Herpes medication does not reduce risk of HIV transmission

January 20 2010

A five-year international multi-center clinical trial has found that acyclovir, a drug widely used as a safe and effective treatment taken twice daily to suppress herpes simplex virus-2 (HSV-2), which is the most common cause of genital herpes, does not reduce the risk of HIV transmission when taken by people infected with both HIV and HSV-2. The results of the study are published in the *New England Journal of Medicine* online today, and will appear in the Feb. 4, 2010 issue of the publication.

Up to 90% of people with HIV infection also have HSV-2 infection. Most people who are infected with HSV-2 do not know they have the virus because symptoms can be mild or absent. HSV-2 infection can cause recurrent sores and breaks in the skin of the genital region, which can be mild and often go unnoticed. HSV-2 infection also attracts immune cells called CD4 T-cells to the genital region, which HIV uses to establish or pass infection.

Multiple studies have shown that frequent genital herpes recurrences increase the amount of HIV in the blood and genital tract. The HIV virus is also shed from genital herpes ulcers and persons with such ulcers transmit HIV to others more efficiently. Five preliminary studies showed that it is possible to decrease the amount of HIV in the blood and genital tract through treatment to suppress HSV-2, but these studies did not measure whether this translated into a reduction in HIV transmission. Researchers had hoped that acyclovir's ability to suppress the herpes virus, which causes symptomatic genital sores and breaks in the skin but

also frequently is active without symptoms, could reduce the likelihood of sexual transmission of HIV from a person with HIV and HSV-2. The study is the first to determine whether twice daily use of acyclovir by individuals who are infected with both HSV-2 and HIV reduced the transmission of HIV to their sexual partners. The authors conclude that daily acyclovir therapy did not reduce the risk of transmission of HIV, in spite of the fact that acyclovir reduced plasma HIV RNA by a Ľ log and the occurrence of genital ulcers due to HSV-2 by 73%.

Led by the University of Washington in Seattle and funded by the Bill & Melinda Gates Foundation, the Partners in Prevention HSV/HIV Transmission Study was conducted among 3,408 African HIV serodiscordant couples, in which one partner had HIV and the other did not. In all the couples, the partner who had HIV also had HSV-2 infection. The study took place at 14 sites in seven countries in eastern and southern Africa (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda and Zambia). In sub-Saharan Africa, the majority of new HIV infections occur among heterosexual HIV discordant couples, many of whom are in stable partnerships and unaware that one partner has HIV and the other does not. Genital herpes is thought to be a factor in a substantial proportion of new HIV infections in Africa.

The study began recruitment in Nov. 2004 and ended follow-up of participants in Oct. 2008. Results were first announced in May 2009 and were presented at the International AIDS Society (IAS) meeting in Cape Town, South Africa, on July 22, 2009.

In the primary analysis of HIV transmissions determined by laboratory testing to have occurred within the couple and not acquired from an outside partner, there were 41 infections in the acyclovir arm and 43 in the placebo arm - not a significant difference. Of the partners who were infected with HIV, 68 % were women. Acyclovir suppressive treatment did show significant reductions in the frequency of genital ulcers (by

73%) and the average amount of HIV in the blood (by 0.25 log10 copies/milliliter, a reduction of 40%), compared to the placebo arm.

"As is often the case with large efficacy trials, you learn to expect surprises," said Dr. Connie Celum, the leader of the study and a UW professor of Global Health and Medicine in the Division of Allergy and Infectious Diseases. "We found that, in spite of a significant reduction in plasma HIV levels and genital ulcer disease with acyclovir suppressive therapy, there was no reduction in HIV transmission. This was a disappointing finding, but a critical outcome of this study is the understanding that interventions must achieve a bigger reduction in HIV levels in order to reduce HIV transmission, especially among persons with high HIV levels. This will be important in informing future interventions to reduce HIV infectiousness."

Celum said the study is a direct assessment of the impact of herpes suppression on HIV transmission and is the most direct way to see if it's possible to make a person less infectious and less likely to transmit HIV to their partner. Although the primary outcome of reducing HIV transmission was not observed, Celum said the study achieved many significant mile¬stones that will help to inform HIV prevention research in a number of ways. Among these were HIV testing of approximately 55,000 couples of unknown HIV serostatus, screening of more than 6,500 HIV serodiscordant couples, and enroll¬ment of 3,408 couples in which the HIV- infected partner was dually infected with HSV-2 and not eligible for antiretroviral therapy, based on national guidelines. Adherence to twice daily acyclovir was high, with 88% of doses dispensed (the drug was not dispensed during pregnancy or if visits were missed), and 96% of dispensed doses taken, as measured by pill counts. Retention of study participants at 24 months of follow-up was 92% for HIV infected partners and 84% for HIV uninfected partners.

The Partners in Prevention HSV/HIV Transmission Study is the first

clinical trial to directly test whether suppressing HSV-2 infection in HIV-infected persons could reduce rates of HIV transmission and HIV disease progression. The study was randomized, placebo-controlled and double-blinded, meaning that both participants and the care providers did not know which treatment the participants were receiving. Both the placebo and treatment groups received standard HIV prevention services, which included being supplied with condoms, treated for other sexually transmitted infections, and provided care for HIV infection. All participants received extensive counseling, both individually and as a couple, throughout the study period, on how to reduce the risk of HIV infection.

"This was an ambitious study, and I applaud our collaborators at the University of Washington, the investigators and study teams in Africa, the study participants, and the communities where the study was done, for their dedication over the past five years," Celum said. "We will continue to learn from this study about risk factors for HIV transmission, which will bear fruit for both the HIV prevention and the vaccine fields for years to come."

Provided by University of Washington