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## QUESTIONS AND ANSWERS

### RMP-02/MTN-006

#### **Phase I Safety, Acceptability and Drug Absorption Study of the Vaginal Microbicide Tenofovir Gel Applied Rectally Compared to Oral Tenofovir Efficacy**

##### **1. What was the aim of RMP-02/MTN-006?**

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.

##### **2. Who conducted and funded the study?**

RMP-02/MTN-006 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.

##### **3. What did the study find?**

RMP-02/MTN-006 found that HIV was significantly inhibited in rectal tissue samples 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. The 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 tenofovir gel 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.

##### **4. Why is this study important?**

Most microbicide research 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 vagina. As such, RMP-02/MTN-006 represents a significant step forward to develop a product for rectal use,

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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.

### **5. Why do men and women need rectal microbicides?**

According to estimates, 5 to 10 percent of men and women practice anal sex. 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. 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, making it easier for the virus to reach cells to infect. If proven safe and effective, rectal microbicides could protect against HIV in men and women who are unable or reluctant to use condoms during anal sex. Unlike condoms, they could provide an alternative way to reduce risk that is not controlled by one's sexual partner and possibly enhance sexual pleasure, helping to motivate consistent use.

### **6. When did the trial begin and how long did it last?**

The study began enrolling participants in September 2009. A total of 18 men and women were enrolled into the study at UCLA and the University of Pittsburgh. Results were announced in February 2011.

### **7. What products were studied in RMP-02/MTN-006?**

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. 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. In its tablet form, tenofovir, known by the brand name Viread<sup>®</sup>, 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.

Both the oral and gel formulations of tenofovir were developed by Gilead Sciences, Inc., of Foster City, Calif., which assigned the 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.

### **8. How was RMP-02/MTN-006 designed?**

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 either tenofovir gel or a placebo gel. 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

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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. Because rectal-specific gel applicators are still being developed, participants in the study inserted the gel using pre-filled applicators designed for vaginal use.

#### **9. What tests did people receive as part of the study?**

The tests and procedures performed 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 time in different parts of the body and observe changes in cells and tissue. Repeating the same tests for both oral tenofovir and tenofovir gel allowed researchers to make comparisons and determine which approach (if any) was likely to achieve optimal drug concentrations in the areas of the rectum most critical for preventing HIV.

#### **10. Were there side effects from using tenofovir gel in the rectum?**

Most participants experienced only minor side effects from using the gel, however two people in the seven-day dose group reported severe lower gastrointestinal side effects, including diarrhea, urgency and cramps.

#### **11. Why study an oral tablet in a microbicide trial?**

Directly evaluating a gel and tablet in a single trial and in the same study participants is an efficient way to compare research findings. This design permits investigators to learn more about how a single dose of tenofovir gel applied topically – directly to the area possibly exposed to HIV during anal sex – differs from a single dose of oral tenofovir in terms of safety, acceptability, absorption and distribution in the body. These approaches are being explored in many clinical trials, so it is important to understand the safety of each in people who have anal sex.

#### **12. The study also assessed the effectiveness of tenofovir gel as a rectal microbicide, but this was done in a laboratory. How was this possible?**

A unique feature of RMP-02/MTN-006 was the use of laboratory tests in which small samples of rectal tissue were periodically obtained from participants (using a standard clinical procedure called sigmoidoscopy) after they had used the study products. The tissue samples were then sent directly to the laboratory where they were exposed to HIV to determine how well the study products protected the tissue from infection. The purpose of these tests was to determine whether tenofovir gel applied in the rectum had the potential to protect against HIV compared to the placebo gel, and to help inform decisions about the safety and suitability of the product for further study in larger clinical trials.

#### **13. Will tenofovir gel continue to be studied for rectal use even though it was not well-liked and caused some side effects?**

Researchers are currently conducting a study of a reformulated version of tenofovir gel that they hope will make the gel more suitable for use in the rectum. The new formulation contains a lower concentration of glycerin, a common additive found in many types of products. Laboratory tests of the “new” gel suggest it is just as effective as the original formulation but less irritating to the epithelium – the layer of cells that serves as a protective barrier inside the rectum. Researchers are hopeful that the new formulation will reduce gastrointestinal side effects and make it more acceptable to use. Additional NIH-funded research on rectal microbicides is also underway.

#### **14. What was done to ensure the safety of the participants?**

RMP-02/MTN-006 was designed according to stringent ethical and scientific guidelines and numerous measures, beginning at the site level, to protect the safety and well-being of participants. As with all NIH-funded studies, the study incorporated a multi-tiered safety review process and was conducted under the watchful eye of regulatory and research authorities. The protocol underwent extensive review by NIAID, the U.S. Food and Drug Administration and the institutional review boards (IRBs) for both UCLA and the

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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 study. Written informed consent was obtained from each participant prior to screening and enrollment, a process that ensures individuals understand the procedures, and possible risks and benefits of the study. Participants were under no obligation to participate and could leave the study at any time, without consequence.

**15. Are there other studies planned or underway that also focus on rectal microbicides?**

The MTN began a Phase I study called MTN-007 in October 2010 to evaluate the safety and acceptability of a reformulated version of tenofovir gel for rectal use. The study is enrolling 60 men and women at the University of Pittsburgh, University of Alabama at Birmingham and Fenway Institute in Boston. Dr. McGowan is leading the study with Kenneth Mayer, M.D., of the Fenway Institute. Results are expected in 2011 or 2012. In other NIH-funded studies, Dr. McGowan is exploring rectal microbicide safety and acceptability in black and Latino men who have sex with men, one of the highest at-risk groups for HIV in the U.S.

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More information about [RMP-02/MTN-006](#) and rectal microbicides, as well as other MTN studies is available at <http://www.mtnstopshiv.org/news>.

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