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MICROBICIDE TRIALS NETWORK QUESTIONS AND ANSWERS

HPTN 059:

A MULTI-CENTER CLINICAL TRIAL EVALUATING THE SAFETY AND ACCEPTABILITY OF THE CANDIDATE MICROBICIDE TENOFOVIR TOPICAL GEL

1. What was the aim of HTPN 059?

HPTN-059 aimed to assess the safety and acceptability of an antiretroviral (ARV)-based microbicide called tenofovir topical gel used either daily or before each act of sex over a six-month period in 200 sexually active HIV-negative women. HPTN-059 also sought to determine how prolonged gel use affects vaginal flora, the vagina's naturally protective population of microorganisms, and whether the activity of certain immune system molecules can be a useful measure for assessing the safety of microbicides.

2. What is a microbicide?

Microbicides are substances that are designed to reduce or prevent the sexual transmission of HIV or other sexually transmitted infections when applied topically to the vagina. A microbicide can be formulated in many ways, such as a gel or cream. Some microbicides are also being developed for rectal use. Several microbicide products are being tested in clinical trials, although none is yet approved or available for use by women.

3. Who conducted the trial?

HPTN 059 was conducted by a team of leading Indian and American researchers working in the Microbicide Trials Network (MTN), a clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. 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. HPTN 059 was led by Sharon Hillier, Ph.D., of the University of Pittsburgh School of Medicine, who also is MTN principal investigator.

4. Who supported the trial?

HPTN 059 was funded by the Division of AIDS, National Institute of Allergy and Infectious Diseases, part of NIH. Tenofovir gel was provided free of charge by its manufacturer, Gilead Sciences, Inc., of Foster City, California. (In December 2006, Gilead granted intellectual property rights for tenofovir topical gel to the International Partnership for Microbicides of Silver Spring, Maryland, and CONRAD, of Arlington, Virginia. Under the licensing agreement, Gilead continued supplying the gel to ongoing clinical studies.)

5. Where did the trial take place?

HPTN 059 was conducted at three sites: the National AIDS Research Institute in Pune, India; and at two sites in the United States, the University of Alabama at Birmingham in Birmingham, Alabama, and, the Bronx-Lebanon Hospital Center, Bronx, New York.

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6. What candidate microbicide was studied?

HPTN 059 researchers evaluated the candidate microbicide tenofovir topical gel. Its active ingredient belongs to a class of anti-retroviral drugs called nucleotide reverse transcriptase inhibitors, which act against HIV by targeting a key enzyme the virus needs to copy itself before taking over a host cell. In its oral form, tenofovir disoproxil fumarate, known by the brand name Viread, is approved as a treatment for HIV infection in combination with other medications. The topical gel form of tenofovir was not developed as treatment for HIV but as an approach to prevent the sexual transmission of HIV. Both the oral and topical formulations of tenofovir were developed by Gilead Sciences, Inc., of Foster City, California, which assigned a royalty-free license for the topical gel to the International Partnership for Microbicides of Silver Spring, Maryland, and CONRAD, of Arlington, Virginia, in December 2006.

Laboratory and nonclinical studies have demonstrated that tenofovir gel acts on the specific cells of the vagina and cervix that are primary targets for HIV infection. In addition, researchers who conducted a Phase I safety study of the gel (called HPTN 050) found it was well tolerated by both HIV-negative and HIV-positive women who applied it up to two times a day for two weeks. Results of these and other studies suggested that tenofovir topical gel could be considered in a larger, expanded safety and acceptability trial, such as HPTN 059.

7. How was the trial designed?

Researchers designed HPTN 059 as a Phase II (expanded safety) randomized, placebo-controlled trial with four study groups. Once enrolled, women were randomly assigned to one of these four groups: tenofovir gel applied daily, tenofovir gel applied up to two hours before sex, placebo gel used daily, or placebo gel applied prior to sex. Because the tenofovir and placebo gels look the same, neither researchers nor participants knew who had been assigned to use which gel during the six-month study period. Throughout the study, participants in all four groups received free condoms and HIV risk-reduction counseling as well as routine testing and treatment for sexually transmitted infections. The women were medically evaluated every four weeks for six months, and at the conclusion of the study, were interviewed by researchers to assess how well they adhered to their assigned study regimen and whether being in the study caused modifications in their sexual practices.

8. When was the trial completed?

The study completed enrollment of 200 women in April 2007 and by October 2007, each of the participants had completed the six-month study-regimen. After the data is “unblinded” and the analysis complete, researchers will be able to make determinations among the four study groups. They will report the first set of results at Microbicides 2008, an international scientific meeting in New Delhi, India, Feb. 24-27, 2008.

9. How does this trial differ from other microbicide trials?

HPTN 059 is the first study of a candidate microbicide to look at both daily use and use just prior to sex. Previous trials of other candidate microbicides have required that women apply the gel only at the time of sexual intercourse. HPTN 059 also is one of the first trials to evaluate a microbicide with specific action against HIV. Tenofovir topical gel contains an anti-retroviral drug that in pill form is a mainstay treatment for HIV.

10. Why was tenofovir topical gel chosen to be evaluated in HPTN 059?

Based on promising pre-clinical and clinical data, as well as estimated product availability, tenofovir topical gel was selected for evaluation. Researchers were particularly interested in evaluating tenofovir topical gel, because as an antiretroviral-based microbicide, it has specific action against HIV. The active ingredient in tenofovir topical gel is approved as an oral drug for the treatment of HIV.

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11. Was there concern that use of this particular microbicide might result in drug resistance?

Some people have raised the possibility that women who acquire HIV while using an ARV-based microbicide will fail to respond to treatment consisting of the oral form of the drug or other drugs in the same class of ARVs, a process referred to as resistance. Others are concerned that becoming infected even years later could also confer drug resistance. Resistance occurs when a pathogen's sensitivity to a particular drug is diminished. With HIV, researchers believe drug resistance occurs as the virus mutates, each time incorporating a new disguise that renders itself unrecognizable as a drug target. While not being conclusive, preliminary evidence from small clinical safety studies of the gel in HIV-positive women do not suggest drug resistance is a problem. Nonetheless, the MTN recognizes that the use of either an ARV-based topical gel or oral tenofovir for prevention of HIV could theoretically lead to resistance, so all its study volunteers are monitored carefully for acquisition of HIV infection.

12. What approvals were required for this trial to get underway?

The trial underwent extensive and rigorous review by NIAID, the U.S. Food and Drug Administration, and regulatory and research authorities in each country, as well as by institutional review boards (IRBs) at each trial site. Local IRBs ensure that studies are scientifically valid and ethically conducted and they provide oversight throughout the duration of the trial. In addition, each trial site has a local community advisory board to provide input on and oversight of trial activities.

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

Written informed consent is obtained from each study participant prior to both screening and enrollment. For participants at the Indian site, the informed consent form was translated into the local Marathi language. The informed consent process ensures that women understand the procedures, risks and benefits of the study; the need to practice safer sex behaviors regardless of which study group they are assigned to; the importance of adherence to study treatment; and the potential medical risks associated with participation. Participants are under no obligation to participate and may leave the study, without consequence, at any time.

14. Were there medical benefits for women participating in the study?

Participants received free risk-reduction counseling and testing for HIV as well as routine physical and pelvic exams. In addition, testing for and treatment of other non-HIV sexually transmitted infections were provided free of charge to both participants and their partners.

15. What was done to ensure the safety of the participants?

HPTN 059 was designed according to the most rigorous international medical practices and ethical standards, and every possible measure was taken to protect the wellbeing of participants. HPTN 059 followed strict national and international procedures for monitoring and reporting, including regular reviews by a Protocol Safety Review Team. Several other layers of safety were employed, beginning at the site level where site staff closely monitored each participant

16. What happens if a participant acquires HIV during a study?

As with all MTN studies, HPTN 059 researchers do their best to reduce participants' risk for acquiring HIV, which includes providing condoms and ongoing HIV prevention counseling. Still, some women may become infected during participation in a study. Women who become infected (or who test positive for HIV during eligibility screening) are counseled and referred by study staff to services at local facilities that provide medical care and treatment, including antiretroviral therapy, and psychological and social support. These services may be available within the same health care facility that houses the research site or at another health care provider.

17. What happens after the trial?

Results of HPTN 059 will help more clearly define current and future directions in research. The study should provide important information about the safety of ARV-based microbicides, which are beginning to be studied in larger trials to determine their potential effectiveness for preventing the sexual transmission of HIV. As well, HPTN 059 will help determine whether women are willing to apply gel on a daily basis, an approach that may provide more sustainable protection against the virus.

MTN already has plans to conduct additional trials of tenofovir gel. Researchers will soon begin enrolling participants into MTN-002, the first trial of a candidate microbicide in pregnant women that seeks to understand the extent of drug absorption during pregnancy and the degree to which the tenofovir gel's active ingredient may be transferred to the fetus. Another trial, MTN-001, will be the first head-to-head comparison of oral and vaginal gel preparations of tenofovir – looking at differences in drug absorption (systemically and locally) and adherence and acceptability of each approach separately and in combination. Finally, the VOICE Study (Vaginal and Oral Interventions to Control the Epidemic) will be the first effectiveness trial of a microbicide that women use every day instead of at the time of sexual intercourse. Moreover, VOICE will be the only trial evaluating two promising HIV prevention approaches in the same study: tenofovir gel and pre-exposure prophylaxis, or PrEP, an HIV prevention approach that involves daily use of oral anti-retrovirals.

More information about the Microbicide Trials Network and HPTN 059 is available at www.mtnstopshiv.org.

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