Factsheet
CAPRISA 004 Trial and the Impact of Tenofovir Gel on Herpes Simplex Virus Type-2 Infections

Summary
- Tenofovir gel provided a 51 percent protective effect against the acquisition of the herpes simplex virus (HSV-2) among trial participants—an encouraging result for the prevention of genital herpes.
- If this protective effect is confirmed by another study, the broader use of tenofovir gel could reduce the prevalence of HSV-2, especially among the most vulnerable populations of the world.
- The prevention of HSV-2 also has consequences for HIV prevention because people who are infected with HSV-2 are more likely to acquire and transmit HIV.
- CAPRISA 004 participants who were HSV-2 negative were consistently less likely to acquire HIV.
- Tenofovir gel reduces HIV risk in women with HSV-2 infection and in women without HSV-2 infection. The effects of tenofovir gel on HIV and HSV-2 infections are separate and independent of each other.

BACKGROUND

Herpes simplex virus type-2 (HSV-2) and public health
Herpes simplex virus type-2 (HSV-2 or genital herpes) is a life-long infection. It is a common cause of sexually transmitted infections and is the most common cause of genital ulcer disease. Globally, about 20 percent of sexually active adults, about 80 percent of people living with HIV, and about 90 percent of women at higher risk (such as sex workers) are infected with HSV-2. In southern Africa, about 50 to 70 percent of HIV-negative women have an HSV-2 infection.

HSV-2 and HIV
People who are infected with HSV-2 are more likely to acquire and transmit HIV. The mechanism is not fully understood, but it may be related to inflammation of the genital mucous membranes and genital ulcers caused by HSV-2, which may provide a path for the entry and exit of HIV. However, clinical trials on the suppression of HSV-2 with the antiviral drug acyclovir have not shown a reduction in the acquisition of HIV.

Tenofovir, HSV-2, and HIV
The precursors to tenofovir, called DHPA and HPMPA, are known to be active against HSV-2 in cell cultures and in mice. Cidofovir, a sister drug with a similar structure to tenofovir, is known to be effective and is licensed as a treatment for HSV-2 infection. However, standard doses of...
tenofovir have not been shown to have a therapeutic effect on HSV-2 infection in mice. The CAPRISA 004 trial provided an opportunity to examine whether tenofovir gel can prevent HSV-2 infection in humans. Specifically, we were interested in assessing: (1) the impact of tenofovir gel on HSV-2 acquisition and (2) the impact of HSV-2 infections (acquired before or during the trial) on the acquisition of HIV.

**HSV-2 RESULTS**

**HSV-2 status of the trial participants**
Of the 889 participants, 454 (51.1 percent) were HSV-2 positive at enrollment. The HSV-2 status of 1 participant could not be determined at baseline. This participant and a further 4 who did not have an HSV-2 result at the end of the trial were excluded from this analysis. The HSV-2 laboratory test sometimes produces a result that is not clearly positive or negative—known as an equivocal result. The 4 women with equivocal results at the end of the study were also excluded. Of the 426 HSV-2 negative participants, 202 received the tenofovir gel and 224 received the placebo gel. During the trial, there were 87 new cases of HSV-2 infection.

**Tenofovir gel and HSV-2 prevention**
Of the 224 women who used the placebo gel, 58 acquired an HSV-2 infection, an incidence of 20.2 per 100 women-years. In contrast, of the 202 women who used tenofovir gel, only 29 acquired an HSV-2 infection, an incidence of 9.9 per 100 women-years. Tenofovir gel reduced the risk of HSV-2 acquisition by 51 percent. The results are statistically significant (p = 0.003): The odds that the trial achieved these results when the gel is actually ineffective against HSV-2 are only 3 in 1,000. The protective effect of the gel increased with increasing use of the gel by the participants. Women who used at least 6 applicators per month experienced a 62 percent protective effect against HSV-2 acquisition (p = 0.008).

**Tenofovir gel, HSV-2, and HIV**
Women who were HSV-2 negative were consistently less likely to acquire HIV compared to women who had an HSV-2 infection. Tenofovir gel reduced the risk of HIV acquisition to a similar extent in women with an HSV-2 infection and in women who did not have an HSV-2 infection. After adjusting for HSV-2 infections, the effect of tenofovir gel on HIV infection did not change significantly. This means that the effects of tenofovir gel on HIV infections and HSV-2 infections were separate and independent of each other.

Since HSV-2 infections enhance the spread of HIV infections, the prevention of HSV-2 infections in the long term should have an indirect effect on the prevention of HIV infections. Hence, tenofovir gel is likely to have an impact on HIV prevention directly through its effects on HIV and indirectly through its effect on HSV-2 infections. The CAPRISA 004 study was not designed to investigate this indirect effect; further studies are needed to quantify the long-term reduction of HIV infections by the prevention of HSV-2 through the use of tenofovir gel.

**IMPLICATIONS FOR THE FUTURE**

Suggested Citation: FHI and the Centre for the AIDS Programme of Research in South Africa. Factsheet: CAPRISA 004 Trial and the impact of tenofovir gel on herpes simplex virus type-2 infections. Research Triangle Park, NC USA, July 2010.
Availability of tenofovir gel for public use

CAPRISA 004 was a test-of-concept study designed to explore whether tenofovir gel was a promising microbicide, rather than a definitive trial designed to provide information for licensure. The results of the CAPRISA 004 study are a critical first step which needs to be confirmed by one or more studies of tenofovir gel to produce the definitive evidence needed for licensure and the public availability of the gel for HSV-2 prevention.

Implications for HSV-2 prevention

If this protective effect is confirmed by another study, the broader use of tenofovir gel could reduce the incidence and prevalence of HSV-2, especially among the most vulnerable populations in the world. The gel would also be a unique tool for the prevention of HSV-2 by women who are not able to insist on a mutually faithful relationship or condom use with their male partners.

If the gel comes to market, all users of the product will need to know that the gel does not provide full protection against HSV-2. It will be important for individuals to continue practicing other proven HSV-2 prevention methods, such as condom use, knowing one’s HSV-2 status and one’s partners’ HSV-2 status, and having fewer partners.