National Institute of Allergy and Infectious Diseases
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QUESTIONS AND ANSWERS

The HPTN 035 Study of Two Candidate Microbicides, BufferGel and PRO 2000 (0.5% dose)

1. What was the purpose of the HPTN 035 study?

HPTN 035, which began in February 2005 and concluded in September 2008, was a multicenter clinical trial evaluating the safety and effectiveness of two investigational microbicide gels, BufferGel and PRO 2000 (0.5% dose), for preventing male-to-female sexual transmission of HIV.

2. What is a microbicide?

Microbicides are gels, foams, creams intended to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside the vagina or rectum. Currently, there are no approved microbicides to prevent HIV infection.

3. Why was this study important?

A microbicide that effectively prevents male-to-female HIV transmission would provide women with an important HIV prevention method they initiate. Currently, women make up half of all people worldwide living with HIV. In most cases, women become infected with HIV through sexual intercourse with an infected male partner. An effective microbicide would provide women with an HIV prevention method they initiate. This would be particularly helpful in situations where it is difficult or impossible for women to refuse sex or negotiate condom use with their male partners.

HPTN 035 was the National Institute of Allergy and Infectious Diseases' (NIAID's) first large study to evaluate the effectiveness of a candidate microbicide in humans.

4. How many participants were involved in the study?

HPTN 035 enrolled 3,099 women ages 18 to 56.

5. Where was HPTN 035 conducted?

The study was conducted at seven sites in five countries. Specifically, the clinical trial was conducted at the following locations:

- Blantyre, Malawi
- Lilongwe Malawi
- Durban, South Africa
- Hlabisa, South Africa
- Philadelphia, Pa., USA
- Lusaka, Zambia
- Harare, Zimbabwe

6. Who conducted and sponsored this trial?

HPTN 035 study was conducted by the Microbicide Trials Network (MTN), an HIV/AIDS clinical trials network established and funded in 2006 by NIAID with co-funding by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the National Institutes of Health (NIH). Prior to the establishment of the MTN, the study was led 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 Center for the AIDS Program of Research in South Africa, led the study as protocol chair.

NIAID sponsored the study. Indevus Pharmaceuticals, Inc., based in Lexington, Mass., provided PRO 2000 (0.5% dose), and ReProtect Inc., based in Baltimore, supplied BufferGel with manufacturing funding support from the U.S. Agency for International Development.

7. What was the study's design?

HPTN 035 was a combination Phase II/IIb clinical trial designed to determine whether BufferGel or PRO 2000 demonstrated sufficient promise to be considered for testing in a larger Phase III clinical trial. Importantly, the study was not designed to compare the two microbicides to each other, but rather to compare each against a placebo gel that contained no active ingredient and no gel at all. The Phase II portion of the study, which enrolled 799 women, involved intensive safety evaluations of the two investigational gels. The Phase IIb portion of the study, which further examined safety as well as the effectiveness of the two gels, involved the initial 799 participants as well as an additional 2,300 participants.

Participants were randomly assigned to one of four equal-sized treatment groups: those who used BufferGel prior to engaging in sexual intercourse; those who used PRO 2000 gel prior to engaging in sexual intercourse; those who used placebo gel prior to engaging in sexual intercourse; and those who used no gel before engaging in sexual intercourse. The participants who were assigned to the three gel groups were instructed to apply the gels up to one hour before sexual intercourse using pre-filled applicators. The three gels were similar in appearance and were packaged in identical applicators, so that neither researchers nor participants would know which participants were using which gel during the study. Women participated in the study for an average of 20 months and were seen monthly to ensure that they had not become pregnant (an excluding factor for the study) and were not experiencing any safety issues and, for those in the gel study groups, to ensure they had sufficient product. Participants were assessed on a quarterly basis for gel and condom use and HIV infection.

All participants received detailed information about the possible risks and benefits of trial participation before enrollment and were monitored closely throughout the study. In addition, all participants were counseled on safe sex practices, given condoms, and tested and treated for sexually transmitted infections throughout the study.

8. What are the two candidate microbicides studied in the trial?

HPTN 035 tested two candidate microbicides with different mechanisms of action: BufferGel and PRO 2000 (0.5% dose). BufferGel is 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 is an entry/fusion inhibitor that is designed to hamper HIV's ability to attach to and infect healthy cells.

9. Why were those two candidate gels selected?

Prior to the initiation of HPTN 035, both investigational gels had undergone extensive laboratory analysis, which suggested that each could potentially reduce sexual transmission of HIV. Both gels also underwent early-phase human safety clinical trials involving women from developed as well as developing countries. These trials found both gels to be well-tolerated and safe and, therefore, suitable for further testing in larger human studies. Additionally, data on the two gels underwent multiple safety and efficacy reviews by HPTN researchers and an external review committee to determine whether the study products were appropriate for advanced clinical studies.

10. Why was a "no gel" study group included in HPTN 035?

Although microbicide studies routinely include a placebo gel for comparison purposes, researchers have not been able to rule out the possibility that a placebo gel may have some effect of its own. For example, if the use of a placebo gel demonstrated a small measure of protection against HIV, the effectiveness of the investigational gel being tested would be underestimated. Similarly, if a placebo gel affected the normal physiology of the vagina in any way, the meaning of the results could also confounded.

The HPTN 035 researchers believed including a no-gel study group and comparing HIV infection rates and other safety and effectiveness parameters between women using placebo gel and those using no gel would provide important insight as to whether there are placebo gel-associated effects and, in turn, provide a clearer interpretation of the study's results.

The no-gel study group also allowed for a more real-world evaluation of a product's effectiveness than is possible in a study that only compares an investigational gel to a placebo gel. This is because researchers have long assumed that the use of a microbicide may influence other behaviors that could impact the risk of acquiring HIV, such as frequency of sexual activity and condom use. In HPTN 035, each of the two candidate microbicides was compared with the placebo gel and with no gel to determine its effectiveness at preventing HIV infection. A comparison of each of the candidate gels to placebo and no gel helps to provide a more accurate assessment of the product's effects.

11. What are the results of the HPTN 035 study?

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. 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 participants 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 (72 percent).

12. What happened to those women who acquired HIV infection during the study?

Participants who became infected with HIV during the study were counseled and referred for access to medical care, support services and treatment, including antiretroviral therapy, through local providers. These same women were also given the opportunity to participate in MTN 015, a clinical study examining the nature of HIV progression and treatment response in HIV-infected women who were using topical microbicides or oral antiretrovirals as an HIV preventive measure when they acquired HIV infection.

13. If the study results were not statistically significant in demonstrating PRO 2000's effectiveness, why study this microbicide further?

Previous analyses of PRO 2000, including laboratory tests and animal studies, suggested that PRO 2000 has a protective effect against HIV. The HPTN 035 results, while not conclusive, provide further data to support these findings. The totality of the pre-clinical and clinical evidence provide a strong case for additional studies to establish definitively whether PRO 2000 effectively prevents male-to-female HIV transmission.

14. What is the next step in determining if PRO 2000 effectively prevents HIV infection in women?

A separate clinical study sponsored by the Medical Research Council (MRC) and the Department for International Development of the United Kingdom that is currently testing PRO 2000 (0.5% dose) in preventing HIV infection among women in Africa is expected to provide additional useful information about the microbicide's effectiveness. That Phase III clinical study involving nearly 9,400 women is set to conclude in August 2009.

15. Is NIAID planning to conduct a phase III trial of PRO 2000?

At this time, NIAID is not planning to test PRO 2000 in a Phase III clinical study. NIAID is entering into discussions with Indevus Pharmaceuticals, the makers of PRO 2000, to discuss the way forward. Any decision to proceed or not to proceed with a NIAID-sponsored Phase III trial will occur after data from the MRC-sponsored study is available.

16. Is NIAID researching other types of microbicides?

Yes, NIAID is exploring other microbicide candidates because different microbicides work in different ways, and it is not yet known which products will work best. Additionally, some microbicides may work better in some women than others, so having more than one potential product available would provide women with more options for preventing HIV infection.

The "next generation" microbicides that NIAID is examining are antiretroviral-based gels that have a specific action against HIV. Antiretrovirals are the drugs that have been used successfully to treat HIV in millions of people around the world. Researchers are testing whether incorporating these antiretrovirals into a vaginal gel may also be effective in preventing HIV infection. Currently, NIAID is examining a vaginal gel containing the antiretroviral drug tenofovir.

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