



National Institute of Allergy and Infectious Diseases

National Institutes of Health

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QUESTIONS AND ANSWERS

The HPTN 039 HIV Prevention/Herpes Suppression Study

1. What is the HPTN 039 study?

The HPTN 039 study, which began in October 2003, is a clinical trial designed to examine whether people infected with herpes simplex virus type 2 (HSV-2), the virus that causes genital herpes, can reduce their risk of becoming infected with HIV by using acyclovir, an approved medicine that suppresses genital herpes. People infected with HSV-2 who have sex with someone infected with HIV are at a much greater risk of acquiring HIV than individuals who are not infected with the herpes virus.

The study was the largest clinical trial to date to examine herpes suppression as a possible means of reducing the risk of HIV transmission.

2. Why was this study important?

This study was important because it could have provided another HIV prevention tool for people at high risk of acquiring HIV infection. Prior research has shown that one in five adults in the United States and more than half of the adult population in some developing countries has HSV-2 infection.

People with HSV-2 are at greater risk of HIV infection. The sores or small breaks in the skin that HSV-2 may make it easier for HIV to transmit during sexual intercourse. Also, HSV-2 infection attracts CD-4 T-cells to the genital area, and HIV can easily attach to this type of cell. Rates of HSV-2 infection are especially high in places with the highest rates of HIV infection, and it is common for individuals infected with HIV to also be infected with HSV-2.

3. How many participants were involved in this study?

The study involved 3,172 volunteers with HSV-2 infection and at high risk of becoming infected with HIV. Roughly half of the study participants were heterosexual women and roughly half were men who have sex with men.

4. Where was the study conducted?

HPTN 039 was conducted at nine sites in the following locations:

- Peru: Iquitos, Lima and Pucallpa

- South Africa: Johannesburg
- United States: New York, NY; San Francisco, CA; and Seattle, WA
- Zambia: Lusaka
- Zimbabwe: Harare

The female study participants were seen at the study sites in South Africa, Zambia and Zimbabwe. The male study participants were seen at the study sites in Peru and the United States.

5. Who conducted and sponsored this trial?

The University of Washington, Seattle, conducted the study in partnership with the HIV Prevention Trials Network (HPTN). The HPTN is funded in part by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and is led by the Family Health International (FHI), the Network Laboratory of Johns Hopkins University, and the Statistical Center for HIV/AIDS Research and Prevention of the Fred Hutchinson Cancer Research Center in Seattle.

NIAID sponsored the study, and GlaxoSmithKline supplied the acyclovir.

6. What is the study design?

HPTN 039 is a randomized, double-blinded, placebo-controlled clinical study designed to determine if the use of acyclovir can protect HSV-2-infected individuals at high risk of HIV infection from becoming infected with HIV. The trial's secondary objective was to determine whether acyclovir could reduce the occurrence and frequency of genital ulcers among HSV-2 infected individuals. Additionally, the researchers wanted to assess how well HSV-2 infected individuals adhere to a twice-daily acyclovir drug regimen.

During the study, volunteers were instructed to take two 400 milligram (mg) acyclovir tablets twice daily for 12 to 18 months. Researchers randomly assigned half of the study volunteers to a group that received 400 mg acyclovir tablets; the other half received placebo tablets. None of the study volunteers, clinical staff or researchers knew which specific group the volunteers were assigned.

Throughout the study, volunteers received safe-sex counseling and information on how to avoid HIV exposure and were supplied with condoms. Clinical study staff regularly met with the volunteers to discuss any symptoms of genital herpes, examine the volunteers for signs of genital herpes, monitor any adverse effects associated with the use of acyclovir, and to test for HIV infection, and, if indicated, other sexually transmitted infections.

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

7. Why was acyclovir chosen for use in this study?

Acyclovir has been available for more than 20 years as a safe and effective treatment for genital herpes, and more than 40 million people worldwide have used it. The drug suppresses HSV-2, the virus that causes genital herpes, thereby reducing genital herpes outbreaks. It also reduces

HSV-2 shedding, where the virus is present on the skin with or 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 used in the HPTN 039 study is the most commonly used drug regimen to suppress genital herpes. Although some newer herpes medications can be taken once daily, none has been shown to be more effective than acyclovir in suppressing HSV-2.

Moreover, acyclovir is available as a generic drug and is, therefore, cheaper than other newer drugs and may be more affordable for governments to provide to their citizens.

8. Why did researchers believe acyclovir could potentially prevent HIV infection?

HSV-2 can cause sores or small breaks in the skin of the genital area that may make it easier for HIV to enter the bloodstream during sexual intercourse. HSV-2 infection also attracts to the genital region CD-4 T-cells, and HIV easily attaches to this type of cell. Acyclovir suppresses the activity of HSV-2 and the biological conditions that make HSV-2 infected individuals more susceptible to HIV infection. By suppressing HSV-2, the researchers theorized that the drug could help HSV-2-infected individuals reduce their risk of becoming infected with HIV.

9. What are the results of the HPTN 039 study?

In the final analysis of the study, which officially ended in November 2007, researchers found no evidence that twice-daily acyclovir prevents HIV infection among HSV-2 infected women and men who have sex with men. Specifically, there was a 3.9 percent HIV incidence rate (75 cases) among those participants who received acyclovir, while there was a 3.3 percent HIV incidence rate (64 cases) among those who received placebo. There was no statistically significant difference in HIV rates between those participants who received acyclovir and those who received placebo.

Additionally, the study provided additional evidence that acyclovir reduces the occurrence of genital ulcers in HSV-2-infected individuals. The volunteers who received acyclovir experienced a 37 percent reduction in genital ulcer incidence.

10. How were the study and the safety of the volunteers monitored?

A data and safety monitoring board (DSMB), an independent committee of clinical research experts, statisticians, ethicists and community representatives, provided continuous oversight of the HPTN 039 study and its participants. DSMBs provide additional oversight of all phase II and phase III clinical research studies involving human volunteers and regularly review unblinded study data while a clinical trial is in progress to ensure the safety of study participants and to ensure that any benefits shown in the study are quickly made available to all participants. A DSMB may recommend that a trial, or part of a trial, be stopped if there are safety concerns or if the trial objectives have either been achieved or are unlikely to be achieved.

The DSMB for the HPTN 039 study met prior to the study's launch in October 2003 and then every six months during the course of the trial to review safety and efficacy data and study

progress. Throughout the study, the DSMB determined that the trial objectives were being met and, therefore, believed the study should be completed as designed to obtain a conclusive answer.

11. Did participation in the study increase the volunteers' risk of HIV infection?

No, it did not. Research has shown that individuals with HSV-2 infection are more susceptible to HIV infection than people who are not infected with HSV-2. Acyclovir suppresses HSV-2 infection in people infected with the virus, and researchers hoped that this effect on HSV-2 would diminish the risk of HIV infection among this patient population. Unfortunately, the HPTN 039 study did not demonstrate that the standard two-dose (400 mg twice daily) regimen of acyclovir protects HSV-2 infected individuals from HIV infection.

In general, people who volunteer in HIV-related clinical trials reduce their risk of HIV infection because they receive regular risk-reduction counseling, condoms and medical treatment for any sexually transmitted infections that occur during the course of the study. Volunteers in the HPTN 039 study regularly received counseling on how to avoid HIV exposure and were supplied with condoms.

Media inquiries can be directed to the NIAID Office of Communications at 301-402-1663, niaidnews@niaid.nih.gov.

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