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## **FOR IMMEDIATE RELEASE**

### **Vaginal gel with integrase inhibitor shows promise in monkeys**

#### **Research on new drugs for preventing HIV presented at International Microbicides Conference May 22-25**

**PITTSBURGH, May 23** – Researchers testing a vaginal microbicide based on a new type of anti-HIV drug found it provided monkeys significant protection against infection with a virus similar to HIV, according to a study reported at the International Microbicides Conference in Pittsburgh today.

The study is the first of a gel with an integrase inhibitor, one of the latest additions to the arsenal of drugs for the treatment of HIV but just one of the many compounds or drug combinations that researchers are hoping will be a stronghold for HIV prevention. These include different types of antiretrovirals (ARVs) than those currently being evaluated in clinical trials of ARV-based microbicides or oral pre-exposure prophylaxis (PrEP).

Microbicides are substances designed to prevent the sexual transmission of HIV when applied topically on the inside of the rectum or vagina, whereas oral PrEP is an approach involving the use of ARVs drugs by HIV-negative people to reduce their risk of acquiring HIV. PrEP trials are focused on two drugs, tenofovir and Truvada,<sup>®</sup> from a class of ARVs called nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). The roster of ongoing microbicide trials are of gels that contain either tenofovir, dapivirine or UC781. Dapivirine and UC781 are non-nucleoside reverse transcriptase inhibitors, a close cousin to the NRTI class of ARVs.

M2010 runs May 22-25 at Pittsburgh's David L. Lawrence Convention Center. Nearly 1,000 participants from 47 different countries are attending to hear about the latest developments in HIV prevention research. Summaries of some of the studies looking at new drugs and drug combinations are provided below.

#### **Vaginal gel with integrase inhibitor shows promise in monkeys**

An experimental vaginal microbicide gel containing a drug from a class of antiretrovirals (ARVs) not previously examined for use as a topical prevention approach provided significant protection in preventing vaginal transmission of simian/human immunodeficiency virus (SHIV) – a combination of HIV and a related monkey virus – among macaques, reported Charles Dobard, Ph.D., and Walid Heneine, Ph.D., of the U.S. Centers for Disease Control and Prevention. The study is the first of a gel with an integrase inhibitor, and these results support further evaluation of integrase inhibitors to examine whether they can be used to prevent transmission of HIV in uninfected individuals, in addition to their current use as treatment for HIV-infected individuals.

Integrase inhibitors, the latest weapon in the HIV treatment armamentarium, stop HIV from incorporating its genetic information into the DNA of an infected T cell, essentially heading off HIV's master plan to hijack all future generations of cells. They are intended to be used in combination with other ARVs that target different steps in the HIV life cycle. Studies have found that integrase inhibitors can suppress virus that is resistant to some

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of these other ARVs, including those in a class called nucleoside/nucleotide reverse transcriptase inhibitors. The researchers tested the ability of the compound L-870812 to protect against infection with SHIV. The gel was applied vaginally to three pigtailed macaques twice a week for seven weeks. Thirty minutes after each gel application, the animals were exposed to SHIV, for a total of 14 “challenges.” A fourth animal received a placebo gel in the same manner. Two of the three macaques receiving the active gel remained uninfected after seven weeks of being exposed to SHIV. The third macaque became infected after seven challenges, while the macaque that received a placebo gel became infected after the third exposure. Importantly, the animal that became infected while using the active gel had no evidence of drug resistant virus even after continuing the gel regimen for an additional 15 weeks. This is significant because one of the concerns with ARV-containing gels is that the inadvertent use of these gels in someone who is HIV-infected could allow the virus to become resistant and limit treatment options in the future. While the results are promising, additional studies will be needed before deciding whether to advance this particular vaginal gel to trials in humans.

### **L'644 leads the way in tests of different fusion inhibitors as possible microbicides**

L'644, a type of drug that prevents HIV from fusing to a healthy cell in order to infect it, was found in laboratory tests to be more effective than drugs in the same class of antiretroviral drugs called fusion inhibitors. Fusion inhibitors work by blocking the interaction between a small protein on the HIV virus called gp41 and proteins on the host cell, leaving the virus without a way to fasten itself to the host cell. The researchers from St. George's, University of London, in the U.K., in collaboration with the International Partnership for Microbicides, wanted to examine the potential of L'644 for possible development as a microbicide for preventing the sexual transmission of HIV. As a way to simulate the infection process, researchers used samples of human vaginal and colorectal tissue and exposed the tissue to normal HIV virus and drug-resistant HIV virus, as well as a unique cell line that can easily tell a researcher if the cell has been infected with HIV-1. In this same environment, they also tested the biocompatibility and efficacy of L'644 compared to other fusion inhibitors. L'644 was more effective than the other fusion inhibitors in blocking infection of the tissues and its activity was not affected by the addition of synthetic cervical mucus or seminal plasma. In other tests, L'644 was able to block infection even after the drug had been washed off the tissue, suggesting the drug finds a way to lock itself onto the cell surface. L'644's effect could possibly be enhanced in a sustained release delivery system formulation, such as a vaginal ring, that would allow the drug to be released slowly over time, reported Carolina Herrera, Ph.D.

### **Study suggests maraviroc is a good candidate for vaginal ring**

Laboratory studies evaluating a microbicide containing a drug called maraviroc found it was the most effective when given on a continuous basis, supporting its development in a formulation that allows for sustained drug delivery, say researchers from St. George's, University of London, in the U.K. Maraviroc belongs to a class of anti-HIV drugs called entry inhibitors, which, as their name implies, block HIV from entering target cells. Maraviroc does this by binding to a co-receptor called CCR5, a protein on the surface of the cell that serves as one of HIV's key docking stations before gaining entry. As a microbicide for preventing sexual transmission of HIV, maraviroc theoretically would work to protect vulnerable cells in the vagina or rectum. To test this notion, researchers conducted two sets of experiments. In one, they examined the drug's effect on T cells – HIV's target cells – as well as dendritic cells and peripheral blood mononuclear cells (PBMCs) because HIV often uses them as unwitting accomplices. What they found is that maraviroc retained activity against these cells and also prevented the dendritic cells and PBMCs from transferring virus to T cells. Moreover, its effect was not altered by the presence of synthetic cervical mucus or seminal plasma. In another set of experiments involving vaginal and colorectal tissue explants, the researchers found maraviroc particularly effective against infection of the colorectal tissue. In vaginal tissue, they found that drug delivered continuously over 14 days was more effective against infection than a hefty single dose or when the tissue essentially was bathed in drug overnight. Taken together, the results provide evidence of maraviroc's potency against key cells and tissue that are prone to infection and demonstrate that the drug's effectiveness can be enhanced through continuous exposure. Its greatest potential for achieving maximal protection against HIV, says Patricia Fletcher, Ph.D., who presented the study's findings, would be in a sustained delivery system, such as a vaginal ring.

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### **Protease inhibitor darunavir shows promise as microbicide, but with dapivirine, has one-two punch**

In studies looking at the potential that anti-HIV drugs called protease inhibitors could be used as microbicides for preventing the sexual transmission of HIV, researchers identified one with particular promise. The drug, called darunavir, was especially effective when used along with dapivirine, a non-nucleoside reverse transcriptase inhibitor, reported Abbey Evans, of St. George's, University of London, in the U.K. Each drug targets a particular enzyme important in the HIV lifecycle. Darunavir disables the enzyme called protease, while dapivirine blocks the reverse transcriptase enzyme. Without either, HIV is unable to copy its genetic material and use the cell to make new viral particles that will go on to infect other cells. Darunavir was one of three protease inhibitors tested for their ability to prevent infection of T cells, HIV's primary target, and dendritic cells. Darunavir and the two others, ritonavir and lopinavir, also were tested with both cell types together as a model of infection of T cells. That's because dendritic cells are used by HIV for the free ride they can provide to reach T cells. The researchers measured effectiveness of each drug by looking to see whether or not they prevented new virus particles from being made. All three drugs were able to inhibit the replication of HIV in both cell types alone as well as in the two-cell model of infection, with darunavir outperforming the other two. Darunavir was then tested to see if it prevented infection in human genital and colorectal tissue samples, with impressive results. But the combination of darunavir and dapivirine proved most effective and showed the best promise for further development as a microbicide.

More than 33 million people are living with HIV, more than two thirds of them in sub-Saharan Africa, according to UNAIDS. The number of new infections continues to outstrip advances in treatment: For every two people who begin treatment, five are newly infected. Globally, women account for half of all HIV infections, and in sub-Saharan Africa, women comprise 60 percent of all infected adults. Young women are especially vulnerable. In southern Africa women aged 15 to 24 are at least three times more likely than their male peers to be infected with HIV. Meanwhile, men who have sex with men (MSM) bear the burden of the epidemic in the United States and in other parts of the world, such as Europe, Latin America, Australia and New Zealand. According to the U.S. Centers for Disease Control and Prevention, MSM of all races is the only risk group in the United States in which new HIV infections are increasing. Black heterosexual women represent the third highest risk group in the United States, after white MSM and black MSM, respectively.

M2010 is the sixth biennial meeting of the International Microbicides Conference and marks the first meeting in the United States since the 2000 inaugural gathering in Washington, D.C. Other previous meetings have been in Antwerp, Belgium; London, England; Cape Town, South Africa; and New Delhi, India. Co-chairs of this year's conference are Sharon Hillier, Ph.D., and Ian McGowan, M.D., Ph.D., both of the University of Pittsburgh; and Gita Ramjee, Ph.D., of the Medical Research Council of South Africa. The scientific program and other information about the meeting can be found at [www.microbicides2010.org](http://www.microbicides2010.org).

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