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QUESTIONS AND ANSWERS

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

1. What was the aim of HPTN 035?

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 male-to-female sexual transmission of HIV.

2. What is a microbicide?

Microbicides are substances that are intended to reduce or prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside of the vagina or rectum. A microbicide can be formulated in many ways, such as a gel or cream or in a vaginal ring. Several candidate microbicides are being tested in clinical trials, although none is yet approved or available for use.

3. Who conducted and funded the study?

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 the establishment of the MTN, 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.

HPTN 035 was funded by NIAID, NICHD and NIMH. Indevus Pharmaceuticals, Inc., in Lexington, Massachusetts, USA, provided PRO 2000 and ReProtect, Inc., based in Baltimore, Maryland, USA, provided BufferGel. The U.S. Agency for International Development (USAID) provided funding to manufacture BufferGel for the study.

4. Where were the study sites located?

HPTN 035 was conducted at seven sites, six in Africa and one in the United States:

- Malawi College of Medicine – Johns Hopkins University Clinical Research Site (Queen Elizabeth Central Hospital), Blantyre, Malawi
- University of North Carolina Lilongwe Clinical Research Site (Kamuzu Central Hospital), Lilongwe, Malawi
- Chatsworth Clinical Research Site (R.K Khan Hospital) of the South African Medical Research Council (MRC), Durban, South Africa
- Hlabisa Clinical Research Site of the MRC, KwaZulu-Natal, South Africa

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- Kamwala Health Centre Clinical Research Site of the Centre for Infectious Disease Research in Zambia, Lusaka, Zambia
- University of Zimbabwe-UCSF Collaborative Research Programme Clinical Research Sites at Spilhaus and Seke South Clinics, Harare, Zimbabwe
- University of Pennsylvania, Philadelphia, U.S.A.

5. When did the trial take place?

HPTN 035 was conducted between February 2005 and September 2008. Enrollment of 3,099 participants was completed in July 2007. Women took part in the study for 12 to 30 months (20 months on average).

6. What candidate microbicides were studied?

HPTN 035 researchers tested two candidate microbicides with different mechanisms of action. BufferGel was developed by ReProtect, Inc., 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, 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 trials involving women from both developed and developing countries. The pre-clinical laboratory research suggested the gels may reduce 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.

7. How was the study designed?

HPTN 035 was 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. The study 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 (i.e., women who relied on the use of condoms to prevent HIV infection). 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. The Phase IIb study did not proceed until a data safety and monitoring board (DSMB) reviewed the Phase II results and approved moving forward.

Participants were randomly assigned in approximately equal number to one of four study groups: BufferGel, PRO 2000 gel, placebo gel (with no active ingredient), no gel. Participants 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 throughout the study. Women completed monthly clinic visits throughout their participation.

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

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 (72 percent).

9. 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.

10. There's another trial testing PRO 2000. Will it tell us more about the gel's effectiveness?

The Microbicides Development Programme (MDP), which is funded by the UK's Medical Research Council, is testing PRO 2000 in a Phase III trial called MDP 301. MDP 301 was originally designed to test two different doses of PRO 2000 gel, but the higher dose gel (2 percent) was discontinued in February 2008 when the study's Independent Data Monitoring Committee concluded the higher dose gel was not likely to show benefit. MDP 301 is continuing to study the low dose gel (0.5 percent), the same dose tested in HPTN 035. MDP 301 involves nearly 9,400 women in South Africa, Tanzania, Uganda and Zambia and is set to conclude in August 2009.

11. Does either NIAID or the MTN plan to conduct a phase III trial of PRO 2000?

At this time, there are no plans 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.

12. How did HPTN 035 differ from other microbicide trials?

Unlike any other microbicide trial to date, HPTN 035 evaluated in the same study two candidate microbicides, each with a different mechanism of action. Another unique feature of HPTN 035 is its inclusion of two control (comparison) groups: one in which women used a placebo gel (with no active ingredient) and one in which women used no gel. While a placebo control group is standard in clinical trials, a control group in which no product is used represents a departure from other microbicide studies.

13. What were the reasons for including a "no-gel" control group in HPTN 035?

Although microbicide studies routinely include a placebo gel for comparison purposes, researchers have not known for certain that the placebo gel does not have some effect of its own. For example, if the placebo gel were to provide even a small measure of protection against HIV, the effectiveness of the product under study would be underestimated. Likewise, if a placebo affected in any way the normal physiology of the vagina, this also could confound the interpretation of study results. HPTN 035 investigators believed that by including a no gel group in its study, and comparing HIV infection rates and other parameters of safety and effectiveness among women using placebo gel and women using no gel, they would gain important insight as to whether there are placebo gel-associated effects and, in turn, be better able to interpret the study's results. Indeed, the finding in the HPTN 035 trial that the number of HIV infections in the two control arms – placebo gel (51) and no gel (53) – was similar provides useful evidence that the placebo gel has no impact on HIV infection

Inclusion of the no-gel group also permits a more "real world" evaluation of a product's effectiveness than is possible in a study that compares only the product against a placebo gel. Researchers assume that the use of a microbicide may influence other behaviors, such as frequency of sexual activity and condom use, which could impact HIV infection risk. In HPTN 035, the effectiveness of each candidate microbicide for preventing HIV will be compared against the effectiveness of the placebo gel and with no gel at all. Such a comparison can take into account any behavioral changes associated with use of a gel and therefore provide a more clear assessment of the product's effectiveness.

14. If all of the women in this trial used condoms, how can you determine if the gels were effective?

In order to reduce their risk of HIV, researchers provide study participants free condoms and ongoing HIV risk-reduction counseling. If every participant used a condom for every act of sexual intercourse, it would be nearly impossible for researchers to evaluate the effectiveness of the microbicides. Prior experience has shown that even

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with counseling and free access to condoms, most women are not able to use condoms 100 percent of the time. Although researchers strive to reduce the risk of HIV infection among study participants in any microbicide trial, the effectiveness of a microbicide will largely be evaluated in those sex acts in which participants are not able to use condoms

15. Why were PRO 2000 and BufferGel chosen to be evaluated in HPTN 035?

The HPTN Microbicide Science Working Group Product Selection Committee conducted a thorough review of available candidate microbicides for testing in HPTN 035. Based on the favorable pre-clinical and clinical data available at the time, as well as estimated product availability, the committee selected PRO 2000 (0.5 percent) and BufferGel for evaluation.

16. What approvals were required to conduct the study?

HPTN 035 was reviewed by NIAID, the U.S. Food and Drug Administration, and government and regulatory authorities in the study site countries. It was also reviewed and approved by institutional review boards (IRBs) and/or ethics committees (ECs) responsible for oversight of research conducted at each site. IRBs and ECs ensure that studies are scientifically valid and ethically sound and provide oversight throughout a trial.

17. Did women participating in the study provide informed consent?

Yes. Written informed consent was obtained from each study participant in her native language. The informed consent process ensured that women 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.

18. What were the medical benefits for women participating in the study?

Participants completed monthly study visits at which any changes in their health status were assessed. They received free HIV risk reduction counseling and testing as well as routine pelvic exams and laboratory tests. Testing and treatment for other sexually transmitted infections were also provided free of charge to both participants and their partners. For medical problems that study staff were not able to treat directly, women were referred to other (non-study) health care providers.

19. How did the local communities benefit?

Like many studies, HPTN 035 helped develop or bolster infrastructure at the site and locally, and helped enhance the capacity of staff and community-level support programs that are essential for the success of current and future trials.

20. How was the safety of the participants protected?

HPTN 035 was designed according to the most rigorous international scientific and ethical standards and with utmost concern for participant safety and well-being. It incorporated a multi-tiered safety review process that included strict U.S. and international procedures 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 at any time the DSMB had identified any safety concerns, it could have recommended the study modify its procedures or be stopped. During HPTN 035, six DSMB reviews took place, and at each review the DSMB recommended the study's continuation.

21. What happened when participants acquired HIV during the study?

HPTN 035 was conducted in the United States and in areas of Africa where women are at high risk for HIV. HPTN 035 researchers did their best to reduce participants' risk. Throughout the study, women in all four groups received free condoms, HIV risk-reduction counseling and routine testing and treatment for sexually transmitted infections as a standard HIV prevention package. Women who acquired HIV during the trial were counseled and referred by study staff to local HIV care and support services. Providers and programs to which participants were referred offer psychosocial services and medical care, including antiretroviral therapy.

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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/hptn035>.