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BACKGROUNDER

MTN-017
Phase II Safety and Acceptability Study of Tenofovir Gel Reformulated for Rectal Use

Study Overview

MTN-017 was a Phase II study that evaluated whether a reduced glycerin formulation of tenofovir gel is safe and acceptable as a rectal microbicide. The study 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. Developed originally as a vaginal microbicide, the gel used in MTN-017 contained the antiretroviral (ARV) drug tenofovir, which is commonly used to treat people with HIV in combination with other ARVs. In MTN-017, tenofovir gel 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 sex, and compared to oral Truvada®.

MTN-017 was a study of the Microbicide Trials Network (MTN), a clinical trials network established and funded in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the National Institute of Mental Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all part of the National Institutes of Health. 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.

As the first extended safety study of a rectal microbicide, MTN-017, which began in September 2013 and completed follow-up of participants in May 2015, is part of a research agenda at the MTN focused on the development of HIV prevention products for men and women who engage in unprotected anal sex, a major risk factor for HIV infection.

What the Study Found

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 anal 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.

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Why this Study is Important

Microbicides are products applied inside the vagina or rectum that are intended to protect against HIV infection through condomless sex. Products currently being tested in clinical trials contain antiretroviral (ARV) drugs, many of which are commonly used to treat people with HIV. Although the majority of microbicide research has focused on products to prevent HIV infection associated with vaginal sex, research also is addressing the need for rectal microbicides. Anal sex is a common sexual behavior practiced by both men and women around the world. According to some estimates, the risk of becoming infected with HIV during anal sex is 20 times greater than vaginal sex because the rectal lining is thinner and more fragile than the vaginal lining.

As an important first step in the development of rectal microbicides, researchers are exploring whether microbicides originally formulated as vaginal gels are safe and effective to use in the rectum. One such product is tenofovir gel, which although found safe and effective in reducing the risk of HIV infection in women who used it before and after vaginal sex in a study called CAPRISA 004, was found safe, but not effective in the MTN's VOICE (Vaginal and Oral Interventions to Control the Epidemic) study, which tested daily use of the gel, and in FACTS 001, which tested the same regimen as CAPRISA 004 (before and after sex). In both VOICE and FACTS 001, adherence to product use was low.

MTN researchers also have been conducting studies of tenofovir gel as a rectal microbicide. Unlike studies of the gel as a vaginal microbicide, this research is focused on a population of individuals who are at high risk of acquiring HIV through unprotected anal sex. Because tenofovir gel may work differently against HIV in rectal tissue, researchers want to learn whether it is safe to use rectally and could potentially reduce the risk of HIV infection through anal sex.

The gel evaluated in MTN-017 was not the original formulation of tenofovir gel used in the effectiveness trials involving women. An earlier study of the vaginal gel used rectally (RMP-02/MTN-006) found it was generally safe but that it also caused unwanted gastrointestinal side effects. Researchers then reduced the gel's glycerin content to make it more amenable for rectal use and found this formulation to be safe and acceptable in the MTN-007 Phase 1 rectal safety study. MTN-017 was an international multi-site follow-up study to MTN-007.

How the Study was Designed

MTN-017 was a Phase II trial designed to evaluate the safety, participant acceptability and drug absorption of a reduced glycerin formulation of tenofovir gel used daily and used before and after sex, as well as daily use of the oral tablet Truvada. The study enrolled 195 HIV-negative MSM and transgender women. Participants followed each of the three study regimens (reduced glycerin tenofovir gel used both daily and before and after sex; and Truvada tablets taken daily) for eight weeks, with a weeklong break between regimens when no product was used. 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 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 if it was found to protect against HIV infection. During the course of MTN-017, 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 adherence counseling sessions on product use. Forthcoming analyses from MTN-017 will provide information on drug absorption and any changes in cells or tissues associated with the use of study products.

The Products Being Studied

Reduced glycerin tenofovir gel:
Tenofovir, the active ingredient in the gel, belongs to a class of ARVs called nucleotide reverse transcriptase inhibitors (NRTIs). Each dose of gel contains approximately 40 mg of active drug. Tenofovir gel was developed by Gilead Sciences, Inc., of Foster City, Calif., which assigned a royalty-free license for tenofovir gel to CONRAD and the International Partnership for Microbicides of Silver Spring, Md. in 2006. The reduced-glycerin formulation of tenofovir gel being tested in MTN-017 was developed by CONRAD in 2011. Clinical input and study supplies of reduced glycerin tenofovir gel were provided by CONRAD, with funding from USAID.

Truvada:
Truvada is the brand name for an oral tablet that contains tenofovir and the nucleoside emtricitabine. Truvada is approved for use in combination with other ARVs for the treatment of HIV. In 2012, the U.S. Food and Drug Administration approved daily use of Truvada for HIV prevention, based in part on a large-scale Phase III study called iPrEx that enrolled MSM and transgender women. Truvada is a registered trademark of Gilead Sciences, Inc.

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More information and materials about MTN-017 and rectal microbicides are available at http://www.mtnstopshiv.org/news/studies/mtn017.

24-February-2016