Questions and Answers
CAPRISA 004 TENOFOVIR GEL TRIAL

A randomized, controlled trial to assess the safety and effectiveness of a vaginal microbicide, tenofovir gel, for the prevention of HIV infection among women in South Africa

Why did CAPRISA conduct a trial of tenofovir gel for HIV prevention?
The CAPRISA 004 study was conducted to establish whether the vaginal use of tenofovir gel is safe and whether it can prevent male-to-female sexual transmission of HIV. Specifically, researchers conducted CAPRISA 004 to evaluate the safety and effectiveness of tenofovir in comparison to a placebo gel (a matched gel with no active ingredient) in sexually active women at risk for human immunodeficiency virus (HIV) infection in South Africa.

Who conducted this trial?
CAPRISA 004 was conducted by a team of South African and American researchers with funds provided by the United States Agency for International Development (USAID) and South Africa's Technology Innovation Agency (TIA), with product supplied by CONRAD, and with collaborating support from FHI. The principal investigators (study leaders) are Professor Quarraisha Abdool Karim and Professor Salim S. Abdool Karim.

When did the trial begin and how was it designed?
CAPRISA 004 was a Phase IIb, two-group, double-blind, randomized, controlled trial to assess the safety and effectiveness of 1% tenofovir gel, a candidate vaginal microbicide, in 889 sexually active HIV-uninfected urban and rural women at risk for HIV infection in South Africa. After undergoing the informed-consent process, each participant was randomly assigned to one of the two study groups: tenofovir gel or placebo gel.

All women were provided with a supply of single-use, pre-filled applicators (with tenofovir gel or placebo gel) and were counseled to apply a first dose of the assigned study product within 12 hours prior to sexual intercourse and to insert a second dose as soon as possible within 12 hours after sexual intercourse. They were advised to use no more than two doses of gel in a 24-hour period. Because the gels and applicators of the placebo and the tenofovir doses look the same, neither researchers nor participants knew who was assigned to use which gel during the 12- to 30-month period they were in the study. Participants in both groups also received condoms, extensive risk-reduction counseling, and treatment of symptomatic sexually transmitted infections.

The trial, which started on 23 May 2007, was conducted at CAPRISA's Vulindlela and eThekwini clinical research sites, and ran for a total of 30 months. Results, which will be presented at the International AIDS Conference in Vienna on 20 July 2010, should indicate whether tenofovir gel is safe and effective as a vaginal microbicide to prevent HIV infection.

Where were the clinical trial sites located?
The CAPRISA 004 tenofovir gel trial was conducted at two sites in South Africa: the CAPRISA eThekwini Clinical Research Site, located in central Durban, and the Vulindlela Clinical Research Site, located in a rural setting approximately 90 minutes outside of Durban.

What is a microbicide?
Microbicides are substances that are designed to reduce or prevent the sexual transmission of HIV or other sexually transmitted infections when applied either in the vagina or the rectum. In South Africa, vaginal microbicides are being evaluated for the prevention of male-to-female transmission when applied vaginally. An effective product would let women at risk of HIV have greater control over preventing an infection. Microbicides are formulated as foams, gels, creams, suppositories, films, and even as sponges or vaginal rings that slowly release the active ingredient. No such products are currently available to the public. However, scientists around the world—including HIV experts in South Africa—are examining several potential microbicides.

Why is CAPRISA's tenofovir gel study important?
According to statistics from UNAIDS and the U.S. Centers for Disease Control and Prevention, nearly half of the 39.5 million people living with HIV/AIDS worldwide are women. In sub-Saharan Africa, women account for 59 percent of all infected adults. Young women are especially vulnerable. Worldwide, 60 percent of the 15- to 24-year olds with HIV are women. In sub-Saharan Africa, women aged 15 to 24 years with HIV represent 76 percent of the total cases in that age group, outnumbering their male peers by three to one.

Between 70 and 90 percent of all HIV infections among women are due to heterosexual intercourse. Moreover, women are twice as likely as their male partners to acquire HIV during sex, due in part to biological factors that make women more vulnerable. Despite the greater vulnerability of women, they have few options to reduce the transmission and acquisition of HIV. New technologies to prevent the sexual transmission of HIV in women are urgently needed. Although the correct and consistent use of male condoms has been shown to prevent HIV transmission, women are often unable to negotiate the use of condoms with their male partners.

If proven effective, microbicides could be an important prevention approach for many women who cannot rely on abstinence or on their male partners to use condoms. Even a moderately effective microbicide could have a profound impact on the dynamics of HIV transmission. According to mathematical models developed by the London School of Hygiene and Tropical Medicine, 2.5 million HIV infections could be averted within three years if a microbicide with 60 percent effectiveness were used in 73 low-income countries.

Which candidate microbicide was studied?
The candidate microbicide, tenofovir gel, is an antiretroviral gel, which is manufactured by Gilead Sciences, Inc., and licensed to CONRAD, a non-profit research organization based in the United States. Tenofovir gel is designed to protect against HIV infection by preventing the virus from reproducing itself inside susceptible cells. An oral formulation of tenofovir was approved by the US Food and Drug Administration (FDA) in October 2001. It has since been actively marketed by Gilead Sciences for the treatment of HIV and is used by thousands of individuals infected with HIV in many countries. The oral formulation has recently been licensed for the treatment of HIV in South Africa.

Tenofovir gel has undergone extensive laboratory study and was evaluated in other early-phase human safety clinical trials before CAPRISA 004. The pre-clinical laboratory research and studies in animals

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suggested the tenofovir gel may prevent sexual transmission of HIV, whereas the early-phase clinical studies indicated the gels were well tolerated and safe to proceed to further testing in larger trials.

If the women in this study used condoms, how will you know whether tenofovir gel is effective?
Researchers provided participants with free condoms and extensive, risk-reduction counseling to reduce the risk of HIV for all women in the trial. If every single participant used a condom for every act of sexual intercourse during the study, it would be nearly impossible for researchers to evaluate the effectiveness of the microbicides, because condoms provide protection against infection. But in reality, women are not always able to convince their partners to use condoms or to use them all the time. The effectiveness of the gel was therefore assessed through the protection it may provide when condoms were not used during intercourse. The study also took into account any additional benefit of the gel when used by participants in those sexual acts that involved condoms.

When was the trial completed?
The study exit visits were completed in December 2009 and the post-trial follow-up visits in March 2010. Results of the trial will be presented at the International AIDS Conference in Vienna on 20 July 2010.

How did this trial differ from other microbicide trials?
This was the first effectiveness study of an antiretroviral drug formulated as a vaginal gel for prevention of HIV. It was also the first microbicide trial where the consortium of partners was led by a developing country institution—the Centre for the AIDS Programme of Research in South Africa (CAPRISA), based at the University of KwaZulu-Natal in Durban, South Africa. It was the first microbicide trial that was co-funded by a developing country government agency, namely TIA, and it was the first microbicide trial where public-sector pricing had been secured for southern Africa and a royalty-free voluntary license for local South African manufacture had been secured up front.

What approvals were required for this trial to get underway?
The trial underwent extensive and rigorous review, by South African regulatory authorities, the Medicines Control Council, and the ethics committees of the University of KwaZulu-Natal and FHI. In addition, both sites that conducted the trial had a local community advisory board to facilitate community involvement in the trial.

Did all women in the study provide informed consent?
Each woman was provided with detailed information on the study. The informed consent process ensured that the women understood (1) the study's procedures as well as the risks and benefits of the study; (2) the need to practice safer sex behaviors regardless of which study group they were assigned to; (3) the importance of adherence to the study's treatment regimen; and (4) the potential medical risks associated with participation. The women were under no obligation to participate and could leave the study, without consequence, at any time. Once a woman completed the study information session, she was asked to answer a comprehensive quiz about the key concepts of the trial. Women who answered all questions correctly were then asked to provide written informed consent prior to both screening and enrollment, using forms translated into isiZulu, where necessary.

What were the medical benefits for women participating in the study?
Participants received free risk-reduction counseling and testing for HIV as well as routine physical and pelvic exams and contraceptive counseling and services. In addition, symptomatic treatment of other non-HIV sexually transmitted infections was provided free of charge to participants and their partners.

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What was done to ensure the safety of the study participants?
CAPRISA 004 was designed according to the most rigorous international ethical standards to protect the wellbeing of the participants. CAPRISA 004 followed strict national and international procedures for monitoring and reporting, including regular reviews by an internal Protocol Safety Review Team (PSRT) and an external independent Data and Safety Monitoring Board (DSMB). The PSRT met every 2 to 3 months to review overall blinded study safety information, whereas the DSMB reviewed trial data (including unblinded data when needed) at pre-defined points to ensure that participants were not being adversely affected by the microbicide. If the DSMB had any safety concerns, it could have recommended that the study modify its procedures or be discontinued. Likewise, the DSMB could have halted the trial if there was compelling evidence for the treatment's effectiveness or if a reliable result was unlikely to be realized by the end of the trial.

What happened when a participant acquired HIV during the study?
CAPRISA 004 was conducted in settings where there is a high background HIV prevalence and many women are at high risk of infection. Potential study participants who volunteered to undergo HIV testing as part of the study screening process might have discovered that they were HIV positive. The CAPRISA 004 researchers provided all HIV test results with post-test counseling and these volunteers were referred to local CAPRISA-run or public AIDS treatment services. Such services included the PEPFAR-supported CAPRISA AIDS Treatment (CAT) Programme, as well as other local facilities that provide medical and psychosocial AIDS care and support. Study participants who acquired HIV were assured that they will receive antiretroviral drugs when they meet the South African criteria for treatment.

The wellbeing of the participants was our highest concern throughout the trial. CAPRISA 004 researchers did their best to reduce each participant's risk. The study provided condoms and frequent HIV prevention counseling to participants. Even so, some women became infected during their participation in the study.

Uninfected study participants who acquired HIV during the follow-up period of the study had a number of options available to them for care. They could choose to participate in one of the long-term CAPRISA acute infection cohort studies, which have excellent provisions for care, antiretroviral therapy, and support for those infected with HIV. Women who did not wish to continue in any of these studies after becoming infected were referred to their preferred AIDS care provider. This could include the CAT Programme, or government or non-governmental AIDS care services of their choice for ongoing clinical management and care.

If tenofovir gel does prove to be effective at preventing HIV infection in this trial, how will it be made available?
Depending on the results of CAPRISA 004, which is a test-of-concept trial, researchers may consider conducting a larger Phase III trial to obtain more conclusive data regarding tenofovir's potential effectiveness for preventing sexual transmission of HIV. If the CAPRISA 004 results indicate that tenofovir is safe and effective, and this is confirmed by another study, the CAPRISA 004 consortium of investigators will work with manufacturers and sponsors to gain regulatory approval of the product by relevant drug regulatory authorities, such as the South African Medicines Control Council. We will also work together with others to try to achieve affordable access in South Africa and resource-poor settings where the needs are greatest.

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CAPRISA is a multi-institutional AIDS research organization, undertaking globally relevant and locally responsive research that contributes to the understanding of HIV pathogenesis, prevention and epidemiology as well as the links between tuberculosis and AIDS care. CAPRISA is also a designated UNAIDS Collaborating Centre for HIV Prevention Research. CAPRISA, an affiliate of the University of KwaZulu-Natal, also provides training through research fellowships. CAPRISA comprises five research programs: HIV pathogenesis, HIV vaccines, HIV and TB treatment, microbicides, and prevention and epidemiology. More information about CAPRISA is available at www.caprisa.org.

CONRAD is dedicated to improving reproductive health, particularly in developing countries where the need is greatest, by supporting the development of better, safer, and more acceptable methods to prevent pregnancy and sexually transmitted infections (STIs), including HIV/AIDS. The program offers both financial support as well as technical assistance for the various stages of product development. Research is conducted at CONRAD's preclinical facility and Clinical Research Center at Eastern Virginia Medical School (EVMS) and in collaboration with investigators at universities, research institutions, and private companies worldwide. CONRAD provided the gel formulation of the microbicide in the CAPRISA 004 trial.

FHI is a public health and development organization working to improve the lives of the world's most vulnerable people. Our staff of 2,500 works in 55 countries, conducting research and implementing programs that advance public health and build local capacity to address development problems. Since 1971, FHI has been a global leader in family planning and reproductive health and, since 1986, in the worldwide response to HIV/AI*DS.* FHI was the primary recipient of USAID funds for the project and provided scientific and operational expertise to the South African scientists in the CAPRISA 004 trial. For more information, please contact: Beth Robinson, Deputy Director, Knowledge Management, FHI, PO Box 13950, Research Triangle Park, NC 27709 USA email: brobinson@fhi.org.