Promising HIV prevention microbicide tenofovir gel being tested for safety of rectal use

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Tenofovir gel, a vaginal microbicide that has shown promise for preventing HIV through vaginal sex, is being tested in a new trial looking at its safety and acceptability when used rectally. The results of the study, being led by the U.S. National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN), will help determine if the gel should be evaluated further for its potential to prevent HIV among both men and women who engage in receptive anal intercourse.

While condoms are generally effective for protecting against HIV and other sexually transmitted infections, most acts of anal sex go unprotected. Moreover, the risk of acquiring HIV through unprotected anal sex is at least 20 times greater than unprotected vaginal sex and increases if other infections are already present in the rectal lining.

Microbicides – substances applied topically on the inside of the rectum or vagina – could potentially help prevent the rectal transmission of HIV, although considerably more research has been conducted looking at microbicides for preventing transmission of HIV through vaginal sex. Tenofovir gel, for example, is a candidate microbicide specifically developed to prevent vaginal transmission of HIV.

The new study, known as MTN-007, is the second early phase trial evaluating the rectal safety of the vaginal product. It also comes on the heels of CAPRISA 004, a Phase IIb study conducted in South Africa

that found tenofovir gel significantly reduced the risk of HIV among at-risk women who were instructed to use the gel before and after vaginal sex. In an ongoing, large-scale effectiveness trial called VOICE – Vaginal and Oral Interventions to Control the Epidemic, the MTN is testing daily use of tenofovir gel in African women, with results expected in 2013.

"We can't just assume that a product developed for use as a vaginal microbicide will be equally safe or effective when used in the rectum for preventing HIV transmitted through receptive anal intercourse. So, while VOICE or other trials may very well prove tenofovir gel is highly effective for preventing vaginal transmission, we need to understand much more about what happens to the cells and tissue when tenofovir gel is used rectally before considering a trial testing its effectiveness against HIV. That's why this study is so important," said Ian McGowan, M.D., Ph.D., professor of medicine in the division of gastroenterology, hepatology and nutrition at the University of Pittsburgh School of Medicine and co-principal investigator of the MTN.

MTN-007 aims to determine if rectal use of tenofovir gel is safe, and in particular, does not cause cells in the rectum to become more vulnerable to HIV than they already are. The study will also help to understand whether men and women would be willing to use a rectal microbicide. In addition, researchers are hoping to identify biological markers – warning flags in the way of specific proteins or biochemical activity –that can be used to better assess the potential safety of different candidate microbicides before they are tested in humans.

The study will enroll 60 men and women across three MTN-affiliated U.S. sites: the University of Pittsburgh, University of Alabama at Birmingham and Fenway Health in Boston.

"Unprotected anal sex is a key driver of the HIV epidemic in this

country and elsewhere in the world, and the practice is not confined to gay men. Significant numbers of women are also engaging in anal sex. If we don't find a method for preventing this mode of HIV transmission, we'll be hard pressed to make a dent in the global toll of HIV/AIDS," noted Kenneth Mayer, M.D., professor of medicine and community health at Brown University in Providence, R.I., and medical research director, the Fenway Institute of Fenway Health, who is helping lead MTN-007 with Dr. McGowan.

In the United States alone, receptive anal intercourse is practiced in up to 90 percent of gay and other men who have sex with men, according to Chicago-based International Rectal Microbicides Advocates. U.S. estimates and surveys in the United Kingdom indicate that between 10 to 35 percent of heterosexual women have engaged in anal sex at least once. Global estimates suggest 5 to 10 percent of sexually active women are having anal sex. In 2009, there were more than 33 million people living with HIV. The number of new infections continues to outstrip advances in treatment: For every two people who begin treatment, five are newly infected. Men who have sex with men account for at least half of all new infections in the developed world; in the United States, this group represents nearly 60 percent of those newly infected, according to recent reports.

Tenofovir gel contains the same active ingredient as the anti-HIV drug tenofovir, which is commonly used in combination with other ARVs in the treatment of HIV. Tenofovir belongs to a class of ARVs called nucleotide/nucleoside 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 is known by the brand name Viread® .

Laboratory and non-clinical studies of tenofovir gel have shown its potential for preventing HIV infection of target cells in vaginal and

cervical tissue. Clinical safety studies have found it is well-tolerated and safe in both HIV-positive and HIV-negative women, and an expanded safety and acceptability trial called HPTN 059 found daily vaginal use of the gel over six months safe and well-tolerated by sexually active HIV-negative women. More recently, the CAPRISA 004 study found tenofovir gel reduced the risk of HIV by 39 percent among women who used it before and after sex compared to women who used a placebo gel.

Less is known about tenofovir gel used rectally. Laboratory and animal studies involving rectal application of tenofovir gel have suggested it safe for testing in humans. In fact, MTN researchers have just completed the first Phase I trial, called RMP-02/MTN-006, in collaboration with the Microbicide Development Program at the University of California, Los Angeles (UCLA).

While results of RMP-02/MTN-006 are not expected until early 2011, researchers have already recommended modifications to the gel's formulation. MTN-007 is evaluating the new formulation, which still contains the same amount of active drug – 1% percent tenofovir – but has a lower concentration of glycerin (an additive found in many types of products) to make it more amenable for rectal use.

MTN-007 was designed according to the most rigorous international medical practice and ethical standards and includes numerous measures, beginning at the site level, intended to protect the safety and well-being of participants. As with all MTN studies, MTN-007 incorporates a multi-tiered safety review process that includes strict national and international standards and procedures for monitoring and reporting. The protocol underwent extensive and rigorous review by the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS), the U.S. Food and Drug Administration and the institutional review boards (IRBs) at each participating institution.

More information: Additional information about MTN-007 is available at www.mtnstopshiv.org/news/studies/mtn007

Provided by Microbicide Trials Network