# Factsheet
# Results of the CAPRISA 004 trial on the effectiveness of tenofovir gel for HIV prevention

**Summary**

- CAPRISA 004 has provided ground-breaking evidence that the use of an antiretroviral drug (tenofovir) in the form of a vaginal gel can prevent HIV infections in women.
- After one year of use, women who used tenofovir gel had 50 percent fewer HIV infections compared to women who used the placebo gel during sex acts.
- After 30 months of gel use, women who used tenofovir gel had 39 percent fewer HIV infections compared to women who used the placebo gel during sex acts. The lower level of effectiveness in the second year of the trial was associated with less use of the gel by women who became infected with HIV.
- Adherence to gel use before and after sex influences the level of protection; women whose returned applicator counts indicated that they followed the prescribed regimen of two doses of tenofovir gel for more than 80 percent of their sex acts had a 54 percent lower risk of HIV.
- More research is needed on microbicides, including studies of different dosing strategies, different formulations and products containing other antiretroviral compounds in order to confirm and preferably improve the level of effectiveness observed in CAPRISA 004.
- If the protective effect shown in CAPRISA 004 is confirmed by another study, the broader use of tenofovir gel could save millions of lives, especially in sub-Saharan Africa.

## BACKGROUND

### Study design

CAPRISA 004 was a Phase IIb, double-blinded, randomized, placebo-controlled trial. The study involved 889 rural and urban South African women (ages 18 to 40 years) who were sexually active and HIV-negative. A total of 445 randomly assigned women received vaginal applicators containing a 1% concentration of tenofovir gel, and 444 received applicators filled with a placebo gel that looks identical to the study gel but does not contain tenofovir.

### Study product

Tenofovir gel contains a well-known antiretroviral (ARV) drug called tenofovir that prevents HIV from replicating inside cells. Tenofovir was first studied for the prevention of simian immunodeficiency virus (SIV)—the monkey equivalent of HIV—in rhesus macaques. Based on the promising results from these early monkey studies, the gel formulation of tenofovir was developed for HIV prevention in parallel with the development of the oral (tablet) form for HIV treatment. The tablet was shown to be effective for the treatment of HIV infection in 2001. Since then, oral tenofovir has been approved by a number of regulatory agencies and has been

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used by hundreds of thousands of HIV-infected individuals in more than 50 countries to treat HIV.

**Measurement of effectiveness in the CAPRISA 004 trial**
The scientists observed 98 HIV infections (which fulfilled the protocol definition) in the study population of 889 women. The effectiveness of tenofovir gel was determined by the relative incidence of HIV infections among women who were using tenofovir gel versus women who were using the placebo gel. The effectiveness observed in the trial is a combination of the true efficacy of the gel with perfect use and the level of adherence achieved in the trial. An effectiveness of 39 percent means that there were 39 percent fewer HIV infections among women who used the tenofovir gel compared to women who used the placebo gel during the trial. Our calculations indicate that this level of risk reduction translates to the prevention of 1 new HIV infection for every 20 women who used tenofovir gel during the trial.

**Animal Studies**
Studies in monkeys show that tenofovir gel can prevent the vaginal (and rectal) transmission of a virus that is similar to HIV, but scientists do not know whether it has the same effect in humans. CAPRISA 004 is the first clinical trial to examine this question in humans.

**Other clinical trials of microbicides**
Several early-stage (Phase I and Phase II) clinical trials are currently assessing the safety of candidate microbicides in women. One advanced-stage clinical trial is also under way. This study, known as the VOICE trial, is assessing whether the daily use of tenofovir gel can reduce the chances that an HIV-negative woman will become infected with HIV. The Microbicide Trials Network (MTN) is currently conducting the VOICE trial in several countries in Africa and its results are expected in 2012. No other microbicide-effectiveness trials are under way.

## CAPRISA 004 TRIAL RESULTS

**Effectiveness of tenofovir gel for HIV prevention**
The CAPRISA 004 trial found that women in the tenofovir gel group had a 39 percent lower risk of being infected with HIV than women who used a placebo gel. The results are statistically significant ($p = 0.017$): The odds that the trial achieved these results when the gel is actually *ineffective* are only 17 in 1,000. These results are very encouraging. CAPRISA 004 has provided evidence that the use of an antiretroviral drug (tenofovir) in the form of a vaginal gel can prevent HIV infection in women. Additional clinical evidence will be needed to determine whether tenofovir gel definitively reduces the risk of HIV infection in women.

**Effectiveness of tenofovir increases with adherence**
Tenofovir gel was most effective when the participants adhered to the prescribed dosing regimen: Each woman was asked to apply a first dose of the assigned study gel within 12 hours before anticipated sexual intercourse, and to insert a second dose as soon as possible after intercourse. Adherence is therefore calculated by dividing the number of reported sex acts by half the number of returned used applicators.

Tenofovir gel was 54 percent effective among women who adhered to the dosing regimen at least 80 percent of the times they had sexual encounters; 38 percent effective among women

who adhered to the regimen from 50 percent to 80 percent of the times they had sex; and 28 percent effective among women who adhered to the regimen less than 50 percent of the times they had sex.

The CAPRISA scientists also found that the effectiveness of the gel declined after the first 18 months of gel use in the study as the amount of gel being used by the participants decreased.

**Tenofovir gel not 100-percent effective**
Very few medical or behavioral interventions provide complete protection. People routinely engage in activities that reduce but do not eliminate risks, including wearing seat belts, brushing teeth and wearing condoms. For women and men who cannot use condoms, especially those living in settings with high rates of HIV, even a partially protective product could prove beneficial.

## IMPLICATIONS FOR THE FUTURE

**Availability of tenofovir gel for public use**
CAPRISA 004 was a test-of-concept study designed to explore whether tenofovir gel could prevent HIV infection, rather than a definitive trial designed to provide information for product licensure. The results of the CAPRISA 004 study are a critical first step that needs to be confirmed by other studies to enable licensure and subsequent public availability for HIV prevention.

**Next steps**
There continues to be an urgent need for additional HIV prevention methods to reduce the sexual transmission of HIV. Scientists must continue to explore future microbicide candidates, including drugs that contain two or more ARVs, using different ARV formulations, and with different doses of ARVs.

**Implications for HIV prevention**
If the results of the CAPRISA 004 trial are confirmed, tenofovir may be licensed by a drug regulatory authority. It can then be implemented in the country where it was approved. The broader use of tenofovir gel could slow the HIV epidemic and save many lives, especially in sub-Saharan Africa. The gel formulation would also be a unique HIV prevention tool for 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 HIV. It will be important for individuals to continue practicing other proven HIV prevention methods, such as condom use, knowing one's HIV status and one's partners' HIV status, and having fewer partners.

We must continue research to find new HIV-prevention tools, including women-controlled microbicides. The search for microbicides, vaccines, and other strategies to reduce sexual transmission of the virus remains critical to enhancing HIV prevention efforts globally.

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