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## QUESTIONS AND ANSWERS

### MTN-007: Phase I Tenofovir Gel Rectal Safety Study

#### 1. What was the aim of MTN-007?

[MTN-007](#) was a Phase I study involving 65 HIV-negative men and women designed 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. The tenofovir gel used in MTN-007 was formulated to contain less glycerin, a common additive found in many gel-like products, to make it more suitable for use in the rectum. Overall, the study represents an important step in efforts to develop products to help curb the high rate of HIV infections attributed to unprotected anal sex.

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

MTN-007 was led by the [Microbicide Trials Network](#) (MTN), 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.

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

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 use the reformulated gel compared to those who used a placebo gel containing no active ingredient or a gel containing the spermicide nonoxynol-9. 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 version of tenofovir 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 underway to better understand these findings.

#### 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 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.

MTN-007 was the first clinical study of a reformulated version of tenofovir gel for rectal use and has provided critical information about its safety. The study results advance efforts to develop a rectal microbicide that researchers hope can help 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

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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.

### **5. When and where was MTN-007 conducted?**

The study began in October 2010 and was conducted at the University of Pittsburgh, University of Alabama at Birmingham and Fenway Health in Boston.

### **6. What is a microbicide?**

Microbicides are products being developed and tested to prevent or reduce the sexual transmission of HIV when applied inside of the vagina or rectum. A microbicide can be formulated in many ways, such as a gel or cream, or as a ring that would release the active ingredient over time. Different microbicide products are being tested in clinical trials although none is currently approved or available for use outside of clinical trials.

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

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 rectal tissue is different than vaginal tissue, it is vitally important to develop products specifically for rectal use.

### **8. What products were studied in MTN-007?**

Products used in MTN-007 included a reformulated version of tenofovir gel, a placebo gel containing no active ingredient, and a gel containing the spermicide nonoxynol-9 (N-9).

### **9. What is known about tenofovir gel?**

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<sup>®</sup>, 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 microbicide, 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. 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.

### **10. What is different about the tenofovir gel being tested in MTN-007?**

The tenofovir gel that was tested in MTN-007 contains less glycerin than the original tenofovir gel formulation that was developed for vaginal use. Researchers conducting an earlier Phase I study of vaginal tenofovir gel for

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rectal use, RMP-02/MTN-006, noted that participants tended to have more diarrhea-related side effects than noted in studies in which the gel was used vaginally. To make the gel more suitable for rectal use, researchers reduced the amount of glycerin – a common additive found in many types of products – so that less fluid would be drawn from cells.

### **11. How is MTN-007 designed?**

MTN-007 was a Phase I study that 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 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 reformulated 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.

### **12. Why study N-9 when it's already been ruled out as a potential microbicide?**

N-9 was one of the first products considered as a potential microbicide for preventing the vaginal transmission of HIV. However, 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. Such frequent use likely induced damage to the vagina's cell lining, causing genital irritation, itching and tissue easily prone to bleeding.

Researchers included N-9 in MTN-007 to construct a detailed profile of its effect on rectal tissue. They conducted gene expression tests to see which immune system cell types are present, the particular genes that are being turned on or off, and which of several chemical proteins are in force. Comparing N-9's profile to tenofovir gel and the placebo gel also may reveal reliable measures for evaluating the safety of potential products and help to determine the specific effects of each product. These analyses are ongoing.

### **13. Is N-9 safe?**

N-9 is a contraceptive spermicide found in many products sold over the counter. It is not recommended for HIV prevention or as a lubricant for receptive anal intercourse, although it is still widely used in the United States by men who have sex with men. In MTN-007, exposure to the product was minimal – eight applications in total, and participants were closely observed and strongly urged to remain sexually abstinent throughout the study period. No serious side effects from N-9 were seen in participants enrolled in MTN-007.

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

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

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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 each of the clinical trial sites. IRBs ensure that studies are scientifically valid and ethically conducted and provide oversight throughout the duration of a trial.

**15. Did participants in the study provide informed consent?**

Written informed consent was obtained from each study participant prior to screening and enrollment. The process ensured that individuals understood 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.

**16. Are other studies of the rectal formulation of tenofovir gel being planned?**

As follow-up study to MTN-007, researchers are now planning a Phase II, multi-site trial called [MTN-017](#) that will involve 186 men who have sex with men and transgender women at clinical sites in Peru, South Africa, Thailand, and the U.S. Participants will cycle through three study regimens: reformulated tenofovir gel used daily and before and after anal sex, and daily use of the ARV tablet Truvada®. MTN-017 will allow researchers to collect additional information about the gel's safety and acceptability in the rectum, and compare it to the use of Truvada.

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For more information about MTN-007 go to <http://www.mtnstopshiv.org/news/studies/mtn007>. Information about other MTN studies can be found at <http://www.mtnstopshiv.org/news>

14-March-2012