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QUESTIONS AND ANSWERS

MTN-014
Phase I Crossover Trial Evaluating Reduced Glycerin Tenofovir Gel in the Rectum and Vagina in Women

1. What was the aim of MTN-014?
MTN-014 was a Phase I study evaluating whether the active drug contained in a reduced glycerin formulation of tenofovir gel is transferred to the rectum when applied in the vagina and, likewise, whether drug gets into the vagina following the gel's use in the rectum. The study, which enrolled 14 HIV-negative women at a U.S. clinical research site, also assessed how much drug is transferred. The gel in the study contained the antiretroviral (ARV) drug tenofovir, which is commonly used to treat people with HIV in combination with other ARVs. Unlike the original formulation of tenofovir gel, which was developed as a vaginal microbicide, the tenofovir gel used in MTN-014 was formulated to contain less glycerin, an additive found in many gel-like products, to make it more suitable for use in the rectum. MTN-014 is small step in determining whether using the reduced glycerin gel in the vagina has the potential to protect against HIV through anal sex, as well as whether drug is absorbed in the vagina after using the gel rectally at levels that could potentially protect against HIV through vaginal sex.

2. Who conducted and funded the study?
MTN-014 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 U.S. National Institutes of Health (NIH). As co-sponsors of MTN-014, CONRAD of Arlington, Va., and Gilead Sciences of Foster City, Calif., provided the study product. The study was led by Gonasagrie Nair, M.B.Ch.B., of the Centre for the AIDS Programme Research in South Africa (CAPRISA) in Durban and Jessica Justman, M.D., of Columbia University and Bronx-Lebanon Hospital Center in New York.

3. What did the study find?
MTN-014 found that reduced glycerin gel was generally safe to use in both the rectum and vagina. The study also found that when reduced glycerin tenofovir gel was applied into the vagina, a low amount of active drug was distributed to the rectum and, similarly, when the gel was applied into the rectum, a low amount of active drug was distributed to the vagina. While there was evidence of drug transfer, it is still unknown whether these low cross-compartment levels would be high enough to provide protection from HIV.

4. Why is this study important?
MTN-014 is part of a research agenda at the MTN focused on the development and testing of HIV prevention products called microbicides for vaginal and anal sex. Anal sex is a common sexual behavior practiced by both men and women around the globe, and carries a greater HIV risk than unprotected vaginal sex, due in part to the rectum's more fragile lining. Because women using a vaginal microbicide may also be engaging in anal sex, it is important to know whether microbicides used in the vagina can potentially provide protection against HIV through both vaginal and anal sex, whether microbicides used in the rectum will lead to high enough drug levels in the vagina to protect against HIV through vaginal sex. As such, MTN-014 was the first clinical study seeking to understand whether a microbicide (vaginal or rectal) has the potential to offer dual protection. The study, which evaluated safety and drug concentrations of the reduced glycerin formulation of tenofovir gel, is follow-up to a primate study conducted by the International Partnership for Microbicides that showed using tenofovir gel in the vagina resulted in significant levels of tenofovir transferred into the rectum, and vice versa.

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4. When and where was MTN-014 conducted?
The study began enrolling participants in April 2014, and was conducted at Bronx-Lebanon Hospital Center in New York.

5. What are microbicides?
Microbicides are products applied inside the vagina or rectum that are intended to protect against HIV through sex. A microbicide can be formulated in many ways, such as a gel or enema, or as a ring that releases the active ingredient over time. Although microbicides are not yet available for widespread use, researchers are making strides in the development and clinical evaluation of both vaginal and rectal microbicide products. Most microbicides being tested include ARV drugs.

6. Why are microbicides needed?
Worldwide, nearly 37 million people are currently living with HIV. Since the epidemic began in the early1980s, almost 78 million people have been infected and about 39 million people have died of HIV-related causes. HIV most often is spread through unprotected vaginal intercourse, with women twice as likely as men to become infected. Women represent more than half (51 percent) of all people living with HIV worldwide, and account for 60 percent of those with HIV in sub-Saharan Africa. Efforts to promote abstinence, monogamy and the use of male condoms have not been enough to stop the epidemic nor are these approaches practical in many settings. At the same time, according to estimates, 5 to 10 percent of the world's population engages in anal sex.

While condoms are an effective method to prevent HIV infection through vaginal and anal sex, many people can't or don't want to use them every time they have sex. Similarly, pre-exposure prophylaxis (PrEP) – an HIV prevention strategy in which people take a pill called Truvada® daily to prevent infection – has been shown to be highly effective, however, not all at risk individuals may be willing and able to access it. (Currently, only a handful of countries have approved Truvada for use as PrEP.) Just as there are multiple contraception options for women who choose to prevent pregnancy, a microbicide could give people an additional choice for HIV prevention.

7. What product was studied in MTN-014?
The product tested in MTN-014 is a reduced glycerin formulation of tenofovir gel, a product that was tested for safety and acceptability as a rectal microbicide in a Phase II study called MTN-017. It differs from the formulation of tenofovir gel that was tested as a vaginal microbicide in VOICE and FACTS 001. The tenofovir gel that is being tested in MTN-014 contains the same amount of the active ingredient – tenofovir – but has less glycerin than the original tenofovir gel formulation developed for vaginal use to make it more suitable for use in the rectum.

8. What is known about tenofovir gel and how did the reduced glycerin formulation come about?
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 conducted a study, called RMP-02/MTN-006, of the vaginal gel used rectally, and found it was generally safe but also caused unpleasant gastrointestinal side effects in study participants. 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, and was subsequently tested in a phase II study called MTN-017, which enrolled 195 men who have sex with men (MSM) and transgender women at trial sites in Peru, South Africa, Thailand and the United States, including Puerto Rico. Results of MTN-017, announced in early 2016, indicated the gel was safe, and most acceptable to participants when used before and after sex compared to daily use.

9. Why was the reduced glycerin formulation of tenofovir gel being evaluated in MTN-014?
The reduced glycerin formulation of tenofovir gel is more amenable for use in the rectum than vaginal formulation, according to an earlier MTN-led study called MTN-007, which found the reformulated gel was safe and acceptable to men and women who used it rectally. MTN-007 was follow-up to a study called RMP-02/MTN-006 that found the original vaginal formulation caused unpleasant side effects when used in the rectum. Since the gel in MTN-014 was being used in both the rectum and the vagina, researchers elected to use the "rectal friendly" formulation.

10. How was MTN-014 designed?
MTN-014 was Phase I study that enrolled 14 HIV-negative women to evaluate the safety and drug absorption of a reduced glycerin formulation of tenofovir in the vagina and rectum. Participants were randomly assigned into two groups: one group who received a daily vaginal application of the gel for two weeks, followed by a daily rectal application of the gel for two weeks, after a six-week break between regimens. A second group who received a daily rectal application of the gel for two weeks, followed by a daily vaginal application of the gel for two weeks, after a six-week break between regimens. Throughout the study, participants received ongoing HIV risk reduction counseling, free condoms and were tested regularly for HIV. Tests and procedures performed as part of the study determined the clinical safety of the product and how much drug was absorbed in blood and tissue.

11. What was done to ensure the safety of the participants?
MTN-014 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 MTN studies, MTN-014 incorporated a multi-tiered safety review process to ensure that participants are monitored closely and the study team could respond to occurrences in a timely manner. The study was also conducted with oversight from regulatory and research authorities. The protocol underwent extensive and rigorous review by NIAID, the U.S. Food and Drug Administration and the site's institutional review board prior to it being implemented.

12. Did participants in the study provide informed consent?
Written informed consent was obtained from each study participant prior to screening and enrollment in MTN-014. 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.

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Information about other MTN studies can be found at http://www.mtnstopshiv.org/news

15-August-2016