CONTACT: **Clare Collins**
+1- 412-641-7299
+1- 412-770-8643 (mobile)
collxc@upmc.edu

Rectal Formulation of Tenofovir Gel Found Safe and Acceptable in Early Phase Clinical Study

Follow-up study planned to further assess gel's potential as a rectal microbicide to prevent HIV

SEATTLE, March 5, 2012 – A gel formulation of the antiretroviral drug tenofovir designed specifically for rectal use was found safe and acceptable, according to a Phase I clinical study led by the U.S. National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN), and presented today at the 19th Conference on Retroviruses and Opportunistic Infections (CROI). The results of the study, which included HIV-negative men and women who used the gel rectally once a day for one week, serve as an important step toward the development and testing of a rectal microbicide to prevent HIV from anal sex.

Microbicides, products applied on the inside of the rectum or vagina, are being studied as an approach for preventing or reducing the sexual transmission of HIV. The majority of microbicide research has focused on products to prevent HIV through vaginal sex, yet the risk of becoming infected with HIV from unprotected anal sex may be 20 times greater than unprotected vaginal sex. Developed as a vaginal microbicide, tenofovir gel was reformulated with less glycerin, a common additive found in many gel-like products, in the hopes of making it more appropriate for rectal use.

The study, known as MTN-007, began in October 2010 and enrolled 65 men and women at three sites – the University of Pittsburgh, University of Alabama at Birmingham and Fenway Health in Boston. It is a follow-up trial to an earlier study, RMP-02/MTN-006, which assessed the rectal use of the vaginal formulation of tenofovir gel. That study found the gel produced a significant antiviral effect when used in the rectum, but gastrointestinal side effects were problematic.

In MTN-007, study participants were randomly assigned to one of four study groups. Three of these groups were assigned to use one of the following products for a one-week period: a rectal formulation of tenofovir gel; a placebo gel containing no active ingredient; or a gel containing the spermicide nonoxynol-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.

Study results indicated no significant differences in side effects among the three gel groups. Eighty percent of participants reported only minor side effects related to the use of study products, while 18 percent reported moderate side effects. (Two study participants reported severe adverse events, but they were not deemed to be related to use of the study products.) Participants' adherence to the use of their 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 rectal formulation of

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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, and noted changes in the activation of some genes in the tenofovir gel group, which they are continuing to evaluate to understand more fully.

"These findings tell us that the 'rectal-friendly' version of tenofovir gel was much better tolerated than the vaginal formulation of the gel when used in the rectum," said Ian McGowan, M.D., Ph.D., co-principal investigator of the MTN and professor of medicine, Division of Gastroenterology, Hepatology and Nutrition and Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine. "We are very encouraged that the rectal gel was quite safe, and that most people who used it said they would be willing to use it in the future."

As follow-up to MTN-007, researchers are now planning a Phase II, multi-site trial called MTN-017 that will involve186 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: rectal tenofovir gel used daily, rectal tenofovir gel used before and after anal sex, and daily use of the antiretroviral 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.

In addition to Dr. McGowan, other authors of MTN-007 are Craig Hoesley, M.D., University of Alabama; Ross Cranston, M.D., University of Pittsburgh; Philip Andrew, FHI 360; Laura Janocko, Ph.D., MTN and Magee-Womens Research Institute; James Dai, Fred Hutchinson Cancer Research Center; Alex Carballo-Dieguez, Ph.D., Columbia University; Ratiya Kunjara Na Ayudhya, BSMT, MTN; Jeanna Piper, M.D., Division of AIDS, National Institute of Allergy and Infectious Diseases; and Ken Mayer, M.D., Fenway Health.

MTN-007 is funded by the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) and the National Institute of Mental Health, both components of the NIH. Tenofovir gel was developed by Gilead Sciences, Inc., of Foster City, Calif., which assigned the rights for tenofovir gel to CONRAD, of Arlington, Va ., and the International Partnership for Microbicides of Silver Spring, Md., in December 2006.

The reduced glycerin formulation of tenofovir gel that was evaluated in MTN-007 is not the same formulation developed for vaginal use. The vaginal formulation of tenofovir gel 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.

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About the Microbicide Trials Network

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners who are devoted to preventing or reducing the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally.

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