June 2011 Update

Background

FEM-PrEP is a Phase III, randomized, placebo-controlled clinical trial designed to assess the safety and effectiveness of a daily oral dose of Truvada for HIV prevention among women. Truvada combines two antiretroviral drugs—tenofovir disoproxil fumarate (TDF, 300 mg) and emtricitabine (FTC, 200 mg)—into a single pill. Truvada has been proven safe and effective as a treatment by preventing HIV from reproducing itself in individuals who are already infected with the virus. The purpose of the FEM-PrEP trial is to test whether Truvada could also be used safely and effectively to *prevent* HIV infection—an approach known as pre-exposure prophylaxis (PrEP).

Following a scheduled interim review of the FEM-PrEP study data in April 2011, the Independent Data Monitoring Committee (IDMC) advised that the FEM-PrEP study will be highly unlikely to demonstrate Truvada's effectiveness in preventing HIV infection in the study population, even if it continued to its originally planned conclusion. FHI subsequently concurred and decided to initiate an orderly closure of the study over the subsequent few months.

The key preliminary findings from data available on February 18, 2011 were:

- The approximate rate of new HIV infections among trial participants was 5 percent per year. A total of 56 new HIV infections had occurred. An equal number of infections occurred in participants assigned to Truvada and those assigned to a placebo pill.
- Observed pregnancy rates among study participants randomly assigned to the Truvada arm were higher than among the women randomly assigned to the placebo arm. This is unexpected and inconsistent with known drug interactions involving tenofovir and contraceptive hormones and with known metabolic effects of emtricitabine.
- The use of Truvada was associated with some known side effects, none of which were considered as serious.

Additional information about the trial design and the preliminary findings are available on FHI's website (http://www.fhi.org/en/Research/Projects/FEM-PrEP.htm).

Possible Explanations for Preliminary Findings

Possible explanations for the preliminary HIV infection outcome of the trial include low adherence to the study pill, study pill sharing between the participants in the Truvada and placebo groups, chance, biological reasons, or a combination of these factors. Possible biological explanations may include insufficient penetration of tenofovir and/or emtricitabine in the female genital tract to provide protection against HIV, interaction of contraceptive hormones with Truvada or other reasons not yet identified.

The possible explanations for the pregnancy outcome include chance, previously unknown interactions between tenofovir and/or emtricitabine and contraceptive hormones, and differential adherence to oral contraceptives between women in the Truvada and placebo groups.

Samples Available for Analysis and Testing to be Performed

The FEM-PrEP study collected and stored biologic samples from study participants, including plasma, serum, upper layer packed cells, and cervico-vaginal fluid (at the Pretoria site only, after the study closure announcement). Analysis of these samples may help explain the preliminary findings. Laboratory testing will be done in accordance with the study protocol, which includes confirmation of all HIV infections, antiretroviral resistance testing of HIV strains from seroconverters and tenofovir and emtricitabine drug level determinations. In addition, contraceptive hormone level testing will be done on selected samples to explore further the preliminary finding of a higher pregnancy rate in the Truvada arm as compared with the placebo arm.

FEM-PrEP Final Analysis and Timeline

The follow-up of participants who were HIV negative is expected to be completed by the end of August 2011. Ongoing data cleaning will be completed by the end of October 2011. Confirmation of all HIV infections, resistance testing and tenofovir and emtricitabine drug level testing will be conducted during August–December 2011, contingent upon receipt of regulatory approvals in each country for export of necessary specimens. The primary statistical analysis will be conducted in November 2011. Publication of the main findings, along with dissemination of the results to site communities, is expected between late 2011 and early 2012. Secondary analyses and associated paper writing will occur in late 2011 and 2012.

Follow-up of participants who seroconverted during the trial will be completed in August 2012, per protocol.

How can I learn more about the FEM-PrEP clinical trial?

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