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Male circumcision reduces risk of genital herpes and HPV infection, but not syphilis

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Heterosexual men who undergo medical circumcision can significantly reduce their risk of acquiring two common sexually transmitted infections--herpes simplex virus type 2 (HSV-2), the cause of genital herpes, and human papillomavirus (HPV), which can cause cancer and genital warts, according to a report in the March 26 issue of the *New England Journal of Medicine* (NEJM). In the study, circumcision had no effect on their risk of becoming infected with the bacterium that causes syphilis, however.

The findings build upon earlier clinical research funded by the National Institute of Allergy and Infectious Disease (NIAID), part of the NIH, which found that circumcision decreases a man's risk of acquiring HIV infection through heterosexual intercourse by more than 50 percent.

"Medically supervised adult male circumcision is a scientifically proven method for reducing a man's risk of acquiring HIV infection through heterosexual intercourse," says NIAID Director Anthony S. Fauci, M.D. "This new research provides compelling evidence that circumcision can provide some protection against genital herpes and human papillomavirus infections as well."

The study was conducted by scientists at the Rakai Health Sciences Program in Uganda in collaboration with researchers at the Johns Hopkins University Bloomberg School of Public Health in Baltimore, Makerere University in Kampala, Uganda, and NIAID's Division of Intramural Research. The collaborators examined samples from two

parallel clinical trials in Rakai that successfully proved male circumcision as an HIV prevention method and also assessed the surgical procedure's ability to prevent other sexually transmitted infections, including syphilis and HSV-2. These infections cause genital ulcers and are associated with an increased risk of HIV acquisition. The research team also assessed circumcision's effect on HPV infections, which can cause anal, cervical and penile cancers and genital warts.

The two trials, one funded by NIAID and the other by the Bill & Melinda Gates Foundation, enrolled 3,393 uncircumcised men between the ages of 15 and 49 who initially tested negative for both HIV and HSV-2. The men were assigned at random to one of two study groups: 1,684 received immediate circumcision performed by trained medical professionals in an outpatient setting (intervention group); and 1,709 received medical circumcision after a delay of 24 months (control group). The researchers evaluated the volunteers at six, 12 and 24 months for HSV-2 and syphilis infection. Additionally, a subgroup of 697 volunteers (352 participants in the intervention group; 345 in the control group) was evaluated for HPV infection at enrollment and at 24 months.

In analyzing the effect of circumcision on HSV-2 acquisition across both studies, the researchers found that the cumulative probability of HSV-2 infection was significantly lower among those volunteers who received immediate circumcision (7.8 percent) than among those in the control group who were circumcised at 24 months (10.3 percent). Overall, the researchers found that medically supervised circumcision reduced the men's risk of HSV-2 infection by 28 percent.

The combined results from both trials also demonstrated a 35 percent reduction in HPV prevalence among men in the intervention group. In evaluating a subgroup of volunteers at 24 months, high-risk HPV strains associated with certain cancers were detected in 42 of 233 men in the

intervention group and in 80 of 287 men in the control group.

Circumcision did not, however, affect the incidence of syphilis. At 24 months, syphilis was detected in 50 men in the intervention group and 45 members of the control group.

"The cumulative scientific evidence supporting the public health value of medically supervised male circumcision is now overwhelming," says Thomas C. Quinn, M.D., study co-investigator, chief of the International HIV/STD Section in NIAID's Laboratory of Immunoregulation and co-author of the study. "This new research confirms the substantial health benefits of male circumcision, including reduced acquisition of HIV, genital herpes, HPV and genital ulcer disease."

Dr. David Serwadda, co-principal investigator and dean of Makerere University's School of Public Health, adds that "these findings have significant public health implications for the control of HIV, genital herpes and HPV in areas of high prevalence, such as Africa, and further suggest that efforts to scale-up male circumcision could have tremendous benefit."

"The next focus of our research will be to analyze additional data collected in the Rakai trials to assess the degree to which male circumcision may reduce transmission of HPV to female sexual partners," says Johns Hopkins professor Ronald H. Gray, M.D., co-principal investigator. "This would be of substantial significance because HPV causes cervical cancer."

The biological reasons why circumcision may reduce the risk of HSV-2 and HPV infection, but not syphilis, are not entirely known. HSV-2 and HPV multiply in epithelial cells found in the surface skin of the penis, and the foreskin may facilitate virus entry into those cells. Once circumcision has been performed, the risk of epithelial infection may be

reduced, the authors note. Additionally, the analysis used to determine the effects of circumcision on syphilis had limited statistical power, and therefore, it is difficult to draw a firm conclusion as to whether or not circumcision may reduce syphilis incidence, the researchers add.

During each clinic visit, volunteers were given physical examinations, counseled on safe sex practices and offered condoms, voluntary HIV counseling and testing. Study staff also interviewed each volunteer to record sociodemographic characteristics and rates of specific sexual risk behaviors. Volunteers who acquired HIV infection during the two clinical trials were referred to Rakai Health Science Program clinics for HIV care funded by the U.S. President's Emergency Plan for AIDS Relief. Volunteers who acquired genital ulcers or syphilis were also provided with appropriate medical care and treatment.

As with most strategies to prevent sexually transmitted infections, including HIV, adult male circumcision is not completely effective. Therefore, the authors note, safe sex practices, including consistent condom use, are still necessary to provide the best protection against such infections.

Source: NIH/National Institute of Allergy and Infectious Diseases (news : web)

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