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BACKGROUNDER

MTN-007: Phase I Tenofovir Gel Rectal Safety Study

Study Overview

MTN-007 was a Phase I study involving 65 HIV-negative men and women designed to to determine whether a reformulated version of tenofovir gel is safe and acceptable as a potential rectal microbicide. Developed originally as a vaginal microbicide, the gel contains the antiretroviral (ARV) drug tenofovir, which is commonly used to treat people with HIV in combination with other ARVs. For MTN-007, tenofovir gel was formulated with less glycerin, a common additive found in many gel-like products, to make it more suitable for use in the rectum.

The study began in October 2010 and was conducted at three U.S. sites affiliated with the Microbicide Trials Network (MTN): the University of Pittsburgh, University of Alabama at Birmingham and Fenway Health in Boston. The MTN is an HIV/AIDS clinical trials network established and funded by the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) with co-funding from the National Institute of Mental Health (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all components of the U.S. National Institutes of Health (NIH). The study itself was funded by DAIDS/NIAID and NIMH. As a co-sponsor of MTN-007, CONRAD of Arlington, Va., provided the study gel free of charge. Ian McGowan, M.D., Ph.D., from the MTN and University of Pittsburgh, led the study, along with Kenneth Mayer, M.D., from Fenway Health in Boston, Mass.

What the Study Found

MTN-007 found that the reformulated version of tenofovir gel was safe and acceptable when used in the rectum daily for a one-week period. Results showed no significant differences in side effects among participants who were randomly assigned to one of three gel groups: reformulated version of tenofovir gel; a placebo gel containing no active ingredient; and a gel containing the spermicide nonoxynol-9. A fourth group did not use any gel, but took part in study-related procedures and tests. Eighty percent of participants reported only minor side effects related to the use of study products, while 18 percent reported moderate side effects. Adherence to assigned study products was high, with 94 percent using the products daily as directed. When asked about the likelihood that they would use the gel in the future, 87 percent of the participants who used the reformulated gel indicated they would likely use the gel again, compared to 93 percent of the placebo gel group, and 63 percent of the nonoxynol-9 gel group. In addition to assessing safety and acceptability, researchers also conducted preliminary gene expression testing that indicated changes in the activation of some genes in the tenofovir gel group. Further analysis is ongoing to better understand these findings.

Why this Study is Important

Worldwide, 33.3 million people are currently living with HIV. Since the epidemic began in the early 1980s, more than 60 million people have been infected and nearly 30 million people have died of HIV-related causes. Although the rate of new infections is stabilizing in many countries around the world, HIV continues to disproportionately affect racial minorities and men who have sex with men. Globally, men who have sex with men are 19 times more likely to be infected with HIV than the general population. Unprotected anal sex is the primary driver of the HIV epidemic among this population.

According to estimates, 5 to 10 percent of the world's population engages in anal sex. While condoms are an extremely effective method to prevent HIV during anal sex, many people can't or don't use them. Because it

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is not known whether microbicides formulated for the vagina will work the same way in the rectum, it is vitally important to test their safety and acceptability when used rectally.

MTN-007 was the first clinical study of a reformulated version of tenofovir gel for rectal use. Not only has the study provided critical information about the safety of the reformulated gel, but MTN-007 has also helped advance efforts to develop a rectal microbicide to curb the high rate of HIV infections attributed to unprotected anal sex. As such, researchers are now planning a Phase II international multi-site trial as follow-up to MTN-007. The study, MTN-017, will involve 186 men who have sex with men and transgender women at clinical sites in Peru, South Africa, Thailand, and the United States.

How the Study was Conducted

MTN-007 enrolled 65 HIV-negative men and women who engaged in receptive anal intercourse at least once in the previous year, and who agreed to be sexually abstinent during the four- to eight-week period they were in the study. Participants were randomly assigned to one of four study groups. Three of the four groups were assigned to use one of the following products during a one-week period: a reformulated version of tenofovir gel; a placebo gel containing no active ingredient; or a gel containing the spermicide nonoxynol-9 (N-9). A fourth group did not use any gel but took part in all of the study-related procedures and tests, including physical and rectal exams. For those in the gel groups, the first set of tests occurred prior to and immediately following administration of their assigned study gel. One week later, participants in the three gel groups were asked to apply their assigned gel once a day (such as at bedtime) for seven consecutive days. They then returned to the research clinic for the same set of tests. Neither the researchers nor the participants knew the particular gel each participant was assigned to use.

The tests and procedures performed at various time points during the study assessed the effects of the assigned gel on blood chemistry and immune reaction, and in rectal tissue. These included blood tests, rectal fluid collection and standard rectal exams that allowed researchers to view inside the rectum and take small tissue samples for microscopic study. Using a series of sophisticated methods, researchers looked for an array of different genes, the specific building blocks of these genes, and various immune cells. These analyses are ongoing.

To explore the acceptability of the rectal formulation of tenofovir gel, study participants were asked about side effects and their likes and dislikes about both the gel and the applicator (which was designed for vaginal use). They were also asked about the likelihood they would use a rectal microbicide in the future, should one become available.

The Products Studied

The active ingredient in tenofovir belongs to a class of ARVs called nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs), which act against HIV by targeting a key enzyme the virus needs to copy its genetic material – an essential step for the virus to multiply and infect other cells. In its tablet form, tenofovir, known by the brand name Viread®, is approved for treating HIV when used in combination with other drugs, and is widely prescribed and well-tolerated by most people. Tenofovir gel was initially developed as a vaginal microbcide, and was found safe and effective in reducing the risk of HIV in women who used it before and after vaginal sex in a study called CAPRISA 004. More recently, however, MTN researchers conducting the VOICE Study closed the tenofovir gel arm of the trial after a routine review of study data determined that the gel, while safe, was not effective in preventing HIV among the women in that study group, who were asked to apply it vaginally every day. Tenofovir gel is currently being evaluated in a Phase III called FACTS 001, with results expected in 2014. In the meantime, a Phase III trial called FACTS 001 is currently evaluating the vaginal formulation of tenofovir gel using the same regimen as CAPRISA 004, with results expected in 2014.

MTN-007 is a follow-up trial to another Phase I study called RMP-02/MTN-006, which assessed the rectal use of the vaginal formulation of tenofovir gel. That study found the vaginal gel produced a strong antiviral effect

when used in the rectum, but gastrointestinal side effects were problematic. Due to these side effects, researchers recommended modifications to the gel's formulation. The new formulation was tested in people for the first time in MTN-007. Tenofovir gel was developed by Gilead Sciences, Inc., of Foster City, Calif., which assigned the rights for the gel to CONRAD of Arlington, Va., and the International Partnership for Microbicides of Silver Spring, Md., in December 2006.

N-9 is a contraceptive spermicide found in many products sold over the counter and was one of the first products considered as a potential microbicide for preventing vaginal transmission of HIV. A large trial involving female sex workers in central Africa found it did not protect against HIV, and its use may have facilitated HIV infection. Many of the women in the study used the gel more than three times a day on average. In MTN-007, exposure to N-9 was minimal – eight applications in total, and participants were closely observed and urged to remain sexually abstinent throughout the study period.

Participant Safety and HIV Monitoring

MTN-007 was designed according to stringent ethical and scientific guidelines with numerous measures, beginning at the site level, to protect the safety and well-being of participants. As with all NIH-funded studies, MTN-007 incorporated a multi-tiered safety review process and was conducted under the watchful eye of regulatory and research authorities. The protocol underwent extensive and rigorous review by NIAID, the U.S. Food and Drug Administration and the institutional review boards (IRBs) at all three clinical research sites. Written informed consent was obtained from each study participant prior to screening and enrollment, a process that ensures individuals understand the procedures, as well as possible risks and benefits of participating in the study.

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More information about MTN-007 and rectal microbicides, as well as other MTN studies is available at http://www.mtnstopshiv.org/news.

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 with co-funding from the Eunice Kennedy Shriver 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. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners who are devoted to preventing or reducing the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally.

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