



CONTACT: Lisa Rossi
PHONE: +1-412-641-8940
+1-412- 916-3315 (mobile)
E-MAIL: rossil@upmc.edu

EMBARGOED FOR MONDAY, FEB. 9 AT 8:30 AM EASTERN/ 3:30 PM AFRICA
BACKGROUNDER

HPTN 035:
A MULTI-CENTER CLINICAL TRIAL EVALUATING THE CANDIDATE MICROBICIDES
BUFFERGEL AND PRO 2000 FOR PREVENTION OF HIV

Study Overview

HPTN 035 was a multi-center clinical trial that evaluated the safety and effectiveness of two candidate microbicides, BufferGel[®] and PRO 2000 (0.5 percent dose) for preventing HIV infection in women. Microbicides are substances intended to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside of the vagina or rectum. The study was conducted between February 2005 and September 2008 among 3,099 HIV-negative women at seven clinical research sites in Malawi, South Africa, Zambia, Zimbabwe and the United States.

HPTN 035 was conducted by a team of leading African and U.S. researchers associated with the Microbicide Trials Network (MTN), an HIV/AIDS clinical trials network established and funded in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID), with co-funding by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the U.S. National Institutes of Health (NIH). Prior to 2006, the study was conducted by the NIAID-funded HIV Prevention Trials Network (HPTN), from which the study gets its name. Salim S. Abdool Karim, MBChB, Ph.D., from the University of KwaZulu-Natal in Durban, South Africa, led the study as protocol chair.

What the Study Found

HPTN 035 demonstrated for the first time the promise of a vaginal microbicide gel for preventing HIV infection in women. In the final analysis, 194 women in the study became infected with HIV. Of these infections, 36 occurred in the PRO 2000 group, 54 in the BufferGel group, 51 in the placebo gel group, and 53 among those who did not use gel. Based on these data, PRO 2000 was 30 percent effective compared with no gel. It was particularly effective among the volunteers who reported low condom use and high gel adherence. BufferGel had no detectable effect on preventing HIV infection. Both microbicides were found to be well-tolerated and did not result in any significant adverse events.

Although the volunteers in the PRO 2000 study arm had a 30 percent lower rate of HIV infection compared with the other three study groups, this finding was not statistically significant. Approximately 33 percent effectiveness would have been considered statistically significant. Therefore, additional clinical evidence is needed to more conclusively determine whether PRO 2000 prevents HIV infection in women.

HPTN 035 successfully retained a majority of its enrollees, with 94 percent completing their participation. Throughout the study, participants reported regular use of the investigational gels (81 percent of sex acts), and nearly all (99 percent) said they would use the products if approved for HIV prevention. Condom usage also was high throughout the course of the trial (74percent).

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Why this Study Was Important

According to current statistics from UNAIDS, women account for half of the 33 million people living with HIV/AIDS worldwide. In sub-Saharan Africa, women account for 60 percent of all infected adults. Young women are especially vulnerable; in several southern African countries, young women aged 15 to 24 are at least three times more likely than their male peers to be infected with HIV.

Among women, heterosexual intercourse remains the primary risk factor for HIV infection and in many parts of the world, heterosexual intercourse is the driving force of the epidemic. 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. Although correct and consistent use of male condoms has been shown to prevent HIV infection, women often cannot negotiate condom use with their male partners. If proven safe and effective, microbicides could be an alternative prevention option for women who cannot rely on condoms or abstinence as methods for protecting themselves from HIV.

How the Study Was Conducted

HPTN 035 was as a combination Phase II/Phase IIb trial designed to determine whether either candidate microbicide had sufficient promise to be considered for testing in a larger Phase III trial. HPTN 035 was not designed to compare the two gels, but rather to compare each against a placebo gel with no active ingredient, and with no gel at all. The Phase II portion of the study involved intensive safety evaluations among the first 799 women enrolled. The Phase IIb portion involved the first 799 women and an additional 2,300 women. Women took part in the study for 12 to 30 months (20 months on average) and completed monthly clinic visits throughout their participation.

Participants were randomly assigned in approximate equal number to one of four study groups: BufferGel, PRO 2000 gel, placebo gel, and no gel. Women assigned to the three gel groups were instructed to apply gel up to one hour before sexual intercourse using pre-filled applicators. The three gels were similar in appearance and packaged in identical applicators so that neither researchers nor participants would know which women were using which gel during the study. Participants in all four groups received free condoms, HIV risk reduction counseling, and routine testing and treatment for sexually transmitted infections (STIs) throughout the study.

The Candidate Microbicides Studied

HPTN 035 tested two microbicide candidates with different mechanisms of action. BufferGel, developed by ReProtect, Inc., of Baltimore, Maryland, U.S.A., was developed as a vaginal defense enhancer designed to boost the natural acidity of the vagina in the presence of seminal fluid. Semen reduces the acidity of the vagina making it more receptive for pathogens that cause sexually transmitted infections, such as HIV. PRO 2000, developed by Indevus Pharmaceuticals, Inc, in Lexington, Massachusetts, U.S.A., is an entry/fusion inhibitor designed to hamper HIV's ability to attach to and infect healthy cells. In HPTN 035, researchers tested the low dose 0.5 percent concentration of PRO 2000.

Both candidate microbicides underwent extensive laboratory study and, before HPTN 035, were tested in other early-phase human safety clinical studies involving women in both developed and developing countries. The pre-clinical laboratory research suggested that the gels may reduce the sexual transmission of HIV, while the early-phase clinical studies indicated the gels were well-tolerated and safe and could be considered for further testing in larger trials.

Participant Safety and HIV Monitoring

HPTN 035 was designed according to the most rigorous international scientific and ethical standards and with utmost concern for participant safety and well-being. A detailed informed consent process ensured that participants understood the procedures, risks and benefits of the study, and that they were not obliged to participate and could leave the study, without consequence, at any time.

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The study incorporated a multi-tiered safety review process that followed strict U.S. and international requirements for monitoring and reporting. Participant safety was monitored by the researchers and clinical staff at each site; by designated researchers and staff that comprised the study's Protocol Safety Review Team; and by an independent Data and Safety Monitoring Board (DSMB) that oversees clinical trials funded by NIAID's Division of AIDS. If the DSMB had identified any safety concerns at any time, it could have recommended that the study modify its procedures or be discontinued. During the course of HPTN 035, six DSMB reviews took place and at each review the DSMB recommended continuation of the study.

HPTN 035 was conducted in the United States and in parts of Africa where women are at high risk for HIV. HPTN 035 researchers did their best to reduce participants' risk, by providing free condoms, risk reduction counseling, and testing and treatment for STIs. Still, some women became infected with HIV while participating in the study, and these women were given the option to remain in the study if they wished. Women who acquired HIV during the study were counseled and referred by study staff to local medical care and support programs offering psychosocial services and HIV care, including antiretroviral therapy. Some MTN research sites are part of health care institutions where HIV care and support is provided, while other sites have established referral agreements with programs such as those funded by the U.S. President's Emergency Plan for AIDS Relief.

Funding

HPTN 035 was funded by NIAID. Indevus Pharmaceuticals, Inc., provided PRO 2000 and ReProtect, Inc., provided BufferGel. The U.S. Agency for International Development (USAID) provided funding to manufacture BufferGel for the study.

About the Microbicide Trials Network

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH). The MTN brings together international investigators and community and industry partners who are devoted to reducing the sexual transmission of HIV through the development and evaluation of products applied topically or administered orally, working within a unique infrastructure specifically designed to facilitate research required to support licensure of these products for widespread use. To face the global urgency of the HIV/AIDS epidemic head-on, the MTN will implement a broad portfolio of clinical trials in Africa, India and the United States between 2006 and 2013. Many of these trials are focused on assessing antiretroviral-based strategies and include studies designed to evaluate microbicides along with other promising HIV prevention approaches, such as oral pre-exposure prophylaxis.

Based at the University of Pittsburgh and Magee-Womens Research Institute in Pittsburgh, Pennsylvania, U.S.A., the MTN is directed by Sharon Hillier, Ph.D., principal investigator. MTN's core operations are supported by a network laboratory at the University of Pittsburgh, a statistical and data management center housed within the Statistical Center for HIV/AIDS Research & Prevention at the Fred Hutchinson Cancer Research Center, and Family Health International, a global organization with expertise conducting clinical protocols. The MTN receives its funding from three NIH institutes: NIAID, the National Institute of Mental Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Among the principals developing and evaluating microbicides for HIV prevention globally, the MTN is the only one funded by NIH. More information about the MTN and HPTN 035 is available at www.mtnstopshiv.org.

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For more information about the HPTN 035 clinical study, see <http://www3.niaid.nih.gov/> or <http://www.mtnstopshiv.org/news/studies/17> .