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Tenofovir Gel Wins Out in Drug Absorption Study, but HIV Prevention Trials Tell a Different Story

Results reported in *PLOS ONE* indicate drug distribution alone does not influence effectiveness

PITTSBURGH, Jan. 30, 2013 –A novel head-to-head study looking at differences in how the antiretroviral (ARV) drug tenofovir gets absorbed in the body as either an oral tablet or a vaginal gel found tenofovir gel can achieve substantially higher concentrations of active drug in vaginal tissue than the oral tablet, suggesting that tenofovir gel should be highly effective in protecting women against HIV transmitted through vaginal sex. Yet, as unequivocal as the study's results may be, they have not been borne out in HIV prevention trials to date, leading the researchers to believe that effectiveness of tenofovir-based products depends on factors other than ARV tissue concentrations alone.

According to the study's findings published Jan. 30 in the online journal *PLOS ONE*, daily use of tenofovir gel was associated with vaginal tissue drug levels more than 130-times that of the oral tablet. The study, known as MTN-001, was conducted by the National Institutes of Health (NIH)-funded Microbicide Trials Network.

The considerable difference between the two formulations not only suggests tenofovir gel should be effective, but that it should be significantly more effective than oral tenofovir when used by women to prevent HIV infection. Yet, tenofovir gel was only moderately effective in one clinical trial and not at all effective in another. In contrast, several trials of daily use of oral tenofovir alone or in combination with another ARV called emtricitabine showed levels of effectiveness that were much higher than MTN-001 data would have predicted.

"The discordance between what we found in terms of drug concentration in vaginal tissue and the expected and actual outcomes of trials to date raises a number of questions warranting further investigation. Clearly, other factors are at play," commented Craig Hendrix, M.D., a professor of medicine and pharmacology and molecular sciences in the Division of Clinical Pharmacology, Johns Hopkins University School of Medicine in Baltimore, Md.,who led MTN-001.

"Perhaps vaginal tissue concentration is not as relevant a predictor of success as we thought. Or, maybe the women in MTN-001 used the products as directed more consistently compared to women in the clinical trials of tenofovir gel. Or, if not due to product adherence, might there be some other factor associated with the gel formulation or vaginal gel delivery of tenofovir that affects its efficacy," he added.

MTN-001 was designed to examine differences in drug absorption, distribution, and elimination (pharmacokinetics) as well as women's preferences for and adherence to oral tenofovir and tenofovir gel. The *PLOS ONE* paper summarizes the study's primary pharmacokinetic results.

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The study enrolled 144 healthy, HIV-uninfected women evenly divided between four sites in the U.S. and three in Uganda and South Africa, who used each product daily for six weeks, as well as the two together, allowing for direct comparisons between the oral tablet and vaginal gel formulations of tenofovir. At the end of each six-week period, researchers collected blood, peripheral blood mononuclear cells (PBMC), vaginal tissue, vaginal fluid and rectal fluid. Laboratory studies were then conducted that looked for the presence of drug in both its active and inactive form.

In addition to finding that use of the gel resulted in more than 130-times greater concentrations of active drug (tenofovir diphosphate) in vaginal tissue, the study also found tenofovir gel was associated with a 56-fold lower systemic (blood) concentration of active drug compared to the oral tablet.

"Considered in isolation, this finding of higher vaginal tissue concentrations with vaginal dosing is highly suggestive that gel would provide substantially greater protection against HIV and also be a regimen more tolerant of missed doses or planned intermittent dosing than oral dosing. But remember, that we never intended MTN-001 to be viewed in isolation. Our data is more meaningful in the context of what we know from clinical trial experience," Dr. Hendrix said.

MTN-001 was designed as a complementary study to MTN's large-scale prevention trial, VOICE, and to provide added insight for better understanding VOICE results as well as results of other ARV-based prevention trials. VOICE – Vaginal and Oral Interventions to Control the Epidemic –tested the safety and effectiveness of oral tenofovir (also known by the brand name Viread®); Truvada®, an oral tablet that contains both tenofovir and emtricitabine; and tenofovir gel, among 5,029 women in Africa.

In early 2011, when MTN-001 researchers presented preliminary data, VOICE and other HIV prevention trials were still ongoing, and the results of two other tenofovir-based prevention trials – CAPRISA 004 and the iPrEx study, were already known. The CAPRISA 004 study found tenofovir gel was safe and 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, a finding that was considered a major milestone for the field. Likewise, the iPrEx Study, conducted in men who have sex with men (MSM), was the first trial to show daily use of an ARV tablet was effective, with 42 percent fewer HIV infections among those assigned to take Truvada compared to placebo.

"The landscape has since changed, and MTN-001 seems all the more relevant to the field, if not a bit perplexing," commented Dr. Hendrix.

FACTS 001 is an ongoing Phase III trial testing tenofovir gel used before and after sex that hopes to replicate the results of CAPRISA 004. Meanwhile, VOICE stopped testing both tenofovir gel and tenofovir tablets in 2011 after separate routine reviews of study data by an independent group of experts determined that while each was safe, neither was effective in preventing HIV compared to the matched placebos among the women in those groups, who were asked to use their assigned products daily. The results of VOICE, which are expected to be reported at the Conference on Retroviruses and Opportunistic Infections (CROI) in early March, may help to understand why tenofovir gel and oral tenofovir were not effective, as well as determine whether Truvada was safe and effective for protecting against HIV in women.

Truvada, a drug that had already been approved for the treatment of HIV, is now also approved by the U.S. Food and Drug Administration for HIV prevention, a decision that was based largely on the results of two trials in two different populations – the iPrEx study involving MSM and the Partners PrEP Study involving heterosexual men and women in committed relationships with an HIV-infected partner. Partners PrEP, which tested both tenofovir and Truvada, found daily use of Truvada resulted in 75 percent fewer HIV infections among participants in that group compared to participants who took a placebo tablet, and there were 67 percent fewer infections among those who took tenofovir. TDF2, a smaller study in heterosexual men and women also found Truvada effective, with a 62.6 percent reduction in HIV risk compared to placebo. Yet, the FEM-PrEP study, which involved women very similar to VOICE, did not find Truvada effective. For reasons not well understood, many of the women did not follow the daily pill-taking regimen as instructed.

Indeed, even in MTN-001, self-reported adherence was very high (94 percent), with many participants saying they liked both products. Drug serum concentrations, however, indicated that only 64 percent of the women, at best, took the tablets consistently. Interestingly, the women enrolled at the U.S. sites were more adherent to pill taking than the women enrolled in Africa. (Those data and other adherence and acceptability results of MTN-001 were published in *AIDS and Behavior* October of last year.)

Women account for 60 percent of adults with HIV in sub-Saharan Africa, where unprotected heterosexual intercourse is primarily to blame for the region's heavy HIV burden. Young women are especially vulnerable. Efforts to promote abstinence, monogamy and male condom use haven't been enough to stop the HIV epidemic nor are these methods feasible in most settings. There is an urgent need for effective and easy-to-use prevention strategies that women can control themselves.

MTN-001 was funded by the National Institute of Allergy and Infectious Diseases (NIAID), a component of the NIH. The study products were provided by Gilead Sciences, Inc., of Foster City, Calif., which donated the oral tenofovir tablets, and by CONRAD, of Arlington, Va., which donated both the gel and gel applicators. Viread (oral tenofovir) and Truvada are registered trademarks of Gilead Sciences; both drugs are approved for the treatment of HIV when used in combination with other ARVs. In 2006, Gilead assigned a royalty-free license for tenofovir gel to CONRAD and the International Partnership for Microbicides of Silver Spring, Md.

U.S. sites for MTN-001 were: Case Western Reserve University in Cleveland; the University of Pittsburgh; University of Alabama Birmingham (UAB); and Bronx Lebanon Hospital, Columbia University, in New York. African sites were: Makerere University-Johns Hopkins University (MU-JHU) Research Collaboration in Kampala, Uganda; the Umkomaas and Botha's Hill clinical research sites of the Medical Research Council (MRC) of South Africa in Durban.

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For more information about MTN-001 go to http://www.mtnstopshiv.org/news/studies/mtn001. Information about VOICE and other MTN studies can be found at http://www.mtnstopshiv.org/news

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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