



FEM-PrEP

Trial Update

Pre-Exposure Prophylaxis for HIV

What is the FEM-PrEP Clinical Trial?

The FEM-PrEP (pre-exposure prophylaxis) clinical trial—led by Family Health International (FHI)—is designed to test the safety and effectiveness of a daily oral dose of a pill called Truvada for HIV prevention.

Truvada combines two antiretroviral drugs—emtricitabine and tenofovir disoproxil fumarate—into a single pill that is taken once a day. Truvada prevents HIV from reproducing itself inside the cells of people already infected with the virus, and it has been proven safe and effective as a *treatment* for HIV-positive people. But it is not known whether Truvada could also help to *prevent* an infection in an HIV-negative person who is exposed to the virus. Another key objective of the trial is to determine whether Truvada is safely tolerated by HIV-negative women.

Nearly 3,900 HIV-negative women (between the ages of 18 and 35)—who have a higher risk of becoming infected with the virus—will be enrolled in the clinical trial. The trial will take place at six different sites in four countries: Bondo (Kenya), Arusha (Tanzania), Blantyre (Malawi), Lilongwe (Malawi), Cape Town (South Africa), and Pretoria (South Africa). Other pre-exposure prophylaxis trials are also being conducted in Asia, South America, the United States, and other parts of Africa.

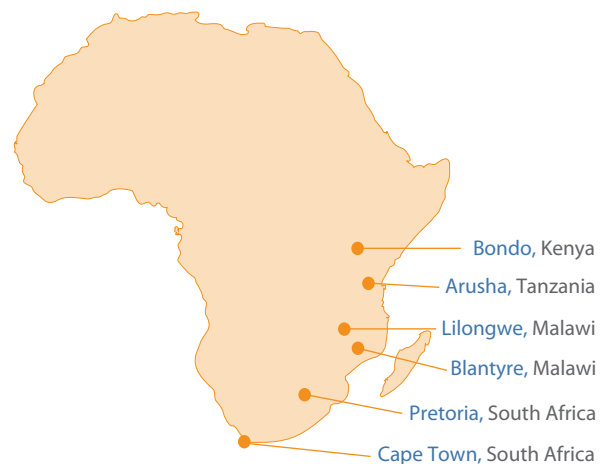
The protocol for the clinical trial has been submitted for approval to the local ethical committees in all countries, and to the regulatory authorities in South Africa and Kenya. Sites and enrollment figures may change as the study progresses, depending on recruitment, retention, and estimated HIV incidence. The local situation may also have an impact on study implementation in any particular site.

The FEM-PrEP clinical trial provides *all* participants with standard HIV-prevention services: free condoms, individual risk-reduction counseling, and screening and treatment for curable sexually transmitted infections. Therefore, this trial will compare the test product plus standard prevention services to a placebo plus standard prevention services. So, all groups will receive standard prevention services.

Participants who become HIV positive during the trial will receive counseling and referrals to medical and social services. If they are willing, the HIV-positive women will be monitored for disease progression and resistance to Truvada for at least 12 more months. These participants will be counseled to use all precautions to limit the transmission of the virus to others.

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Truvada Study Sites



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The health and safety of the participants is the foremost priority of the scientists who are conducting the FEM-PrEP trial. The trial will be reviewed and approved by ethics committees in each country and in the United States. The trial will also follow universally accepted international ethical guidelines and Good Clinical Practice Guidelines, which include international standards on the roles and responsibilities of sponsors, research investigators, and monitors.

If Truvada is proven safe and effective for HIV prevention, public and private funding sources—such as the World Health Organization, the Joint United Nations Programme on HIV/AIDS, the Global Fund, and national ministries of health—will determine how to make the drug available in the regions of the world where it is needed most. Advocates and policy-makers are now working with scientists to address issues of access and affordability.



Lut Van Damme/FHI

Lut Van Damme, clinical principal investigator of FEM-PrEP.



Michael Szpir/FHI

Amy Corneli, behavioral investigator of FEM-PrEP and principal investigator of the SBC preparedness protocol.

FEM-PrEP Trial Highlights

Clinical Trial

The clinical team—consisting of physicians, scientists, and other research staff—conducts the clinical trial and ensures the safety of the participants and the validity of the clinical results.

- In October 2007, the main investigators met in Nairobi, Kenya, to discuss the clinical protocol.
- The first meeting of the independent data monitoring committee took place in January 2008.
- FHI's institutional review board approved the clinical protocol in March 2008.
- The protocol has been submitted for approval to the local ethical committees in all countries, and to the regulatory authorities in South Africa and Kenya. We have obtained local ethical approval in South Africa and Kenya.
- In July 2008, the first training for the clinical trial took place in Bondo, Kenya.
- The South African sites will probably be trained in the second quarter of 2009.
- The first participant will probably be enrolled at the Bondo site in the first quarter of 2009.

Socio-Behavioral and Community (SBC) Activities

The SBC research team works closely with members of the community at each site of the clinical trial. Team members prepare for the clinical trial by talking to community members about the trial, and they collect socio-behavioral data to facilitate the success of the trial.

- In June 2007, a new community advisory board (CAB) in Bondo, Kenya, was trained on research ethics, the basics of clinical trials, and an overview and discussion of the FEM-PrEP clinical trial. Ten more CAB members were trained in Bondo in May 2008.
- In September 2007, SBC team members visited prospective CABs in the Cape Town and Pretoria sites in South Africa.
- The Pretoria site established a new CAB and participated in a three-day training in March 2008.
- The Cape Town site conducted a three-day training for community stakeholders in March 2008.
- In October 2007, the CAB members in Lilongwe and Blantyre, Malawi, participated in a training session on research ethics.
- Arusha established a new CAB, and its members participated in a three-day training in June 2008.
- The SBC preparedness research training was conducted with Bondo in August 2007, with Lilongwe and Blantyre in October 2007, with Pretoria and Cape Town in January 2008, and with Arusha in April 2008.
- The main components of the SBC preparedness research have been completed in Bondo, Pretoria, Cape Town, Lilongwe, and Blantyre.
- Activities are currently under way to integrate SBC data into clinical trial procedures on recruitment, retention, adherence, informed consent, risk-reduction counseling, community engagement, and counseling on contraceptives.

Prepping for PrEP in Bondo

The HIV epidemic is wreaking havoc on the district of Bondo in southwestern Kenya. By some estimates, nearly one-fifth of the adults are infected with the virus. Already burdened with poverty and hunger, many people have a poor understanding of HIV and follow traditional practices that help to transmit the virus. The tragic scale of the epidemic in Bondo is one of the reasons the site was chosen for the FEM-PrEP HIV-prevention trial.

For the past 18 months, FEM-PrEP's socio-behavioral and community (SBC) team has been diligently laying the groundwork for the proposed clinical trial at the Bondo site. The demands of the task require a diverse group of about 20 people—local social scientists, community educators, community mobilizers, and other professionals who are trained in various aspects of qualitative research, clinical trials, ethics, and community education.

The SBC team has been talking to Bondo's residents, such as community stakeholders and potential trial participants, to determine whether the proposed research protocol meets the needs of the community and whether it is culturally appropriate.

"Through our formative research and community program activities, we aim to meaningfully involve the community through a variety of methods. These range from fostering partnerships with civil society and community stakeholders to collecting data to inform site-specific study procedures, such as recruitment and counseling strategies," says Amy Corneli, the principal investigator on the SBC team.



Stella Kirkendall/FHI

Paul Omullo, community liaison officer, and Kawango Agot, principal investigator of the FEM-PrEP study in Bondo.

The team has also been holding educational sessions with members of the community to help them understand basic research methods and research ethics. These meetings offer a valuable forum for community members to ask questions about the FEM-PrEP clinical trial.

"We meet with people in barazas [community forums], churches, and social groups to ensure that the community has the proper information about the clinical trial," says Paul Omullo, the community liaison officer.

The team also encourages citizens to voice their concerns about the study through their community advisory board (CAB). Bondo's CAB consists of 18 volunteers from the

Luanda K'otieno, a beach community in the Bondo district.



Christina Misa Wong/FHI

Prepping for Success

What will happen if a daily oral dose of Truvada is shown to be safe and effective? That is the subject of a parallel “rollout” study on the best way to introduce a successful PrEP drug to the communities hosting the FEM-PrEP clinical trial.

“This research is answering a call to be prepared to translate research results into national policy as soon as we find a new method to prevent HIV infection,” says Natasha Mack, principal investigator of the PrEP rollout study.

Mack’s socio-behavioral investigations are based on the idea that the strategies for providing a PrEP drug should be supported by research in local communities. If Truvada works, Mack’s results will help to inform pilot interventions at each FEM-PrEP site.

“Some people might say that we are taking a leap of faith by doing this study before we have efficacy results,” says Mack. “But how much will be lost in lives and expenditures if there is a lag time of several years between the discovery of a new HIV-prevention method and its provision after the trial?”

community—including government officials, community leaders, health care professionals, religious leaders, teachers, widows, young people, and potential participants.

“We hope to establish and maintain genuine collaborations between the researchers and the community,” says Stella Kirkendale, the community program manager for the FEM-PrEP trial. “This goes beyond mere ‘participation’ or ‘consultation’ to strengthening the role and capacity of community stakeholders and integrating their contributions into the research process.”

Over the many months of their preparatory work, the team has encountered and overcome some daunting challenges, including the weeks of violence and pandemonium that followed Kenya’s divisive presidential election in December 2007. “We were holed up in our houses, occasionally venturing out to look for milk for our children, and feeling blessed to get a packet [of food] here or there, and then getting back to our homes in one piece,” says Kawango Agot, the principal investigator of the FEM-PrEP study in Bondo.

The Bondo team survived the riots but has since encountered other obstacles. For one thing, they have been sidetracked by delays in the renovation of the research clinic. It was supposed to be completed by December 1, 2007, but a year later, it is still not ready, says Kawango. “We had to ferry staff from Bondo to Kisumu and back

everyday, and a number of staff ended up paying rent for houses in both towns for months because we did not have the funds or the means to transport everyone. It’s been a major expense and inconvenience,” she says. Fortunately, everything should be in place soon.

Perhaps the most insidious challenge the Bondo team must conquer is the prejudice and social stigma that surround HIV. “Many think HIV/AIDS is linked to promiscuity, so participants may be seen to be promiscuous women,” says Omullo. He worries that potential participants may shy away from the study for fear of public disapproval.

To make matters worse, some people may intentionally spread misinformation. “People who are not in the study, and those who are excluded (for whatever reason), start rumors saying that the study is recruiting only HIV-positive women,” says Kawango. (Of course, HIV-positive women are specifically excluded from participating in an HIV-prevention trial. In fact, all participants must meet a long list of medical, behavioral, and age-related eligibility criteria.)

The difficulty of recruiting and retaining the trial participants will also be aggravated by the local economy, according to Jacob Odhiambo, the SBC coordinator in Bondo. “Some of the women we wish to enroll are on the move, looking for work,” he says. “It may become difficult to reach them as they move from one area to another.”

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Stella Kirkendale/FHI

Jacob Odhiambo, SBC coordinator in Bondo.

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Despite the challenges, Odhiambo believes that the SBC team will develop a workable strategy to recruit and retain the participants over the 56 weeks of the clinical trial. “We have the goodwill of the community, and they have been very receptive to us,” he says.

People at the community forums even seem eager to enroll. “We have had some women come to the trial site to inquire if we have started recruiting participants,” says Odhiambo.

The Bondo team has now completed much of their preparatory work and will take part in site-initiation training—a refresher course on Good Clinical Practice, Good Laboratory Practice, study procedures, and research ethics—early this year. If all goes as planned, the SBC team and the clinical team will begin recruiting the first participants before the end of February.



Stella Kirkendole/FHI

The community advisory board in Bondo.

HIV-Prevention News

Of “Humanized” Mice and PrEP

Daily therapy with antiretroviral drugs (ARVs) can prevent HIV transmission through vaginal tissue in “humanized” mice, according to a report in the January 2008 issue of *PLoS Medicine*. The test mice—created in 2006 by scientists at the University of Texas Southwestern Medical Center and the University of Minnesota—are immune-deficient animals that are systematically repopulated with human immune cells.

The humanized mice were injected with two ARVs—emtricitabine and tenofovir disoproxil fumarate—the primary components of Truvada. The study also demonstrates that humanized mice are susceptible to HIV infection through vaginal exposure and that many aspects of HIV infection in these mice closely mimic the infection in humans. Before the creation of these mice, most laboratory animals could not be studied in HIV drug trials because they were not vulnerable to the human virus.

PrEP in a Simian Model

A combination of two antiretroviral drugs—emtricitabine and high-dose tenofovir—can prevent rectal transmission of simian HIV (SHIV) in rhesus macaques, according to a

study by Walid Heneine, of the U. S. Centers for Disease Control and Prevention, and his colleagues. Their results appeared in the February 2008 issue of *PLoS Medicine*.

The macaques were exposed to repeated low doses of SHIV—given rectally once a week to simulate a common route of HIV transmission in humans. None of the macaques that received a combination of emtricitabine and high-dose tenofovir became infected with the virus. This was true whether the animals were given the high-dose combination daily or intermittently (only before and after the weekly viral exposure).

Some macaques in two other test groups—which were given a low-dose combination or emtricitabine alone—did become infected with SHIV. But these animals had lower levels of the virus in their blood compared to a control group of SHIV-infected macaques that was not given any pre-exposure prophylaxis drugs.

The authors of the study note that the high-dose combination, which provided maximum protection for the macaques, may not be safe in humans. They suggest that further studies are needed to evaluate different drug combinations, dose requirements, and dose timing relative to viral exposure.



Paul Denton/UT Southwestern Medical Center

Humanized mouse.

Current HIV PrEP Trials

STUDY/FUNDER	LOCATION	STRATEGY	POPULATION	STATUS	COMPLETION
CDC	United States	Oral tenofovir	400 men who have sex with men	Fully enrolled	2009
CDC	Thailand	Oral tenofovir	2,400 injectable-drug users	Enrolling participants	2009
CDC	Botswana (2 sites)	Oral Truvada	1,200 heterosexual men and women	Enrolling participants	2010
iPrEX Study/ NIH, BMGF	Peru, Ecuador, United States, other sites TBD	Oral Truvada	3,000 men who have sex with men	Enrolling participants	2010
Partners PrEP Study/BMGF	Kenya, Uganda	Oral tenofovir, oral Truvada	3,900 serodiscordant heterosexual couples	Enrolling participants	2012
FHI FEM-PrEP Study/USAID, BMGF	Kenya, Malawi, South Africa, Tanzania (6 sites)	Oral Truvada	3,900 higher-risk women	Planning/ expected start Q1, 2009	2012
MTN VOICE Study/NIH	Southern Africa (sites to be determined)	Oral tenofovir, oral Truvada, vaginal tenofovir gel	4,200 sexually active women	Planning/ expected start Q1, 2009	2012

Abbreviations: BMGF—Bill & Melinda Gates Foundation; CDC—U. S. Centers for Disease Control and Prevention; FHI—Family Health International; iPrEX—Iniciativa Profilaxis Pre-Exposición; MTN—Microbicide Trials Network; NIH—U. S. National Institutes of Health; USAID—U. S. Agency for International Development.

Note: This table does not include vaccine trials.



FEM-PrEP

Family Health International (FHI), a nonprofit public health organization, leads the FEM-PrEP trial in collaboration with local scientists at each site. FHI provides scientific oversight, supports the trial's management, monitors the clinical trial activities and the socio-behavioral and community research, and assists with community activities. FHI works closely with the study sites in the day-to-day conduct of the clinical trial.

Gilead Sciences, which makes Truvada, is providing the drug free for this clinical trial. If Truvada is found to be safe and effective for HIV prevention, Gilead Sciences will make a good-faith effort to provide Truvada for this use. The company has also provided technology transfer of Truvada to companies that produce generic drugs.

The U. S. Agency for International Development and the Bill & Melinda Gates Foundation are funding the FEM-PrEP trial.

To learn more about HIV-prevention research

Prepwatch: www.prepwatch.org/trials.htm

Global Campaign for Microbicides:

www.global-campaign.org/download.htm

AIDS Vaccine Advocacy Coalition (AVAC): www.avac.org

HIV Prevention Trials Network (HPTN): www.hptn.org

Microbicide Trials Network (MTN):

www.mtnstopshiv.org/node/studies

For more information about the FEM-PrEP trial

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