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Tenofovir Gel Provides High Level of Protection Against HIV in Rectal Tissue

Strongest effect seen in tissue taken from participants after one week of use

BOSTON, Feb. 28, 2011 – A gel developed to protect against HIV during vaginal sex produced a strong antiviral effect when used in the rectum, according to an early-phase study presented today at the 18th Conference on Retroviruses and Opportunistic Infections (CROI). The results, based on rectal tissue biopsies sampled from HIV-negative men and women who used the product daily for one week, provide the first-ever evidence that tenofovir gel could help reduce the risk of HIV from anal sex, even though the vaginal gel formulation may not be optimal for rectal use.

Tenofovir gel was not especially well-liked by a majority of men and women in the study, yet most reported they would be likely to use the gel if it became available in the future as a method for preventing HIV. Although the study found use of the gel generally safe, side effects were problematic to a few study participants. In hopes of making tenofovir gel more acceptable to for rectal use, researchers have since modified the gel and are now testing it in another study.

"We are very encouraged about these findings that indicate applying tenofovir gel topically to the rectum could be a promising approach to HIV prevention," said Peter Anton, M.D., professor of medicine and director of the Center for Prevention Research at the University of California, Los Angeles (UCLA), who led the study with Ian McGowan, M.D., Ph.D., co-principal investigator of the Microbicide Trials Network (MTN) and professor of medicine at the University of Pittsburgh.

"These are early results, but help set the stage for current and future trials of rectal microbicides and the development of a rectal-specific formulation of tenofovir gel," added Dr. McGowan, who is leading the second study of the new gel formulation.

Microbicides, products applied on the inside of the rectum or vagina, are being designed and tested to help prevent or reduce the sexual transmission of HIV or other sexually transmitted infections. The majority of microbicide research thus far has focused on products to prevent HIV during vaginal sex. Yet, the risk of becoming infected with HIV from unprotected anal sex may be at least 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, making it easier for the virus to reach cells to infect.

The study, known as RMP-02/MTN-006, is the first clinical trial of tenofovir gel for rectal use. Last year, tenofovir gel was shown in a trial called CAPRISA 004 to reduce the risk of HIV infection in women who used it before and after vaginal sex.

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Conducted at UCLA and the University of Pittsburgh, RMP-02/MTN-006 tested two products – tenofovir gel and oral tenofovir – in 18 sexually abstinent, HIV-negative men and women. Oral tenofovir, an antiretroviral (ARV) tablet commonly used to treat people with HIV in combination with other ARVs, is being explored as a means to prevent infection in people who are HIV-negative through an approach called pre-exposure prophylaxis, or PrEP.

The trial directly compared the anti-HIV activity of a single dose of oral tenofovir to a single dose of rectally-applied tenofovir gel. This was followed by six days of at-home dosing of tenofovir gel or a placebo gel, with the last and seventh dose given in the clinic. A novel approach was used to determine whether any actual protection was provided by the drug given in the different regimens – single oral, single gel and seven-day gel (or placebo) – in which small biopsies were taken from the rectal lining of the participants using a standard clinical procedure called sigmoidoscopy. The tissue samples were then sent directly to the laboratory where they were exposed to HIV to determine how well study products protected the tissue from infection.

The researchers found that HIV was significantly inhibited in tissue samples from participants who used tenofovir gel daily for one week compared to tissue from participants who used the placebo gel. While a slight anti-viral effect was noted in tissue from participants who received a single dose of tenofovir gel, the finding was not statistically significant. The single dose of oral tenofovir did not provide any protection against HIV in rectal tissue samples.

“These kinds of efforts early in the development phase of rectal microbicides can give us insight into a particular product’s potential efficacy, which enables us to better design and hasten the pace of future clinical trials,” said Dr. Anton.

According to self-reports, only 25 percent of men and women who had used the tenofovir gel said they liked it. However, when asked whether they would consider using the product in the future, 75 percent of these participants reported a high likelihood of future use. Two of the 12 participants who received tenofovir gel reported severe gastrointestinal side effects, including diarrhea and lower abdominal cramps.

“These results tell us that tenofovir gel was relatively safe to use in the rectum for most participants, but we need to address side effects to make it more acceptable to use,” said Dr. Anton, who reported the findings at CROI. “Even though three-quarters of the participants reported they didn’t like the gel, we are very encouraged that the majority would consider using such a product in the future.”

Another study, MTN-007, now underway is using a formulation of tenofovir gel with less glycerin, a common additive found in many gel-like products, in the hope that this will make it better tolerated when used in the rectum. Laboratory tests of the reformulated gel suggest it is just as effective as the original formulation but less irritating to the epithelium – the layer of cells that serves as a protective barrier inside the rectum. The study began in October 2010 and is enrolling 60 men and women at three sites – University of Pittsburgh, University of Alabama at Birmingham and Fenway Health in Boston.

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In addition to Drs. Anton and McGowan, other authors of RMP-02/MTN-006 are Ross Cranston, M.D., University of Pittsburgh; Alex Carballo-Dieguez, Ph.D., Columbia University; Angela Kashuba, PharmD, University of North Carolina; Elena Khanukhova, UCLA; Julie Elliott, UCLA; Laura Janocko, Ph.D., MTN and Magee-Womens Research Institute; William Cumberland, Ph.D., UCLA; and Christine Mauck, M.D., M.P.H., CONRAD.

RMP-02/MTN-006 was a collaboration between the Microbicide Development Program at UCLA and the MTN. UCLA's Microbicide Development Program is funded by the Division of AIDS Integrated Preclinical/Clinical Program for HIV Topical Microbicides at the National Institute of Allergy and Infectious Diseases. The study products were developed by Gilead Sciences, Inc., of Foster City, Calif., which assigned the rights for tenofovir gel to the International Partnership for Microbicides of Silver Spring, Md., and CONRAD, of Arlington, Va., in December 2006. Gilead Sciences and CONRAD provided the study products free of charge.

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Additional information about the study and rectal microbicides is available at http://www.mtnstopshiv.org/news/studies/mtn006.

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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