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MICROBICIDE TRIALS NETWORK BACKGROUNDER

HPTN 059:

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

Study Overview

HPTN 059 was a Phase II (expanded safety) trial aiming to assess the safety and acceptability of an antiretroviral-based candidate microbicide called tenofovir topical gel used either daily or before each act of sex. HPTN-059 also sought to determine how six months of 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 useful measures for assessing the safety of microbicides. Microbicides are substances designed to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically to the vagina. The trial, which was launched in August of 2006, involved 200 sexually active HIV-negative women and was conducted at three sites: the National AIDS Research Institute in Pune, India; and two sites in the United States, the University of Alabama at Birmingham in Birmingham, Alabama; and the Bronx-Lebanon Hospital Center, Bronx, New York. Researchers will report the trial's results at Microbicides 2008, an international scientific meeting in New Delhi, India, Feb. 24-27, 2008.

HPTN 059 is the first study of a candidate microbicide looking 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 gel contains an anti-retroviral drug that in pill form is a mainstay treatment for HIV.

The study was conducted by 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.

How the Study Was Conducted

To best compare the safety of tenofovir topical gel when used either daily or just prior to sex and evaluate which of these two regimens is more acceptable to women, researchers designed HPTN 059 as a 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, and 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 received free condoms and HIV risk-reduction counseling as well as routine testing and treatment for sexually transmitted infections.

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The Candidate Microbicide Being Studied

HPTN 059 evaluated the candidate microbicide tenofovir 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.

Participant Safety and HIV Monitoring

HPTN 059 was designed according to the most rigorous international medical practices and ethical standards, and included every possible measure to protect the wellbeing of participants. Strict national and international procedures for monitoring and reporting were followed, 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.

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.

Why this Study is Important

According to the most recent statistics from UNAIDS and the U.S. Centers for Disease Control and Prevention, nearly half, or 46 percent, of the 33.2 million people living with HIV/AIDS worldwide are women. Young women are especially vulnerable. Worldwide, it has been estimated that 60 percent of the 15- to 24-year-olds with HIV are women.

Due to both biological and cultural factors, women are more than twice as likely as their male partners to acquire HIV through sexual intercourse. In fact, between 70 and 90 percent of all HIV infections in women are due to heterosexual intercourse. 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 effective, microbicides could be an inexpensive and readily available approach for many women who cannot simply rely on condoms or abstinence as methods for protecting themselves from HIV. Moreover, a microbicide that can be used without a partner's knowledge, such as one that is applied more discreetly in a non-sex dependent manner, may be a preferred prevention option for many women. Even a partially effective microbicide could have a profound impact on the dynamics of HIV transmission, say researchers.

Funding

HPTN 059 was funded by the Division of AIDS, National Institute of Allergy and Infectious Diseases, part of NIH. The study microbicide was provided free of charge by its manufacturer, Gilead Sciences, Inc. (Although Gilead granted intellectual property rights for tenofovir topical gel to the International Partnership for Microbicides and CONRAD after HPTN 059 began, the licensing agreement provided that Gilead continue supplying the gel to ongoing clinical studies.)

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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 microbicides, working within a unique infrastructure specifically designed to facilitate research required to support licensure of topical microbicide 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 microbicides and include studies designed to evaluate microbicides along with other promising HIV prevention approaches, such as pre-exposure oral antiretroviral prophylaxis, or PrEP.

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. It receives its funding from three NIH institutes: NIAID, the National Institute of Mental Health and the 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 059 is available at www.mtnstopshiv.org.

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