



CAPRISA 004 Questions and Answers

The CAPRISA 004 clinical trial assessed the effectiveness and safety of 1% tenofovir gel in preventing HIV infection in women and was conducted at two sites in South Africa from 2007 to 2009.

Did the tenofovir microbicide gel tested in the CAPRISA 004 trial reduce the risk of HIV infection for women?

Yes. The CAPRISA 004 trial showed that 1% tenofovir gel, when used up to 12 hours before sex and within 12 hours after sex, provided moderate protection from HIV infection for women. At the end of the trial, researchers found that tenofovir reduced HIV infections by 39%. This result was statistically significant.

Did tenofovir gel protect women against any other sexually transmitted infections?

Yes. CAPRISA 004 found that tenofovir gel provided a 51% 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, a broad use of tenofovir gel could reduce the prevalence of HSV-2, especially among the most vulnerable populations of the world. This is very good news because the prevention of HSV-2 also has consequences for HIV prevention, as people who are infected with HSV-2 are more likely to acquire and transmit HIV.

What do these results mean for microbicides and HIV-prevention research?

CAPRISA 004 is the first clinical trial to show that a vaginal microbicide can help prevent the sexual transmission of HIV. This is also the first effectiveness trial of an antiretroviral (ARV)-based microbicide candidate, so the findings that it offers protection from HIV and HSV-2 infection are especially notable. It is especially promising for the field of HIV prevention that there is now proof of concept that ARV-based microbicides work.

This is good news for the field of HIV prevention research and provides hope for the millions of women at risk of HIV.

Is tenofovir gel safe to use?

The trial showed that 1% tenofovir gel was safe when women used the product 12 hours before sex and 12 hours after sex, inserting no more than two doses in a 24-hour period. There were no serious side effects or major safety concerns observed. Additionally, evidence shows that the drug remains at low levels in the blood when it is applied to the vagina. This means that the drug remains in the vagina where it is needed to prevent the sexual transmission of HIV and does not spread throughout the body's bloodstream.



What happened to women who became HIV positive during the trial?

Women who sero-converted during the trial were given the option of receiving ongoing care, and treatment when necessary, via participation in other CAPRISA trials and referral to treatment programs and other non-governmental services in the area.

It is important to remember that the CAPRISA 004 trial was conducted in areas where many women are at high risk of HIV infection. Women enrolled in the trial were at risk of HIV infection if they had sex without a condom with an infected partner. Therefore, some women became HIV positive despite being in the trial and receiving the best possible HIV-prevention package.

Did women who became HIV-positive during the time they were in the trial become resistant to tenofovir?

The trial monitored drug resistance very carefully to assess whether women who became HIV-positive (sero-converted) during the trial were at risk of becoming resistant to tenofovir. The CAPRISA 004 trial conducted monthly HIV testing, and the gel was stopped as soon as a woman was found to be HIV positive.

During the trial, there was no evidence of any major drug resistance to tenofovir emerging among women who were given the tenofovir gel and became HIV positive. Drug resistance will continue to be monitored among women who became HIV positive while in the trial. They have been enrolled in another related study that will investigate whether drug resistance evolves over time. The absence of drug resistance would be good news as it demonstrates that if ARV-based microbicides are licensed for use in the future, women's HIV treatment options may not need to be limited by the HIV-prevention options available to them.

The reasons for monitoring drug resistance in ARV-based microbicide trials are explained in the Global Campaign for Microbicides Fact Sheet on Understanding HIV Drug Resistance ([http://www.global-campaign.org/clientfiles/FS-DrugResistance\[E\].pdf](http://www.global-campaign.org/clientfiles/FS-DrugResistance[E].pdf)).


What did the study find in terms of the viral load of the women who became HIV positive?

Viral load refers to the amount of HIV in the blood. If the viral load is high, HIV disease progresses more rapidly. In HIV treatment, the viral load is measured to see if ARV treatment is working by reducing the viral load.

The CAPRISA 004 trial measured the viral load of sero-converters to assess whether the use of tenofovir gel affected the viral load during the period after they were infected and before HIV symptoms appeared, called the acute phase. CAPRISA 004 found that women who were given tenofovir gel and sero-converted during the trial had the same level of virus in their blood after infection as women who were given placebo gel and sero-converted.

What are the next steps in evaluating tenofovir gel for women in Africa?

The evidence from CAPRISA 004 should justify the development of further trials to evaluate the use of tenofovir gel. However, clinical research takes considerable time and resources.



VOICE (Vaginal and Oral Interventions to Control the Epidemic) is another trial testing tenofovir gel. VOICE started in September 2009 at research centres in Malawi, South Africa, Zimbabwe, and Uganda. Unlike CAPRISA 004, it tests tenofovir gel used daily, as well as two candidates as oral pre-exposure prophylaxis (PrEP): tenofovir and Truvada (a combination of tenofovir and emtricitabine). The results of the VOICE trial are expected in 2013.

What do we know about pregnant women using tenofovir gel?

Women who became pregnant during the CAPRISA 004 trial were immediately taken off the gel. The short-term exposure to tenofovir gel for up to one month in early pregnancy during the trial did not raise any safety concerns for the pregnant women or their babies.

The Microbicides Trial Network (MTN) conducted a small safety study that involved 16 healthy HIV-negative women applying tenofovir gel vaginally approximately two hours before they gave birth by scheduled caesarean delivery. The study found that only small amounts of the drug were absorbed into the mother's blood, amniotic fluid, and umbilical cord (fetal) blood. This evidence supports further evaluation of tenofovir gel in pregnant women but is not yet sufficient to confirm that tenofovir gel is absolutely safe to use during pregnancy.

What do the CAPRISA 004 results mean for other ongoing or planned microbicide trials?

The CAPRISA 004 study evaluated the use of tenofovir gel used up to 12 hours before and within 12 hours after sex and is contributing information about safety and drug resistance, which is vital to future ARV-based microbicide research. The CAPRISA 004 results add to the body of knowledge around ARV-based microbicides. It is important to continue to test tenofovir gel used every day as well as other microbicide candidates that can help reduce the risk of HIV infection for women.

The need for additional HIV-prevention options for women remains urgent. Microbicides, PrEP, and vaccines are all viable HIV-prevention options for the future. It is critical that research continues in the search for HIV-prevention options for women.

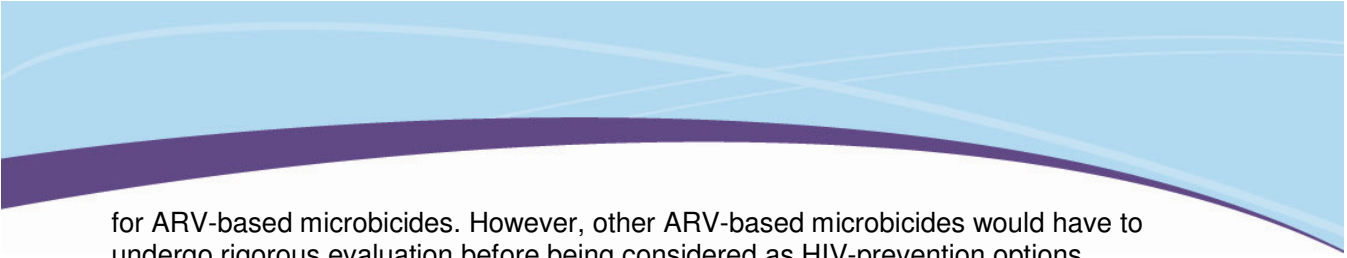
Are other ARV-based candidate microbicides being tested to prevent HIV infection in women?

At the moment, tenofovir is the only ARV-based candidate microbicide in clinical testing for long-term safety and effectiveness against HIV infection.

However, there are a number of other ARV-based microbicide candidates in early safety studies including dapivirine and UC781, and others in pre-clinical laboratory studies. Dapivirine is being evaluated as a vaginal gel as well as in a slow-release vaginal ring. This is the first trial in Africa testing a vaginal ring that contains an ARV as a candidate microbicide.

Do the CAPRISA 004 findings mean that other ARV-based microbicides will also reduce the risk of HIV infection for women?

No. CAPRISA 004 has shown that 1% tenofovir gel, applied up to 12 hours before sex and within 12 hours after sex, can reduce the risk of HIV infection. This provides proof of concept



for ARV-based microbicides. However, other ARV-based microbicides would have to undergo rigorous evaluation before being considered as HIV-prevention options.

Will women who were in the trial be given tenofovir gel?

No. It would be premature to promote tenofovir gel as an effective HIV-prevention option for women until we have conclusive evidence from further confirmatory trials.

When will women in Africa be able to access an effective microbicide?

There is no clear answer to this question yet. The CAPRISA 004 trial has taken us one step closer to finding an effective microbicide gel. These results will add to the body of knowledge around microbicides. However, setting up confirmatory trials, licensing a new drug, and setting up distribution mechanisms for a new drug can all take several years.

We need to continue to prioritize investments in HIV-prevention options that can meet the diverse needs of women in Africa and the rest of the world.

What do the CAPRISA 004 results mean for the future of HIV-prevention research for women?

The CAPRISA 004 results will increase attention to tenofovir gel and other ARV-based microbicide candidates. We urge support for more investment in and research on microbicides and additional HIV-prevention options for women.

We must also encourage operational research into practical distribution and marketing strategies. With this knowledge, the field will be able to respond quickly to ensure that when scientists identify effective HIV-prevention products, the millions of women who most need them will be able to readily access them.

The need for additional HIV-prevention options for women remains urgent. Microbicides, PrEP, and vaccines are all viable HIV-prevention approaches for the future. It is critical that research continues in the search for HIV-prevention options for women. Further, we will continue to advocate for improved access to existing prevention methods including voluntary counseling and testing and the female condom.