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**Researchers report on progress developing vaginal rings, tablets and films –
Microbicides that do more than gel**

New research presented at International Microbicides Conference May 22-25

PITTSBURGH, May 24 – A flexible ring containing two anti-HIV drugs showed in laboratory tests that it can deliver therapeutic levels of both drugs for up to 30 days, researchers reported today at the International Microbicides Conference (M2010) in Pittsburgh, adding that they consider the ring near ready for testing of its safety in women.

Vaginal rings have been used to deliver contraceptives and now this strategy is being applied for delivering formulations of microbicides to protect against HIV. Unlike gels that must be used every day or at the time of sex, rings can be inserted into the vagina and stay in for a month or longer. And, for certain drugs or drug combinations, these formulations may be the more optimal vehicles for delivery.

Another option to deliver drugs with less fuss or muss, are quick-dissolve films. In one study presented today, researchers described their progress in developing a vaginal film – smaller than a stick of gum and as thin as a sheet of paper – that after insertion into the vagina would melt away and disperse drug to cells to protect against HIV. Laboratory tests of a similar approach – an almond-shaped vaginal tablet – found the tablets dissolved quickly yet still delivered sustained levels of anti-HIV drugs over several hours.

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

Vaginal ring with two anti-HIV drugs nears benchmark for clinical testing of its safety in women

An intravaginal ring formulated with two anti-HIV drugs – dapivirine and maraviroc – can deliver therapeutic levels of both drugs for as long as a month, according to laboratory studies. Based on these and other findings, the ring is a good candidate for testing in clinical safety trials, reported Andrew Loxley, Ph.D., from Particle Sciences, Inc., of Bethlehem, Pa. Vaginal rings are small, flexible devices designed to allow for the slow delivery of a drug or multiple drugs over time. As a potential method for preventing sexual transmission of HIV, rings are seen as an alternative to microbicide gels that must be used every day or at the time of sex. Dapivirine, also known as TMC-120, belongs to a class of anti-HIV drugs called non-nucleoside reverse transcriptase inhibitors that bind to and disable HIV's reverse transcriptase enzyme, a protein that HIV needs to make more

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copies of itself. Maraviroc is a type of drug called an entry inhibitor that prevents HIV from entering a healthy cell. The current study indicates that inside the vaginal ring, the two drugs work well side-by-side with the activity and structure of each drug not being affected by the presence of the other. High amounts of each drug were still being released from the ring at 15 days and continued to be delivered for up to 30 days. Even after being stored in harsh conditions for six months, both drugs maintained their stability and structure, suggesting that under more normal temperature conditions, the rings remain viable for a year or even longer. The rings are made of a type of plastic called ethylene-vinyl acetate copolymer (EVA) and share many of the same properties as rings currently used for contraception. They are manufactured using standard processes called hot metal extrusion and injection molding. If clinical trials prove the rings safe and effective, manufacturing and scale-up should be relatively easy, say the researchers who made the rings with the support of the International Partnership for Microbicides located in Silver Springs, Md.

Early studies suggest promise for vaginal tablet containing ARV combination

Seeking an alternative to microbicides in the form of the more traditional gel, researchers have developed an almond-shaped vaginal tablet that according to laboratory tests can dissolve quickly and deliver sustained levels of anti-HIV drugs over 12 hours. Additional studies will be needed before it can be considered for testing in clinical trials for its safety and effectiveness for preventing sexual transmission of HIV in women, reported Sanjay Garg, Ph.D., an associate professor in the School of Pharmacy, Faculty of Medical and Health Sciences, at the University of Auckland in New Zealand. The research, which was conducted in collaboration with the International Partnership for Microbicides of Silver Spring, Md., focused on combining two antiretroviral (ARV) drugs – dapivirine, a non-nucleoside reverse transcriptase inhibitor; and an entry inhibitor called DS003 – into a vaginal tablet formulation. Dapivirine has already been formulated as a vaginal ring and a gel, both of which are being tested in early phase clinical trials, while DS003 (BMS 793) is in earlier development as a candidate microbicide. The vaginal tablet is based on a pharmaceutically acceptable bioadhesive polymer that binds to the moist lining inside the vagina, allowing the drug to transfer to key cells that comprise the epithelium. In their studies, Dr. Garg and colleagues demonstrated it is feasible to formulate a vaginal tablet containing the two ARVs and that the formulation is stable and the drugs are compatible. Moreover, they showed that the tablet dissolves within three minutes yet the steady, slow delivery of drug was sustained for several hours from the dispersion formed. Next steps include performing toxicology studies of the vaginal tablet.

Vaginal film with novel dual-action ARV passes early laboratory tests

IQP-0528 is a new antiretroviral (ARV) compound that although is classified as a non-nucleoside reverse transcriptase inhibitor, works against HIV in two ways. It prevents HIV from entering a cell and inhibits the activity of reverse transcriptase, a key enzyme that HIV needs in order to make more copies of itself. Now, researchers report they have developed a potential microbicide containing this novel ARV. But rather than formulate the drug as a traditional gel, the researchers created a vaginal film smaller than a stick of gum and as thin as a sheet of paper. Laboratory tests indicate it is potent against HIV, non-toxic to cells and that it can dissolve quickly to release nearly all the compound. The results suggest the film formulation is worth further study as a topical microbicide for the prevention of HIV infection, reported Anthony Ham, Ph.D., who led the study for ImQuest BioSciences of Frederick, Md. The film is made of a thin polyvinyl alcohol polymer, a water-soluble synthetic plastic used in multiple consumer and biomedical products, including contraceptive films, contact lens solutions and mouthwash strips. Many believe that when it comes to a microbicide for preventing HIV, women will prefer using a vaginal film over a gel, especially if a long-acting formula allowed for less frequent use. To evaluate the potential of IQP-0528 as a vaginal film, the researchers performed a series of tests. In those looking at its antiviral activity, IQP-0528 films were found effective against multiple strains of HIV. Other tests indicated the film was not toxic to cells and had no negative effect on normal vaginal flora. The film visibly disintegrated in solution within 10 minutes and within the same time period a sufficient level of drug was released from the film to have activity against HIV. Results of these early laboratory tests are encouraging but will need to be validated in further studies.

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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.

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