

## QUESTIONS AND ANSWERS

### MTN-017

#### Phase II Safety and Acceptability Study of Tenofovir Gel Reformulated for Rectal Use

##### 1. What was the aim of MTN-017?

[MTN-017](#) was a Phase II study designed to determine whether a reformulated version of vaginal tenofovir gel is safe and acceptable as a potential [rectal microbicide](#) among HIV-negative men who have sex with men (MSM) and transgender women. 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-017 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, and its use was tested daily and before and after sex, and compared to oral Truvada®.

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

MTN-017 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) 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 National Institutes of Health (NIH). [Ross D. Cranston, M.D., F.R.C.P.](#), of the University of Pittsburgh School of Medicine, was protocol chair, and [Javier R. Lama, M.D., M.P.H.](#), of IMPACTA PERU Clinical Trials Unit in Lima, Peru, was protocol co-chair.

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

MTN-017 found that reduced glycerin tenofovir gel was safe – most side effects from study products were minor, and there were no significant differences in adverse events with the gel regimens (daily and before and after sex) compared to oral Truvada. Overall, participants were highly adherent to the use of study products, with most following through in using their assigned products 80 percent of the time or more. Participants were similarly adherent to using gel before and after sex (93 percent) as they were to taking daily Truvada (94 percent). They were less adherent when using the gel on a daily basis (83 percent).

Participants reported they preferred oral Truvada to the gel, but found the before and after sex gel regimen as easy to use as oral Truvada. When asked about the likelihood that they would use the study products in the future, participants said that they would be just as likely to use the gel, if found effective, before and after sex as they would to take oral Truvada. Forthcoming analyses from MTN-017 will shed light on how much drug was absorbed in the blood, rectal fluid and tissue, and assess whether use of the products caused changes in cells or tissue.

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

Globally, racial and ethnic minorities, MSM and transgender women are disproportionately affected by HIV. Although most microbicide research has focused on products for vaginal use, 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. Because it 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 in the rectum.

MTN-017 is an international multi-site follow-up study to MTN-007, which found that a reduced glycerin formulation of tenofovir gel was safe and acceptable by men and women who used it in the rectum daily for one week. As such, MTN-017 has advanced efforts to develop a rectal microbicide that researchers hope can help curb the high rate of HIV infections attributed to condomless anal sex.

-more-

## **5. When and where was MTN-017 conducted?**

MTN-017 began in September 2013 and completed follow-up of participants in May 2015. The study was conducted at eight clinical sites in Peru, South Africa, Thailand and the United States, including Puerto Rico.

## **6. What are microbicides?**

Microbicides are products applied inside the vagina or rectum that are intended to protect against HIV acquired through sex. A microbicide can be formulated in many ways, such as a gel, enema or fast-dissolving tablet, or as a ring that releases the active ingredient over time.

## **7. Why are rectal microbicides needed?**

Worldwide, 37 million people are currently living with HIV. Since the epidemic began in the early 1980s, about 78 million people have been infected and 39 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, MSM and transgender populations.

Both men and women around the world engage 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 every time they have sex for a number of reasons – dynamics in sexual relationships, stigma about the practice of anal sex, or because they aren't readily available in some countries. If proven safe and effective, rectal microbicides could provide an important additional prevention option.

## **8. What products were studied in MTN-017?**

Products tested in MTN-017 included a reduced glycerin formulation of tenofovir gel and oral Truvada, a tablet that contains a combination of the ARVs tenofovir and emtricitabine that is commonly used with other ARVs as treatment for HIV. Truvada was approved for use as HIV prevention, or pre-exposure prophylaxis (PrEP), by the U.S. Food and Drug Administration in 2012.

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

Tenofovir gel was initially developed as a vaginal microbicide by Gilead Sciences, Inc., 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. The active ingredient, tenofovir, belongs to a class of ARVs called nucleotide 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.

Effectiveness trials of tenofovir gel as a vaginal microbicide have indicated it does not reduce the risk of HIV in women. Although it was found safe and moderately effective in reducing the risk of HIV in women who used it before and after vaginal sex in a study called CAPRISA 004, results from MTN's VOICE (Vaginal and Oral Interventions to Control the Epidemic) study, which was designed to evaluate daily use of tenofovir gel (as well as daily use of an oral ARV tablet tenofovir or Truvada), and FACTS 001 (a Phase III trial testing the same regimen as CAPRISA 004), found it was not effective. An analysis of blood samples from a subset of participants in VOICE found adherence to product use was low across all groups, and for women in the tenofovir gel group, drug was detected in only 23 percent of blood samples. Adherence was similarly low in FACTS 001, with only 22 percent of women using the gel consistently.

Researchers have conducted one study of the vaginal gel used rectally by both men and women. That study, called [RMP-02/MTN-006](#), found it was generally safe but that it also caused unpleasant gastrointestinal side effects. As a result, CONRAD reformulated the vaginal tenofovir gel to contain less glycerin so that it would be more amenable for rectal use. The reduced glycerin formulation was then tested in [MTN-007](#), which found it was safe and acceptable to men and women who used the gel in the rectum daily for one week.

## **10. How was the gel tested in MTN-017 different from the vaginal formulation of tenofovir gel?**

The tenofovir gel tested in MTN-017 contained the same amount of the active ingredient – tenofovir – but had

**-more-**

less glycerin than the original tenofovir gel formulation developed for vaginal use. 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 and decrease gastrointestinal side effects.

#### **11. How was MTN-017 designed?**

MTN-017 was Phase II study to evaluate the safety, acceptability and drug absorption of a reduced glycerin formulation of tenofovir gel used daily and before and after sex, as well as daily use of the oral tablet Truvada. Participants followed each of the three study regimens (reduced glycerin tenofovir gel used both daily and before and after anal sex; and Truvada tablets taken daily) for eight weeks, with a weeklong break between regimens when no product was used. Throughout the study, participants also received ongoing HIV risk reduction counseling, free condoms and were tested regularly for HIV.

Tests and procedures performed as part of the study sought to determine the clinical safety of the products, how much drug was absorbed in blood, rectal fluid and tissue, and whether use of the products caused changes in cells or tissue. To explore the acceptability of the gel, study participants were asked about any side effects they may have experienced, their likes and dislikes about using the gel either daily or with sex, and whether they would consider using it in the future.

#### **12. How many people were enrolled into MTN-017?**

MTN-017 enrolled 195 MSM and transgender women. Of these, 23 participants (or 12 percent) were transgender women. The average age of participants enrolled into the study was 31.

#### **13. Why were only MSM and transgender women included in MTN-017?**

At this stage, to find out if rectal microbicides are safe and acceptable, MTN-017 focused on enrolling populations at greatest risk for HIV from condomless anal sex – MSM and transgender women. Importantly, however, non-transgender women who practice anal sex have been included in earlier MTN studies or rectal microbicides to ensure products are safe for both men and women, and will continue to be eligible for upcoming studies.

#### **14. How did you measure adherence to the study products during MTN-017?**

Many types of participant self-reported adherence measures were built into MTN-017. Additionally, throughout the study, researchers regularly tested participants' blood to assess the presence of drug – a determinant of whether they were using their assigned study products. Testing was conducted every four weeks and results were shared with participants as part of their ongoing adherence counseling sessions.

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

MTN-017 was designed according to stringent ethical and scientific guidelines with numerous measures to protect the safety and well-being of participants. As with all NIH-funded studies, MTN-017 incorporated a multi-tiered safety review process and was conducted with oversight from regulatory and research authorities. Before study activation, the protocol underwent extensive and rigorous review by NIAID, the U.S. Food and Drug Administration, institutional review boards (IRBs), and received approval by in-country regulatory and ethics bodies for each of the clinical trial sites before it was implemented. IRBs ensure that studies are scientifically valid and ethically conducted and provide oversight throughout the duration of a trial.

#### **16. How did MTN consult community members before launching MTN-017?**

MTN subscribes to the Good Participatory Practice Guidelines for HIV prevention research, developed by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and AVAC, that address the importance of effective communications and meaningful community engagement for the successful and ethical conduct of HIV prevention trials. For MTN-017, face-to-face consultations were conducted in all of the countries with clinical sites for the study. The meetings, planned in close partnership with the sites and local community member and advocacy organizations, addressed questions and concerns about the protocol and solicited feedback that led to changes in the protocol's design and implementation plan.

-more-

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

Written informed consent was obtained from each participant prior to screening and enrollment in MTN-017. The process ensured 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.

**18. What are next steps after MTN-017?**

Data is still being analyzed from MTN-017 to determine how much drug was absorbed in blood, rectal fluid and tissue, and whether the gel caused any changes in cells or tissue. The availability of this data will help guide the development of next steps after MTN-017.

In the meantime, researchers have developed a Phase I safety study to look at whether an antiretroviral drug called dapivirine is safe as a rectal gel. This study, MTN-026/IPM 038, will include about 30 men and women in the U.S. and Thailand. Researchers are interested in the potential of dapivirine as a potential rectal microbicide because it's a more potent drug than tenofovir and has been studied extensively as a vaginal ring for HIV prevention in women.

**19. Are there any other studies looking at rectal microbicides?**

In addition to exploring the safety of the reduced glycerin formulation of tenofovir gel, researchers are working on the development of products designed specifically for use in the rectum. Two Phase I studies, CHARM-01 and CHARM-02, comparing the safety, acceptability and distribution of three formulations of tenofovir gel – the vaginal formulation, the reduced glycerin formulation and a rectal-specific formulation of tenofovir have been completed. Another recently completed study, CHARM-03, comparing the safety, acceptability and distribution of maraviroc gel to oral maraviroc, is expecting results later in 2016. These studies, funded by the NIH, are being led by the Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program based at the University of Pittsburgh.

Other research-based programs, such as DREAM (Delivery of Rectal Enema as Microbicide), which is exploring the delivery of tenofovir as a single dose enema, and PREVENT (Griffithsin-based Rectal Microbicides for Prevention of Viral Entry), which is addressing the need for a non-ARV based rectal microbicide, are also underway. Both DREAM and PREVENT are funded by the NIH.

# # #

More information and materials about [MTN-017](http://www.mtnstopshiv.org/news/studies/mtn017) and rectal microbicides are available at <http://www.mtnstopshiv.org/news/studies/mtn017>.

24-February-2016