



HPTN 039 Study Background

Acyclovir, HSV-2 and HIV Prevention

One of the most common sexually transmitted infections in the world, genital herpes, may be contributing to the rapid spread of HIV. This is because people infected with HSV-2 (herpes simplex virus type 2), the virus that causes genital herpes, have a much greater risk of becoming infected by HIV. That increased risk is the basis for a study, called HPTN 039, which investigated whether acyclovir—a drug that suppresses genital herpes—may reduce the risk of an HIV infection in someone with HSV-2.

Researchers at the University of Washington, Seattle, conducted the study in partnership with the HIV Prevention Trials Network (HPTN), a global collaboration of experts who develop and test HIV prevention strategies. The research took place at nine study sites in five countries—Zambia, South Africa, Zimbabwe, Peru and the United States. The study began in October 2003 and ended November 2007.

Prior studies have shown that one in five adults in the United States and more than half of the adult population in some developing nations has an HSV-2 infection. The majority of people with the HSV-2 infection are unaware that they have it, in part because the symptoms of genital herpes outbreaks are intermittent, often mild, and nonspecific.

Rates of HSV-2 infection are especially high in areas with the highest rates of HIV infection. Because HSV-2 infection is so common among HIV uninfected people living in these communities, a positive result from HPTN 039 could provide a way for a substantial number of people to reduce their risk of HIV infection.

HPTN 039 was a randomized, double-blind, placebo-controlled study of 3,172 volunteers who have HSV-2 infection and are at high risk of becoming infected with HIV. About half of the volunteers were heterosexual women and half were homosexual men. The women volunteered at study sites in South Africa, Zambia, and Zimbabwe. The men volunteered at three study sites in Peru and three study sites in the United States.

The study examined whether the suppression of HSV-2 through use of acyclovir twice daily can provide additional protection against HIV infection. All participants received intensive counseling, condoms, and treatment of curable sexually-transmitted infections. Researchers asked participants to take two tablets each day for the 12 or 18 months that they were in the study. Researchers randomly assigned half of these volunteers to a group that received 400 mg acyclovir tablets and half of them to a group that received placebo tablets. The placebo tablets looked like acyclovir but contained no medicine. No

study volunteers, clinical staff members, or researchers knew which group any volunteer was assigned to, which is why the study is described as being double-blind. Double-blind studies reduce the likelihood that clinical staff members or participants will alter their behavior in ways that could jeopardize the validity of study results.

Acyclovir is the first and most widely used drug for treating herpes. Researchers selected acyclovir as the study drug because it is safe and effective and has been used by millions of people over the past 20 years. Additionally, generic acyclovir is relatively inexpensive, with annual acyclovir suppression costing approximately US \$45 per person.

Researchers selected study sites in communities at which adults had high rates of HSV-2 infection and high rates of HIV. The communities selected also had the medical staff and resources needed to properly conduct the study and provide high standards of care to study volunteers. Study staff members met regularly with participants to discuss any genital herpes symptoms, examine them for genital herpes, monitor them for adverse effects of acyclovir, and test them for HIV and, if indicated, other sexually transmitted infections. They also used these visits to provide participants with condoms, instruct participants to use condoms during all sexual acts, and counsel them on other approaches for reducing their risk of acquiring HIV and other sexually transmitted infections. Participants also received treatment, if needed, for sexually transmitted infections and genital herpes outbreaks.

Participants who acquired HIV during the study received HIV counseling and referrals for medical treatment, care, and support. Most of them also became eligible to participate in a six-month ancillary study to assess the effect of acyclovir on HIV levels after infection.

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HPTN 039 Key Findings

Acyclovir Did Not Prevent HIV Infection

Suppression of HSV-2, with a standard dose of acyclovir (400 mg twice daily), did not prevent HIV infection among men and women infected with HSV-2.

Acyclovir Reduced Genital Herpes Recurrences

There was a significant reduction in ulcers and HSV-2 breakthrough ulcers, but less than in prior studies.

Additional research is needed to determine the cause for this. A few possibilities are that:

- 1) higher doses, new drugs, or combination drugs are needed to suppress HSV-2,
- 2) genital immune activation that is caused by HSV-2 but is unresponsive to treatment with acyclovir increased the risk for HIV infection,
- 3) other causes of genital ulcers (in addition to HSV-2) are important in increasing the risk for HIV infection,
- 4) metabolism of acyclovir, or susceptibility of HSV-2 to acyclovir, may differ in some populations, or
- 5) adherence to study was not as high as indicated by monthly pill count or self-report.

Partners in Prevention HSV/HIV Transmission Study

The same group of University of Washington researchers that led HPTN 039 is leading a sister study called the Partners in Prevention HSV/HIV Transmission Study. The Partners study is looking at whether the use of acyclovir by persons who are infected with both HSV-2 and HIV can reduce the likelihood that they will transmit HIV to their HIV uninfected sexual partners. Unlike HPTN 039, which studied whether suppressing HSV-2 prevents someone from *becoming* infected with HIV, Partners in Prevention is studying whether suppressing HSV-2 prevents someone with HIV from *infecting others* with HIV. The Partners researchers are following monogamous heterosexual couples who are HIV discordant, which means that one partner is HIV infected and the other one is HIV uninfected. The HIV infected partner must also have the HSV-2 infection to participate in the study. Partners has enrolled more than 3,400 couples from 14 sites in seven countries (Botswana, Kenya, Rwanda, South Africa, Uganda, Tanzania, Zambia) in Africa, and researchers expect to complete the trial in early 2009.