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**HIV PREVENTION RESEARCHERS TO COMPARE COMMON ARV
AS A PILL AND VAGINAL GEL IN UNIQUE STUDY**

Getting inside the cells and minds of women: trial looks at drug absorption and adherence of different formulations of tenofovir

PITTSBURGH, July 9 , 2008 – In battle with an epidemic that has outpaced nearly all efforts to contain it, researchers are turning to strategies centered on the same antiretroviral (ARV) drugs that have been used successfully to treat HIV in hopes they will be as effective a stronghold for preventing the virus. For women, who make up nearly half of the 33 million people living with HIV/AIDS worldwide, the ARV tenofovir has particular promise because it can be formulated as either an oral tablet or a vaginal gel to be used daily. But ARV-based prevention approaches are not without scientific and practical challenges. The Microbicide Trials Network (MTN) is taking aim at among the most pressing of these challenges in the first clinical trial to directly compare the tablet and vaginal gel formulations of tenofovir.

In part because certain cells in the vagina are easy targets for the virus, women are more than twice as likely as their male partners to acquire HIV through sexual intercourse. As such, the clinical study, known as MTN-001, seeks to understand how each formulation of tenofovir works in these infection-prone cells, information that will help researchers determine the optimal doses needed to achieve drug concentrations most likely to prevent HIV in women.

MTN-001 also looks to understand the factors that influence women's preferences for one daily approach over another, because not even the best approach will be effective if women don't use it.

MTN-001 is a Phase II study designed to evaluate women's adherence to and acceptance of three daily regimens of tenofovir – tenofovir gel, tenofovir disoproxil fumarate tablets and the two together – and the pharmacokinetics, or how the drug is absorbed by and distributed in the body over time, of each regimen. The study will enroll 144 sexually active HIV-negative women who will follow all three regimens, each for six weeks with one week between when no study product is used. In the United States, Case Western Reserve University in Cleveland and the University of Pittsburgh are now beginning to screen potential participants.

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Additional sites, including in South Africa and Uganda, will also be participating in the study, which is funded by the National Institute of Allergy and Infectious Diseases, a component of the U.S. National Institutes of Health. Researchers expect to complete the study in 2009.

“Being able to capture in one study, and in all women, information about adherence, acceptability, and pharmacokinetics will help us answer critical questions about the three regimens more efficiently and with greater confidence than we could in separate studies. We will be able to more clearly discern the differences between each formulation, including at the cellular level, and get a more accurate reading on women’s preferences and adherence patterns,” said Craig W. Hendrix, M.D., associate professor of medicine, Division of Clinical Pharmacology, Johns Hopkins University School of Medicine in Baltimore, Maryland, who, as MTN-001 protocol chair, is leading the multi-site study.

In its tablet form, tenofovir disoproxil fumarate, known by the brand name Viread, is a mainstay of one of the most widely used regimens for treating HIV. The active ingredient in 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 make a copy of its genetic material – an essential step for the virus to multiply and infect other cells. Tenofovir is being evaluated in clinical trials to determine if this first-line treatment can also prevent HIV when used every day by people who are HIV-negative, an approach known as pre-exposure prophylaxis, or PrEP. As a vaginal gel, tenofovir is among a newer class of candidate microbicides with specific activity against HIV. Microbicides are substances designed to prevent or reduce the sexual transmission of HIV when applied topically on the inside of the vagina or rectum.

In MTN-001, researchers will assess women’s adherence to each of the three tenofovir regimens through structured interviews and questionnaires. Questions will focus on their overall experience using the product regimen, asking how sexual activity may have changed, how well the regimen was adhered to and why the product was not always used— did they forget, dislike using the product or give the tablet or gel to other people? A small number of participants from each site also will take part in in-depth interviews at the end of the 21-week study so researchers can collect more detailed information, including about women’s adherence to and preferences between oral and vaginal formulations and between single and dual-use regimens.

Researchers will conduct pharmacokinetic studies of blood plasma (the liquid component of blood), white blood cells, vaginal tissue and cells taken from inside the vagina. For instance, at each mid-study period, participants will provide a small amount of blood that will be used to determine how much tenofovir is circulating in the blood. At sites with laboratory capacity, blood will also be used to determine if tenofovir is present inside blood cells and, if so, whether the drug is in its active or inactive state. Such studies are important because tenofovir is not effective against HIV unless it has been activated by the addition of two molecules called phosphates, much like a lamp can only be turned on if it has both a light bulb and switch.

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At the end of each study period, participants will follow their assigned regimen at the clinic, and similar tests will be conducted of both blood and vaginal fluid. The 48 women enrolled at the two U.S. sites will be involved in more intensive assessments of each approach whereby researchers will look at blood and tissue samples at different periods of time after taking the drug.

“Information gathered in these intensive studies, plus information from other trials, will help us build a picture showing the relationship between plasma blood levels of drug and the amount of activated drug inside the HIV target cells of vaginal tissue. It may be possible to determine the concentration of drug inside vaginal cells with a simple blood test, and then extrapolate the required drug dose to reach the target concentration for preventing HIV,” explained Dr. Hendrix.

MTN-001 is part of a portfolio of trials evaluating the oral and gel forms of tenofovir. Recently, MTN researchers launched the first trial in pregnant women, seeking to understand the extent that pregnancy affects how the body absorbs the active drug in the gel and whether the drug can be transferred to the fetus. The VOICE Study (Vaginal and Oral Interventions to Control the Epidemic), a trial involving 4,300 women that is expected to begin early 2009, will be the first effectiveness trial evaluating in the same study both a microbicide (tenofovir gel) and PrEP (oral tenofovir and oral Truvada, a combination of tenofovir disoproxil fumarate and another antiretroviral agent called emtricitabine).

Both oral and vaginal gel formulations of tenofovir were developed by Gilead Sciences, Inc., of Foster City, California, USA, which assigned a royalty-free license for the topical gel to the International Partnership for Microbicides of Silver Spring, Maryland, and CONRAD, of Arlington, Virginia, in December 2006. For MTN-001, Gilead is providing tenofovir tablets free of charge, and CONRAD is providing both the gel and gel applicators at no cost.

Other microbicide products have been or are currently being tested in clinical trials, although none is yet approved or available for use by women.

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More information about MTN-001 and other MTN studies can be found at <http://www.mtnstopshiv.org/news>.

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH). The MTN brings together international investigators, community and industry partners who are devoted to reducing the sexual transmission of HIV through the development and evaluation of microbicides, working within a unique infrastructure specifically designed to facilitate research required to support licensure of topical microbicide products for widespread use. Based at the University of Pittsburgh and Magee-Womens Research Institute, MTN’s principal investigator is Sharon Hillier, Ph.D. MTN’s core operations are supported by a network laboratory at the University of Pittsburgh, a statistical and data management center housed within the Statistical Center for HIV/AIDS Research & Prevention at the Fred Hutchinson Cancer Research Center, and Family Health International, a global organization with expertise conducting clinical protocols. It receives its funding from three NIH institutes: NIAID, the National Institute of Mental Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.