FACTS 001 Trial: Questions and Answers

1. What is the FACTS 001 Trial?

FACTS 001 was a double-blinded, randomized, placebo-controlled trial that tested whether tenofovir (TFV) 1% gel inserted vaginally before and after sex could prevent or reduce HIV and HSV (herpes) infections. The trial consisted of two groups: a treatment group and a control group. One group received gel with tenofovir, the "active" gel. The other group received gel without tenofovir – a "placebo" gel. Neither the investigators nor the participants knew which gel was received by each individual.

2. Why did researchers conduct the FACTS 001 trial of tenofovir gel for HIV prevention?

FACTS 001 was designed to replicate the CAPRISA 004 study on a larger scale. CAPRISA 004 had shown 39% protection by intent-to-treat analysis and 54% protection in women who adhered to the protocol. In both studies, women were asked to insert their assigned gel within 12 hours before sex and again up to 12 hours after sex, with no more than two gel doses in a 24-hour period.

3. Who conducted this trial?

The Follow-on African Consortium for Tenofovir Studies (FACTS) conducted the FACTS 001 trial, led by the Wits Reproductive Health and HIV Institute in Johannesburg and sponsored by CONRAD. The trial involved a consortium of 9 South African sites.

4. Who funded the trial?

The trial was funded by the South African Department of Science and Technology; the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through the United States Agency for International Development (USAID); the Bill & Melinda Gates Foundation; and the South African Department of Health, with support from Gilead Sciences.

5. When did the trial begin?

The FACTS 001 study began enrolling participants in October 2011.

6. When was the trial completed?

All participants in the trial had exited by September 2014 and a primary analysis of the results was completed by the end of 2014. Results of the trial will be presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, WA on February 24, 2015. However, further analysis is ongoing.

7. How many women were enrolled in the study?

A total of 2059 HIV-negative, sexually active women aged 18-30 were enrolled at nine sites in South Africa.

8. What was the incidence rate of HIV infections among participants?

The incidence rate of both groups, the placebo group and treatment group receiving the tenofovir gel, was 4%.

9. Did the FACTS 001 study confirm the results of CAPRISA 004 demonstrating efficacy among women who used the tenofovir gel consistently?

By intent-to-treat (ITT) analysis, a method of analysis where all study participants are analyzed together whether they adhered to the treatment or not, FACTS 001 did not confirm the results of CAPRISA 004. Out of the 2059 enrolled participants, a total of 123 HIV infections occurred with 61 in the tenofovir (TFV) group and 62 in the placebo group.

Tenofovir gel effectiveness was observed in a subgroup of women who appeared to use the product consistently (i.e. in greater than 72% of sex acts based on applicator return); however, these high adherers represented only 20% of participants. Within this group of high adherers, there were 8 infections in the placebo arm and 4 infections in the TFV arm, which would be consistent with an effect of tenovofir gel in reducing HIV acquisition but these numbers are too small to be statistically significant for the entire trial. It is also difficult to determine adherence in a study such as FACTS 001, because the gel is applied on-demand rather than on a daily basis. Therefore, adherence data is very difficult to confirm by objective means such as measuring drug levels in participants.

In a subgroup analysis consisting of 214 participants in the TFV-treated group, having high tenofovir drug levels in genital fluids was significantly associated with a 48% lower risk of HIV acquisition. However, it is important to note that there are caveats to such subgroup analyses that are conducted in the active arm of a randomized trial. In both the active and placebo arms of the trial, women who had high adherence as measured by returned applicators had lower rates of infection than women who had low adherence, which illustrates that even in the placebo arm, those women who were adherent may have had lower risk because they were in some other ways different than non-adherent women. Such differences may influence risk of HIV acquisition apart from tenofovir gel use, even after adjusting for known risk factors.

10. How do these results compare to the results of other microbicide trials?

These results are very similar to those of the VOICE study, which, in a similar population of women, demonstrated a modest non-significant effect of TFV gel in the ITT analysis, but found in secondary analysis that women who showed high adherence by objective markers, such as tenofovir in plasma, had

more than a 60% lower risk of HIV acquisition after adjusting for demographic variables and known risk factors.

11. Why is the FACTS 001 tenofovir gel study important?

The CAPRISA 004 trial was the first proof of concept that a microbicide gel could prevent HIV acquisition in women. It was critically important to attempt to confirm these results using the same "on-demand" pericoital dosing regimen, which was different than the daily dosing regimen used in VOICE. Since regulatory agencies like the Food and Drug Administration (FDA) require two trials for licensure, demonstrated efficacy in FACTS 001 along with the results of CAPRISA 004 could have led to licensure of the first microbicide product that women could use to protect themselves from HIV acquisition.

12. What do these results mean for women at high risk of HIV infection?

Young women, especially those who are poor, living with parents, and in unstable partnerships, have generally low adherence to prevention methods and remain at high risk for acquiring HIV. Therefore, USAID is committed to finding other ways to enable these women to protect themselves from HIV through other products currently in various stages of testing.

13. What was done to ensure the safety of study participants?

FACTS 001 was designed according to the most rigorous international ethical standards to protect the well-being of participants. FACTS 001 followed strict national and international procedures for monitoring and reporting in accordance with the United States Code of Federal Regulations (CFR) and the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (GCP) and South African GCP (SAGCP). The study was conducted in accordance with all local regulations, policies, and guidelines applicable to human subjects research in general, and the conduct of study procedures in particular. FACTS 001 was approved by the South African Medicines Control Council (MCC) and local ethics committees. An ongoing data and safety monitoring board (DSMB) reviewed the data regularly to ensure the safety of participants and to determine if the study should continue. ACRO, an independent monitor, visited the study sites regularly to make sure the study was being conducted ethically and to the highest standard.

14. What happened when a participant acquired HIV during the study?

FACTS 001 was conducted in settings where there is a high HIV prevalence in the community 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 FACTS 001 researchers provided post-test counseling for all women, and those volunteers with HIV-positive test results were referred to local treatment services.

The wellbeing of the participants was of the utmost concern throughout the trial. FACTS 001 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. Study participants who acquired HIV during the follow-up period of the study were given opportunities for provision of care, antiretroviral therapy, and support.

15. Are there other ongoing trials to test the efficacy of tenofovir gel?

There are currently no other randomized control trials with vaginal application of tenofovir gel, but other studies using tenofovir gel for HIV prevention are ongoing. CAPRISA 008, an open-label trial for women who participated in CAPRISA 004, continues but is not testing efficacy because all participants are receiving tenofovir gel. CAPRISA 008, nearing completion, was created to allow participants from CAPRISA 004 to continue using the tenofovir gel and to assess the implementation of tenofovir gel provision through family planning services in KwaZulu-Natal, South Africa. MTN 017, sponsored by the Microbicide Trials Network and funded by the US National Institute of Allergy and Infectious Diseases, is testing the safety of a reduced glycerin formulation of tenofovir gel, which is applied rectally in men who have sex with men and transgender women in Peru, South Africa, Thailand, and the United States, including Puerto Rico. Other smaller studies using tenofovir gel are also ongoing or have just been completed.

16. What's next?

Without tenofovir gel, women still lack a safe, user-friendly option to protect themselves from HIV transmission. To fulfill changing needs and lifestyles, USAID will continue to support development of newer dosage forms and delivery systems that are less user-dependent, especially focusing on increasing acceptability and adherence. Delivery systems such as vaginal rings and long-acting topical and systemic dosage forms of anti-retroviral-based prevention tools may prove to be more suitable for women whose circumstances do not favor daily or pericoital dosing regimens. One such example is the dapivirine vaginal ring. USAID, along with the Bill & Melinda Gates Foundation and several European donors, is currently supporting the Ring Study of the International Partnership for Microbicides (IPM), a clinical trial of a monthly dapivirine vaginal ring aimed at licensure in partnership with other studies, such as the NIH-funded ASPIRE trial of the dapivirine ring.

17. How can adherence be improved?

User-centered research into barriers and motivators of product use needs to be incorporated into every stage of HIV product development. It is also important to find products with easier adherence, such as long-lasting topical treatments, the dapivirine vaginal ring, and other products currently in various stages of development.

If you would like to learn more, visit the FACTS website at http://www.facts-consortium.co.za.