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Herpes medication does not reduce risk of HIV transmission from individuals with HIV and genital herpes but demonstrates modest reduction in HIV disease progression and leads to new important insights about HIV transmission, UW-led international study finds

A recently completed international multi-center clinical trial has found that acyclovir, a drug widely used as a safe and effective treatment 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 majority of people with HIV infection also have HSV-2 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 being reported today 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.

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 discordant 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.

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. Acyclovir suppressive treatment reduced 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.

“The Partners in Prevention Study is a direct assessment of the impact of herpes suppression on HIV transmission,” explained 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. “A clinical trial of genital herpes suppression in HIV discordant couples is the most direct way to see if we can make a person less infectious and less likely to transmit HIV to their partner. The study did find that acyclovir significantly reduced genital ulcers due to HSV-2 and modestly reduced HIV levels in the blood, consistent with what the preliminary studies of HSV-2 suppressive treatment had shown. However, it appears that these effects were not sufficient to reduce the risk of HIV transmission.”

The study also determined whether acyclovir can slow HIV disease progression among individuals with HIV and HSV-2 who also have CD4 T-cell counts that are too high for HIV antiretroviral treatment under current national guidelines. Specifically, the investigators studied the number of participants in the acyclovir and placebo arms whose CD4 T cell counts declined to below 200, who started HIV medications, or who died. In this analysis, HIV disease

progression was slowed by 17% by acyclovir, an effect that was statistically significant. Given that low cost, safe ways to delay progression of HIV disease are needed for persons who are not yet taking HIV medications, this result is encouraging, but the modest effect observed in this study may not be sufficient to promote use of this dose of acyclovir for slowing HIV disease.

“Although the primary outcome of reducing HIV transmission was not observed, the study yielded important information that will inform HIV prevention research in a number of ways,” Celum said. “Most importantly, we have demonstrated that interventions must achieve a bigger reduction in HIV levels in order to reduce HIV transmission, especially among persons with high HIV levels. This was an ambitious study, which required testing of an estimated 50,000 couples of unknown HIV status in Africa to recruit the 3,408 HIV discordant couples who volunteered to enroll in the study. This was an important and courageous study to undertake, 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 5 years. The findings will bear fruit for both the HIV prevention and the vaccine fields for years to come.”

HSV-2 is one of the most common sexually transmitted infections worldwide and is especially prevalent in areas with high rates of HIV infection, with up to 90% of persons who have HIV also being infected with HSV-2. 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.

The Partners in Prevention HSV/HIV Transmission Study is the first clinical trial to directly test whether suppressing HSV-2 infection could reduce rates of HIV transmission and HIV disease progression. The study, which began recruitment at the 14 African sites in November 2004, ended follow-up of participants in October 2008. 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.

“Based on the findings from this study, we now better understand the relationship between HIV levels and HIV transmission. This shows us that the ‘bar’ is higher than we anticipated for the amount of reduction in HIV levels needed in order to reduce HIV infectiousness and transmission. This is relevant for other interventions,” Celum said, “such as anti-retroviral drugs to treat HIV, treatment of co-infections such as malaria, and therapeutic HIV vaccines. This understanding is a major contribution to HIV research that will help guide our search for new HIV prevention and treatment strategies.”