CONTACT: **Clare Collins**
+1- 412-641-7299
+1- 412-770-8643 (mobile)
collcx@upmc.edu

BACKGROUNDER

RMP-02/MTN-006
Phase I Safety, Acceptability and Drug Absorption Study of the Vaginal Microbicide Tenofovir Gel Applied Rectally Compared to Oral Tenofovir

Study Overview

RMP-02/MTN-006 was a Phase I study involving 18 HIV-negative men and women to determine whether tenofovir gel is safe to use in the rectum to protect against HIV during anal sex. Tenofovir gel is a microbicide that has shown promise for preventing HIV when topically applied to the vagina. It contains the antiretroviral (ARV) drug tenofovir, which is commonly used to treat people with HIV in combination with other ARVs. In addition to safety, the study assessed the extent to which active drug in the gel was absorbed and distributed through the body, and whether participants found the product acceptable and easy to use. In novel laboratory studies, researchers also explored how effective tenofovir gel was in preventing HIV infection in rectal tissue sampled from study participants.

The study was funded by the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), a component of the U.S. National Institutes of Health (NIH), through both the Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM) and the Microbicide Trials Network (MTN). The study was a collaboration between the IPCP-HTM-funded Microbicide Development Program based at the University of California, Los Angeles (UCLA), which focuses on preclinical and early Phase I development of ARV-based rectal microbicides, and the MTN, based at the University of Pittsburgh. The MTN is an HIV/AIDS clinical trials network established and funded by DAIDS/NIAID with co-funding from the National Institute of Mental Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all components of NIH. RMP-02/MTN-006 was led by Peter Anton, M.D., from UCLA, and Ian McGowan, M.D., Ph.D., from the MTN. The study was conducted at UCLA and the University of Pittsburgh.

What the Study Found

RMP-02/MTN-006 found that HIV infection was significantly inhibited in laboratory tests of rectal tissue sampled from participants who used tenofovir gel daily for one week compared to tissue from those who used a placebo gel. While a slight anti-HIV effect was noted in tissue from participants who received a single dose of tenofovir gel, the finding was not statistically significant. A single dose of oral tenofovir did not provide any protection against HIV in rectal tissue samples. According to self-reports, only 25 percent of men and women who had used tenofovir gel said they liked it, compared to 50 percent who had used the placebo gel. However, when asked whether they would consider using the product in the future, 75 percent of these participants reported a high likelihood of future use. Most participants experienced only minor side effects, however, two of the 12 participants in the seven-day dose group, reported severe gastrointestinal side effects, including diarrhea and lower abdominal cramps.

Why this Study is Important

Most microbicide research to date has been focused on products for vaginal use, yet the risk of becoming infected with HIV from unprotected anal sex may be at least 20 times greater than unprotected vaginal sex, in part, because the rectal lining is only one-cell thick compared to the vagina's multiple layers. In addition, there are far more cells vulnerable to HIV infection just under the lining in the rectum compared to the cervix and

-more-

vagina. As such, RMP-02/MTN-006 represents a significant step forward to develop a product for rectal use, which is especially important given the significant proportion of HIV infections caused by unprotected anal sex in both men and women.

RMP-02/MTN-006 was the first rectal safety study of tenofovir gel, a microbicide previously shown to reduce vaginal transmission of HIV among high-risk women. Through unique laboratory tissue tests, the study has provided the first-ever evidence that tenofovir gel could help reduce the risk of HIV from anal sex. The study also showed that the gel did not cause changes to the rectal lining and cells that could make the rectum more vulnerable to HIV. It has also indicated the need for modifications to the gel's formulation to address side effects and make it more acceptable to use. Indeed, the MTN has launched a second study called MTN-007 to evaluate the safety and acceptability of a reformulated version of tenofovir gel based on early observations from RMP-02/MTN-006. The new formulation of gel contains a reduced amount of glycerin, a common additive found in many gel-like products, in the hope that this will make it better tolerated when used in the rectum.

How the Study was Conducted

RMP-02/MTN-006 was a Phase I study that enrolled 18 sexually abstinent, HIV-negative men and women who followed two study regimens – oral tenofovir and then either tenofovir gel or a placebo gel applied in the rectum. In the first part of the study, all participants were given a single dose of oral tenofovir and then underwent a series of tests and examinations over a two-week period, which were followed by two weeks without study product. For the second part of the study, participants were randomized to one of two groups. One group received a single dose of tenofovir gel and the other group received a dose of placebo gel with no active ingredient. Both groups went through a similar two-week period of tests as they did during the oral regimen, followed by two weeks of rest. Participants were then instructed to apply one dose of their assigned study gel rectally at home for six consecutive days and return to the clinic to receive the seventh dose of study product and undergo final testing.

The tests and procedures performed at various times during the study included blood tests, vaginal and rectal fluid collection. Rectal exams and tissue collection were performed using a standard procedure called sigmoidoscopy. The tests helped researchers determine how much drug was absorbed and remained in its active form over the two- week time period in different parts of the body and to evaluate if there were changes to cells and tissue. Repeating the same tests for both oral tenofovir and tenofovir gel allowed researchers to make direct comparisons of the two and determine which single-dose approach (if either) was likely to achieve optimal drug concentrations in the areas of the rectum most critical for preventing HIV transmission. Laboratory tests were performed in which small samples of rectal tissue were obtained from participants over the same two-week sampling periods during the study and then were sent directly to the laboratory where they were exposed to HIV. The purpose of these novel studies was to determine whether tenofovir gel applied in the rectum had the potential to protect against HIV. To explore the acceptability of the gel, study participants were asked about side effects, likes and dislikes and whether they would consider using the product in the future.

The Products Studied

Two products – tenofovir vaginal gel and oral tenofovir – were studied in RMP-02/MTN-006. The active ingredient in tenofovir gel 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 as a treatment for HIV infection when used in combination with other drugs and has been widely prescribed and well tolerated by most people. Oral tenofovir is also under study for its potential to prevent HIV, an approach known as pre-exposure prophylaxis, or PrEP. Tenofovir gel, a candidate microbicide specifically developed to prevent the sexual transmission of HIV through vaginal

intercourse, was recently found to reduce HIV risk by 39 percent in women who used it before and after vaginal sex, providing proof of concept that a microbicide can help prevent HIV. RMP-02/MTN-006 was the first clinical study testing tenofovir gel in the rectum.

Both the oral and gel formulations of tenofovir were developed by Gilead Sciences, Inc., of Foster City, Calif., which assigned a rights for the gel to the International Partnership for Microbicides of Silver Spring, Md., and CONRAD, of Arlington, Va., in December 2006. For RMP-02/MTN-006, Gilead Sciences and CONRAD provided the study products free of charge.

Participant Safety and HIV Monitoring

RMP-02/MTN-006 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, RMP-02/MTN-006 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) for both UCLA and the University of Pittsburgh. IRBs ensure that studies are scientifically valid and ethically conducted and provide oversight throughout the duration of a trial. Because this was the first study of tenofovir gel applied rectally, as an added precaution, participants were strongly urged to remain sexually abstinent during the periods that study products were being evaluated. 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 the study. Participants were under no obligation to participate and could leave the study at any time, without consequence.

# # #

More information about RMP-02/MTN-006 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.

28-February-2011