



Partners in Prevention HSV/HIV Transmission Study:

*Studying HSV-2 Suppression as a Potential Tool
to Prevent HIV Transmission and Delay HIV Disease Progression*

BACKGROUND

HIV discordant couples, where one partner has HIV and the other does not have HIV infection, are in urgent need of prevention strategies. Stable, heterosexual, HIV discordant couples are the largest risk group for HIV infection in Africa, accounting for more than half of new infections. Many of these couples are in committed relationships and desire children; thus, abstinence and condoms are not sufficient to prevent HIV transmission.

Herpes Simplex Virus Type 2 (HSV-2) is a sexually-transmitted infection and the most common cause of genital herpes. HSV-2 is a chronic infection and when symptomatic, produces symptoms such as tenderness, ulcers, and breaks in the skin, which are commonly called herpes outbreaks or recurrences. Most people who have HSV-2 infection do not know that they have it, because the symptoms are mild or non-specific. Commonly, persons with HSV-2 infection may not notice any symptoms of genital herpes, unless they are tested and counseled. Importantly, people with HSV-2 infection can have the virus present in the genital area without having any signs or symptoms, and during these times, HSV-2 can be transmitted during sexual contact.

HSV-2 is one of the most common sexually transmitted infections worldwide. A study in sub-Saharan Africa showed that approximately 50% of people who are HIV uninfected have HSV-2 infection and between 60-90% of people who are HIV infected have HSV-2 infection. A national study in the United States showed that one of five sexually-active adults is infected with HSV-2. In all populations studied, HSV-2 infection is more common in women than in men.

HSV-2 appears to be a major factor in fueling the HIV epidemic. Data from multiple studies indicates that HSV-2 increases an HIV uninfected person's risk of becoming HIV infected by creating easier entry of HIV as well as increasing the number of 'target cells' for HIV in the genital tract. Relevant to this study, when a person is infected with both HSV-2 and HIV, they are more infectious for HIV. During HSV-2 reactivations, the amount of HIV in the blood and genital tract is increased, and as a result, HIV infected persons with HSV-2 infection expose their partner to higher amounts of HIV. Small studies have indicated that during HSV-2 suppression with daily use of anti-herpes drugs (acyclovir or valacyclovir), HIV levels can be decreased in persons with both HIV and HSV-2 infection. Lastly, HSV-2 infection may have an effect on the rate that a person with both HIV and HSV-2 infection progresses to AIDS. Thus, there are multiple ways in which HSV-2 and HIV interact, and the question is whether a currently available anti-herpes drug, acyclovir, can provide public health and/or clinical benefits to persons who have both HSV-2 and HIV infection.

Purpose of the Study

The Partners in Prevention HSV/HIV Transmission Study (Partners HSV/HIV Study) was designed to determine whether the twice daily use of acyclovir by people who are infected with both HSV-2 and HIV can reduce their risk of transmitting HIV to their HIV uninfected partner, in addition to the protection offered by standard HIV prevention practices. The Partners HSV/HIV

Transmission Study was also designed to determine whether acyclovir can reduce HIV disease progression among persons who have both HIV and HSV-2 infection, and who have higher CD4 counts than recommended by national guidelines for initiation of antiretrovirals for HIV treatment. Although many previous observational studies have suggested that HSV-2 increases the risk of HIV acquisition, transmission and disease progression, this was the first clinical study that attempted to directly test whether suppressing HSV-2 infection could reduce rates of HIV transmission and HIV disease progression.

Study Design

The Partners HSV/HIV Study enrolled 3,408 HIV discordant couples, where the HIV infected partner was also infected with HSV-2, had a CD4 count of ≥ 250 cells/mm³ and was not on anti-retroviral drugs at the time of enrollment. Couples were in the study for 12-24 months and participation was voluntary.

The study was randomized, double-blind, and placebo-controlled. For each couple, the partner infected with both HSV-2 and HIV was randomly assigned to receive either acyclovir or placebo to be taken twice a day. Those in the acyclovir group took 400 milligram (mg) acyclovir tablets, and those in the placebo group took tablets that looked like acyclovir but did not have any medication in them. This was a “double-blind” study, meaning that neither the researchers, health care providers nor the participants knew to which group the participants were assigned. This blinding ensured that provider’s counseling and participants’ behavior (i.e. drug adherence, sexual behavior, etc.) was not affected by knowledge of whether the person was taking acyclovir or placebo.

HIV infected partners were seen monthly to receive their acyclovir or placebo tablets, counseling about adherence to the study drug, provided condoms and counseled about risk reduction practices. Every six months they had their CD4 T cell count measured, and if they dropped below the threshold for initiation of antiretrovirals used in the national guidelines, they were referred for or provided antiretrovirals. HIV infected women were tested for pregnancy monthly, and if they had a positive pregnancy test, their study drug was stopped during the pregnancy and they were referred for services to prevent HIV transmission. HIV uninfected partners were seen every 3 months for HIV testing, provision of condoms, and counseling about risk reduction.

Enrollment began in November 2004 and follow-up was completed in October 2008. The study was conducted at 14 sites in 7 countries in east and southern Africa: Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia. The study sites were overseen by researchers affiliated with 16 collaborating partners, including: Botswana Harvard Partnership, Harvard University, Emory University, Indiana University, Infectious Disease Institute, Kenya Medical Research Institute, Kenyatta National Hospital, Makerere University, Moi University, Perinatal HIV Research Unit, Project San Francisco, Reproductive Health Research Unit, Zambia Emory HIV Research Project, University of California San Francisco, University of Cape Town, and University of Washington. The study was chaired by researchers from the University of Washington in Seattle, USA, and funded by the Bill & Melinda Gates Foundation.

Participant Safety

The Partners HSV/HIV Study was designed to protect the safety of all participants. All participants were provided standard HIV prevention services. Specifically, condoms and treatment for curable sexually transmitted infections, including a 5 day treatment course for symptomatic genital herpes outbreaks, were provided. A unique feature of this study is that couples were already engaged in long-term relationships when they enrolled in the study, and most had recently learned that they were in an HIV discordant partnership. Thus, all couples

received specialized couples counseling to help them address the challenges of being in an HIV discordant relationship, and to reduce their risks of transmitting HIV.

This study was overseen by multiple institutional review boards and was designed with the safety of the participants as the highest priority. Each study site had one or more institutional review boards, which reviewed and approved the research study to be conducted at the site. A data and safety monitoring board (DSMB) met six times over the course of the study to monitor the safety of participants and review the progress of the study.

Participants who became HIV infected during the study received counseling, supportive services, CD4 T cell counts every 3 months, clinical evaluation, and referrals to necessary health services, including antiretroviral therapy based on national guidelines.

Why this Study is Important

This study will provide much needed information on the impact of HSV-2 on transmission of HIV from persons who have both HIV and HSV-2 infection, as well as the rate of progression of their HIV infection. If either HIV transmission and/or disease progression can be reduced, it will prove that the HSV-2/HIV link is real, and will determine the role of HSV-2 suppression for HIV prevention and clinical care of HIV infected persons, the majority of whom have HSV-2 infection.

Acyclovir has been available for more than 20 years for safe and effective management of genital herpes, used by more than 40 million people worldwide. The drug suppresses HSV-2 thereby reducing genital herpes outbreaks as well as shedding, where HSV-2 is present in the genital area, often without symptoms. Acyclovir can be used to treat genital herpes outbreaks when they occur or can be taken daily to prevent outbreaks. The twice-daily 400 mg dose of acyclovir is the most commonly used drug regimen to suppress HSV-2.

The newer genital herpes drugs (valacyclovir and famciclovir) have a modestly longer half-life and valacyclovir can be taken once daily in an HIV uninfected person. However, for optimal effect in HIV infected persons, valacyclovir and famciclovir need to be taken twice daily and neither have been shown to be more effective than acyclovir in suppressing HSV-2. Moreover, acyclovir is currently available as a generic drug and is, therefore, less expensive than other newer drugs and thus is more affordable for governments and donor programs.