



## Partners in Prevention HSV/HIV Transmission Study:

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

### Frequently Asked Questions (FAQs)

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#### 1. What is the Partners in Prevention HSV/HIV Transmission 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 in persons who have higher CD4 counts than recommended for initiation of HIV antiretroviral treatment by national guidelines. 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. The study was conducted among heterosexual couples who were in a stable sexual relationship where one partner was infected with both the HIV virus and HSV-2 virus and the other partner was not infected with HIV. The study was conducted in seven countries in eastern and southern Africa (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia).

#### 2. Why was the Partners HSV/HIV Study important?

There is an urgent need to identify new methods of preventing the spread of HIV. In particular, HIV discordant couples, where one partner has HIV and the other does not have HIV infection, need additional 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.

About 33 million people worldwide are living with HIV/AIDS. A UNAIDS/WHO report estimates that about 2.5 million people will become newly infected with HIV and about 2.1 million people worldwide will die of AIDS-related causes in 2007. Worldwide, 15-80% of adults have HSV-2 infections and HSV-2 infections are especially high in places where HIV infections are high. Further, HSV-2 is one of the most common sexually transmitted infections worldwide and HSV-2 infections are especially high in places where HIV infections are high. 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. The HSV/HIV Study was the first clinical trial to directly test whether suppressing HSV-2 infection could reduce rates of HIV transmission and HIV disease progression.

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 demonstrate 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.

### 3. When are results expected?

Enrollment was completed in May 2007, follow-up concluded in October 2008, and results from the study will be publicly announced in May 2009. Results will be presented on July 22, 2009 at the International AIDS Society conference in Cape Town, South Africa.

### 4. How many participants were involved in the study?

The study enrolled 3,408 HIV discordant couples. Participants were heterosexual HIV discordant couples, where the HIV infected partner was also infected with HSV-2, had a CD4 count of  $\geq 250$  cells/mm<sup>3</sup> and was not on anti-retroviral drugs at the time of enrollment. Participants were in the study for 12-24 months. Participation in the study was voluntary.

### 5. Where was the study conducted?

The study was conducted at 14 sites in seven east and southern African countries:

- **Botswana:** Gaborone
- **Kenya:** Nairobi, Thika, Kisumu, Eldoret
- **Rwanda:** Kigali
- **South Africa:** Cape Town/Gugulethu, Johannesburg/Soweto, Johannesburg/Orange Farm
- **Tanzania:** Moshi
- **Uganda:** Kampala
- **Zambia:** Lusaka, Ndola, Kitwe

### 6. Who conducted and sponsored the study?

The study was chaired by researchers from the University of Washington in Seattle, USA, and funded by the Bill & Melinda Gates Foundation. It 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, Indiana University, Emory 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 the University of Washington.

### 7. What is the study design?

The Partners HSV/HIV 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.

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. Participants who became infected with HIV during the study were provided access to medical treatment, care, and support through local providers.

## **8. Within a couple, how can one partner have HIV and not the other one?**

HIV discordance in couples is very common. Studies in Africa have found that the partner of an HIV infected person has about a 50:50 chance of being HIV uninfected, even if the couple has been together for several years. In the Partners HSV/HIV Study, the couples were in stable heterosexual relationships, and most were married.

The factors that lead some couples to be HIV discordant are not well understood. Some of these factors include higher HIV levels in the HIV infected partner, HSV-2 infection in either or both partners, and the HIV negative male partner being uncircumcised. Many couples have been in relationships for years and may not have been tested or may not have disclosed their HIV status and are thus unaware of their HIV discordance. This does not mean the HIV negative partner is immune to HIV; the HIV uninfected partner in a discordant couple can become infected at any time. In fact, the majority of new HIV infections among adults in Africa are thought to occur among stable couples that are HIV discordant. Thus, HIV uninfected individuals within HIV discordant couples are at considerable risk for getting HIV.

## **9. What is the relationship between Herpes Simplex Virus Type 2 and HIV?**

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 appears to be a major factor in fueling the HIV epidemic. Research has shown that people who have HSV-2 are two times more likely to acquire HIV compared to those who are not infected with HSV-2. Individuals who are HIV and HSV-2 infected are five times more likely to transmit HIV to their partner and have higher levels of HIV in their blood and genital secretions. 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.

## **10. Why was acyclovir chosen for this study?**

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 has 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 these other drugs and thus is more affordable for governments and donor programs.

**11. Why would researchers believe acyclovir could potentially prevent HIV transmission?**

HSV-2 can cause sores or small breaks in the skin that may make it easier for HIV infection to be transmitted from a person who has both HIV and HSV-2 infection. HSV-2 infection also attracts to the genital area the type of cells (e.g., CD4 T cells) that are infected with HIV. Acyclovir suppresses the activity of HSV-2 that make HSV-2 infected individuals more infectious as has been demonstrated by five pilot studies of HSV-2 suppression which reduced the HIV levels in blood by 0.3 to 0.5 log<sub>10</sub> and in genital fluids by 0.3 log<sub>10</sub>. By suppressing HSV-2, researchers theorize that the drug could help HSV2 infected individuals reduce their risk of transmitting HIV.

**12. Why a randomized controlled study?**

A randomized controlled study is the most effective way of finding out if using acyclovir to suppress HSV-2 will work to prevent HIV from being transmitted from the HIV infected partner to the partner who does not have HIV.

For the HSV/HIV Study, 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. Throughout the study, all participants received condoms and treatment for STIs and HSV-2 if they had symptoms.

**13. What is a placebo?**

A placebo is an inactive tablet, liquid, or powder that has no medicine in it that looks exactly like the active medication. In clinical trials or research studies, medicine is often compared with a matching placebo to prevent bias from developing during the conduct of the study and during the analyses for effectiveness.

**14. What were the benefits of participating in the study?**

- Couples HIV counseling and testing by individuals with specialized training in couples counselling.
- Regular HIV risk reduction counseling including provision of condoms as well as linkage with other support and care services for people living with HIV.
- Regular ongoing support counseling for the HIV discordant couple to help them deal with the HIV status of their relationship.
- Management of health related problems including sexually transmitted infections.
- Regular monitoring of the immune system through CD4 T cell counts for the HIV infected partner.
- Treatment and care for participants who became HIV infected during the study including 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.
- Regular counseling, treatment of STI’s and condoms were provided to all couples to prevent the spread of HIV.
- Though an indirect benefit, information obtained from the study may benefit the general community by helping researchers determine new methods of reducing the spread of HIV and encouraging couples to be tested together and learn their HIV status.

**15. What happened to participants whose CD4 T cell count fell below 200 cells/mm<sup>3</sup>?**

CD4 counts were measured at regular intervals. If they were found to be less than 200 cells/mm<sup>3</sup>, the participant was referred to local HIV treatment programs for antiretroviral treatments and continued to take part in the study.

**16. What happened if a female study participant became pregnant?**

HIV infected women were tested for pregnancy monthly, and if they had a positive pregnancy test, their study drug was stopped during pregnancy and they were referred for services to prevent HIV transmission to their babies. HIV uninfected partners were seen every 3 months for HIV testing, provision of condoms, and counseling about risk reduction.

Acyclovir is not known to cause problems during pregnancy and in some clinical situations acyclovir is used to reduce transmission of herpes from a pregnant woman to her baby during delivery. However, research studies have not been done to specifically look at the effects of acyclovir particularly during early pregnancy. Therefore, if a female participant became pregnant, the study medicine was stopped and she was referred for routine care for her pregnancy while continuing to be followed in the study.

**17. How were participants' records kept confidential?**

Confidentiality of participants is of utmost importance and strictly maintained. Participants were identified by numbers – no names were written on any files or specimen bottles. Participant files were safely kept in locked cabinets.

**18. What happened if a participant became infected with HIV?**

Participants who acquired HIV were counseled with their partner and helped to cope with the reality of living with HIV. They received supportive services, CD4 T cell counts every 3 months, clinical evaluation, and referrals to necessary health services, including antiretroviral therapy based on national guidelines.

**19. If acyclovir proves to be effective in preventing people from becoming infected with HIV, will it be availed to study participants?**

If the results show that acyclovir significantly reduces an HIV infected person's chances of transmitting HIV at the end of the study, the HIV infected participants will be offered twice daily acyclovir for one year free-of-charge. Governments, non-governmental organizations and healthcare providers will determine if acyclovir should become part of prevention and treatment programs.