Circumcising Adult Men Prevented HIV Infections

A South African trial of heterosexual men found a 65% protective effect, after controlling for behavior.

BY CHARLENE LAINO
Contributing Writer

RIO DE JANEIRO — Adult circumcision may protect against infection with HIV in heterosexual men, according to the first randomized controlled trial to test the procedure.

After 21 months of follow-up observation, "Circumcision prevented 6 to 7 out of 10 potential HIV infections" in young heterosexual South African men who were circumcised as adults, compared with those who were not, said Bertran Auvert, M.D., at the International AIDS Society Conference on HIV Pathogenesis and Treatment.

Circumcision was found to be so effective at preventing infection with HIV that the trial was stopped early so that all the young men in the study could be offered the procedure, said Dr. Auvert, professor of public health at the University of Versailles Saint Quentin, France.

A feasibility study that was conducted prior to the trial demonstrated that approximately 70% of uncircumcised young men will opt to undergo the procedure if it has been shown to reduce the risk of HIV infection.

Observational studies dating back to the 1980s, and a more recent meta-analysis suggesting that circumcision may be protective against HIV, led to the randomized trial of 3,128 men, aged 18-24 years, Dr. Auvert said.

Other researchers were cautiously optimistic about the South African findings, but one said circumcision should not be used as an excuse for unsafe sex.

The participants lived in a neighborhood outside of Johannesburg, South Africa, that has historically high rates of HIV transmission.

The men, 90% of whom were sexually active, were randomly assigned either to undergo the procedure or to remain uncircumcised.

In the intervention group, circumcision was performed by trained physicians using sterile surgical procedures to remove the penile foreskin under local anesthesia.

After 21 months, 51 men who had not been circumcised had been infected with HIV, compared with only 18 of the men who had undergone the procedure. This translates into a statistically significant 65% protective effect—an outcome that remained unchanged even after controlling for sexual behavior variables, Dr. Auvert said.

Upon hearing the findings, other researchers expressed cautious optimism.

Helene Gayle, M.D., president of the International AIDS Society and director for HIV, TB, and reproductive health at the Bill and Melinda Gates Foundation, said, "If [the] results are confirmed by other ongoing studies, this could be an important tool for HIV prevention."

"But it would be premature to recommend widespread circumcision for HIV prevention at this time," she said. The findings come at a time when only one in five at-risk persons have access to prevention, she noted.

Dr. Gayle advised clinicians to caution young patients that circumcision should not be used as an excuse for unsafe sex or other risky behaviors. "We want to make sure people do not develop a false sense of security and increase their high-risk behaviors," she said.

Dr. Auvert agreed, adding that since all the men were heterosexual, the results apply only to transmission from women to men; no conclusions can be drawn regarding male-to-male transmission or male-to-female transmission. Also still unknown is whether the findings will hold up over the long term. Last year, there were 5 million new HIV infections worldwide—more than in any other year. ■

Tests Deflate Fears of New Rapid HIV Strain

BY CHARLENE LAINO
Contributing Writer

RIO DE JANEIRO — Fears that a new, multidrug-resistant, rapidly progressing strain of HIV-1 had surfaced in New York City have been alleviated, with medical researchers reporting that they have tracked down the most likely source of the infection.

Concerns have existed since February, when officials from the New York City Department of Health and Mental Hygiene announced that a middle-aged man had purportedly been infected with a unique, highly virulent strain of HIV.

The New York City patient had rapidly progressed to late-stage HIV infection, with a CD4 cell count of 60 cells/mcL within 20 months of infection.

But viral testing suggested that the New York City patient was infected by a Connecticut man whose disease has followed a more typical clinical course, said Gary Blick, M.D., medical and research director of Circle Medical LLC in Norwalk, Conn.

"The Connecticut man's virus is a 99.5% pol[ymerase] gene match to that of the New York City man. They're essentially identical," Dr. Blick reported at the International AIDS Society Conference on HIV Pathogenesis and Treatment.

The man from Connecticut, referred to as "Patient Zero," and the New York City man have acknowledged having had unprotected sex together after using crystal methamphetamine in October 2004.

Since Patient Zero has become compliant with highly active antiretroviral treatment, he has had a stable CD4 count and viral load.

"He is not a rapidly progressive patient," Dr. Blick said.

So why did the New York City man's disease progress so quickly?

Most likely, his behavior is the culprit, Dr. Blick commented. The New York City patient admitted not only to being promiscuous, but also to being a heavy user of crystal methamphetamine, a street drug that lowers inhibitions and increases risky sexual behavior. Genetic susceptibility also may have played a role.

Mark A. Wainberg, Ph.D., director of the McGill University AIDS Centre, Montreal, pointed out that having multiple sex partners and repeatedly using crystal "meth" may pummel the immune system, facilitating infection with multidrug-resistant HIV.

Dr. Wainberg said that these findings should end talk of a new HIV strain.

"It's a well-done analysis that shows the strains are virtually identical," he explained. ■

Drug Resistance, Other Patient Factors Called Key to HIV Treatment Failures

BY HEIDI SPLETE
Senior Writer

BETHESDA, MD. — Drug resistance poses a problem in treating HIV patients, in part because of the virus's high mutation rate, Roy M. Gulick, M.D., said at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

Factors affecting HIV drug resistance include the virus itself, the antiretroviral drugs used, and the characteristics of the individual patient. Drug resistance is one of the main reasons why HIV treatments fail, said Dr. Gulick, director of the Cornell HIV Clinical Trials Unit at Weill Medical College of Cornell University, New York.

The goal of antiretroviral therapy (ART) is to suppress the viral load to as low a level as possible for as long as possible, he noted. Due to the high rate of mutation in the HIV virus, viral diversity is extensive. Failure to suppress viral load levels in the presence of antiretroviral drugs leads to the development of a resistant strain, Dr. Gulick explained.

Patient-related factors that can contribute to the development of resistance include the stage of disease, use of other medications, medication adherence, and side effects.

"We used to follow resistance clinically. If someone was taking their drugs, and their viral load went down, but then rose again, if we were sure that they were taking the medication, we assumed that they had developed resistance," he said. Today, genotypic tests provide viral sequencing of a patient's viral strain, and phenotypic tests can grow the patient's virus in vitro and assess resistance in the presence of the available antiretroviral drugs.

Are resistance tests clinically valuable? Dr. Gulick cited three studies, including one published in the Lancet, in which several hundred patients who had failed drug therapies were randomized to either genotypic or phenotypic drug-resistance testing or standard care (Lancet 1999;353:2195-9).

Overall, the patients who fared better in terms of viral load reduction on their new regimens were the ones who had the resistance tests.

"Simply put, resistance tests help clinicians choose active drugs for the next regimen," Dr. Gulick said. Guidelines from the Department of Health and Human Services recommend resistance tests in the clinical setting in cases of virologic failure, suboptimal virologic suppression, and acute HIV infection.

These tests could be considered in cases of HIV infection before starting ART, but they are generally not recommended for patients more than 4 weeks after ART drug use ends, or when viral load levels are less than 1,000 copies per million.

However, studies of the effectiveness of resistance testing are limited by several factors, including problems with the clinical cutoffs—when the drugs lose activity over time—and questions as to whether the studies had enrolled patients who had failed multiple treatments.

Other studies have shown conflicting results regarding the use of resistance tests, especially for highly resistant patients. "The best resistance tests can't help a patient if they have no drug options to go to," Dr. Gulick said.

Asked whether he recommends genotypic or phenotypic testing for patients who are just starting antiretroviral therapy or who already have resistance, Dr. Gulick commented that although sufficient clinical evidence is lacking, most experts recommend a genotype test for patients who are treatment naive or have failed their first regimen, when it is relatively easy to figure out what the mutations mean. But in patients who have been through multiple regimens, phenotype is easier to interpret.

"Many people say that if cost is not an issue, they would get both tests, because they tell you different things—particularly in the late stages of infection," he added. ■