given that viral load is such a significant factor in the transmission of HIV, Dr. Quinn argues that “research is urgently needed to develop and evaluate cost-effective methods, such as effective and inexpensive antiretroviral therapy or vaccines, for reducing viral load in HIV-infected persons. If we could find a way to reduce viral load by 68%—that’s a half log—in people with viral loads greater than 50,000 copies/mL, we stand a good chance of reducing transmission rates by 50%. If we can decrease viral load by 1.5 log, we can feasibly halt the epidemic. Figuring out how to do this is the challenge.” 

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