



CONTACT: Lisa Rossi
+1- 412-641-8940
+1- 412- 916-3315 (mobile)
rossil@upmc.edu

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New findings reported by Microbicide Trials Network at International HIV Prevention Meeting
No added HIV risk with hormonal contraceptives, one study finds: Results presented at Microbicides 2012

SYDNEY, April 17 – An HIV prevention trial that pre-dates the shift to antiretroviral (ARV)-based approaches is nonetheless helping to answer some of the most relevant and topical questions the field is facing today. More than three years after reporting the primary results of HPTN 035, one of the last trials of the so-called first generation microbicides, researchers from the National Institutes of Health-funded Microbicide Trials Network (MTN) reported two new sets of findings gleaned from the study's trove of statistical data and laboratory specimens. The results of both analyses were presented at the International Microbicides Conference (M2012). The meeting, which started Sunday, April 15 and ends tomorrow, April 18, is being held in Sydney.

Are women who use hormonal contraception at greater risk of acquiring HIV? No, according to a retrospective analysis of HPTN 035 data reported earlier today, the latest round of conflicting information about an issue that has perplexed researchers and health advocates alike.

Are some women more biologically susceptible to HIV than others, and if so, is there a way to identify who they are? Yes, suggests the other study, a series of laboratory tests of vaginal fluid samples from former HPTN 035 participants, additionally pointing to a need for developing more targeted HIV prevention approaches for women who may be especially vulnerable.

Worldwide, an estimated 34 million people are living with HIV, more than two-thirds of whom live in sub-Saharan Africa. The number of new infections continues to outstrip advances in treatment: For every person starting HIV treatment, there are two new infections. In 2010, approximately 2.7 million people were newly infected with HIV— more than 7,000 every day.

Microbicides are products being developed to prevent or reduce the sexual transmission of HIV or other sexually transmitted infections (STIs) when used in the vagina or rectum. Vaginal microbicides are being designed in many forms, including gels, films or rings that release an active ingredient gradually over time. If proven effective, microbicides could help prevent HIV in women in developing countries where it most often is spread through unprotected heterosexual intercourse despite efforts to promote abstinence, monogamy and the use of condoms. Microbicides also could help prevent HIV in both men and women who practice anal sex. Unlike condoms, microbicides provide an HIV prevention strategy that is not controlled by one's sexual partner. Different products at various stages in the development pipeline are being tested; with those that incorporate ARV drugs the furthest along in testing and the only products in clinical trials. Another promising ARV-based prevention approach is called oral pre-exposure prophylaxis, or PrEP, which involves the daily use of an ARV tablet more commonly used in the treatment of HIV by people who are uninfected.

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More than 40 oral and poster presentations by MTN investigators have or will be presented at M2012, including those highlighted and summarized below:

Use of hormonal contraception not associated with increased risk of HIV infection, according to analysis of data involving nearly 3,000 women in HPTN 035

The use of hormonal contraceptives – either injectable or oral – did not place women at greater risk of acquiring HIV, according to a retrospective review of data from HPTN 035, a Phase IIb HIV prevention trial that evaluated the vaginal microbicides PRO 2000 and BufferGel. However, coupled with a diagnosis of either gonorrhea or Chlamydia, hormonal contraceptive use was associated with statistically significant greater risk of HIV infection, reported Zvavahera Mike Chirenje, M.D., of the University of Zimbabwe in Harare and HPTN 035 protocol co-chair. “In many ways, our data reflects the overall body of evidence so far, which has seen inconsistent study results.”

The analysis involved 2,887 women who had enrolled at one of the study’s seven African research sites. (U.S. participants were excluded from the analysis.) According to participant self-reports, 51 percent said they were using an injectable contraceptive, such as Depo-Provera (DMPA); 21 percent indicated oral contraceptive use and 18 percent said they were using a non-hormonal contraceptive. HPTN 035 was conducted between 2005 and 2008. Results, which were reported in early 2009, found PRO 2000 was 30 percent more effective than a placebo in preventing HIV, although this finding was not statistically significant, and that BufferGel had no protective effect. In recent months, the researchers looked at contraception and HIV risk in this cohort of participants. Their analysis comes on the heels of the World Health Organization (WHO) announcing it will maintain its current guidance on the use of hormonal contraceptives, which do not restrict their use by women living with HIV or at high risk of HIV. The WHO said that although some studies have suggested a possible increased risk of HIV acquisition with the use of progesterone-only injectable contraception, the totality of data is inconclusive. Nonetheless, the WHO is recommending that women who wish to use progesterone –only injectables be told of the possible risks and advised to always use condoms and other HIV preventive measures.

“If there’s one conclusion to be made from our analysis, as well as the other studies to date, it’s that there are no clear answers about hormonal contraception and HIV risk,” Dr. Chirenje added.

Simple laboratory test of vaginal fluid may indicate susceptibility to HIV

Testing vaginal fluid for its activity against *E. coli* could help identify women who are more susceptible to HIV infection, new research suggests. Researchers from the Microbicide Trials Network (MTN) examined vaginal fluid samples from a subset of women who were participants in HPTN 035 to see if they could identify any biological factors that predisposed some of these women to become infected and others not, and if so, whether this information could in the future help identify those who may be at greater risk. Indeed, their work showed that there had been clues, which may have remained hidden, if not for one particular laboratory approach.

HPTN 035 evaluated the safety and effectiveness of the vaginal microbicides BufferGel® and PRO 2000 among more than 3,000 women in Africa and the United States. The primary results, which were reported in February 2009, found PRO 2000 was 30 percent more effective than a placebo in preventing HIV, although this finding was not statistically significant, and that BufferGel had no protective effect. In total, 194 women became infected during the trial. During the trial, researchers collected more than 3,500 vaginal fluid samples from 2,031 of the women for future study. The current analysis involved 26 samples from eight of the 194 women who acquired HIV that were collected within three months of the women testing positive; 11 of these samples were provided before they were known to be infected. An additional 78 samples from HIV-negative participants were used for comparison. Standard measures for detecting various immune system molecules and proteins showed no differences between the two groups of women. But in a laboratory test whereby vaginal fluid was combined with *E. coli*, women who later became HIV infected showed higher activity against the bacteria than those women who remained HIV negative. “We don’t understand exactly what this assay is telling us other than that these women had some underlying level of immune activity that placed them at greater risk,” said Charlene Dezzutti, Ph.D., of the University of Pittsburgh. “We’d like to be able to identify women who may be more susceptible to HIV – *before* they become infected, but there’s still more work ahead. We need to test the approach in more samples and dig deeper.”

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Study finds dapivirine gel, a potential vaginal microbicide, poses no harm to men

Results of a Phase I study involving sexually abstinent men found a vaginal microbicide containing the antiretroviral drug dapivirine was safe and well tolerated when applied topically to the penis. The study was conducted to provide additional safety data in support of dapivirine's potential use as vaginal microbicide formulated as either a gel or a ring. "Although the gel is not intended to be used on the penis, it is important to know that its use by women in the vagina would also be safe for men during intercourse," explained Ross Cranston, M.D., of the University of Pittsburgh, who led study for the Microbicide Trials Network (MTN). Dapivirine, also known as TMC-120, is a type of antiretroviral called a non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTIs bind to and disable HIV's reverse transcriptase enzyme, a protein that HIV needs to make copies of itself. Although dapivirine was initially developed as an oral therapeutic agent to be used in the treatment of HIV, dapivirine is a promising candidate for development as a microbicide due to its favorable safety profile as well as its physical and chemical properties. The study, which was conducted in collaboration with the International Partnership for Microbicides, involved 48 men – 24 circumcised and 24 uncircumcised – who applied the gel daily for seven days. Penile application of dapivirine 0.05% gel was well tolerated with no safety concerns, reported Dr. Cranston.

Baseline portrait of bone health in African women will be especially relevant if PrEP rolled out

Researchers have created what may be the most complete portrait of bone health in healthy African women of reproductive age to date, as well as identified the factors most associated with loss of bone mineral density, or the thinning of bone. The information will help to understand the potential effects to bone, if any, that daily use of either of the antiretroviral (ARV) drugs tenofovir or Truvada may have when used by HIV-negative women to prevent HIV infection, an approach called oral pre-exposure prophylaxis (PrEP). Although tenofovir and Truvada, an oral tablet that contains both tenofovir and emtricitabine, are considered safe and effective for treating people with HIV, modest decreases in bone mineral density have been observed in HIV-infected people during treatment with tenofovir. Additionally, small changes in bone density were observed in HIV-negative men who have sex with men who received Truvada in the iPrEx study. But for HIV-negative women who may be using PrEP, other factors could also contribute to changes in bone health including nutrition, hormonal contraception, pregnancy, and current or prior breastfeeding. "There's been limited information about bone health in African women. That's why we felt it important to do this study," said Nyaradzo Mgodzi, M.D., from the University of Zimbabwe in Harare. "We have to have a starting place before we can understand the potential effects of these drugs as HIV prevention. The data will be critical for consideration of PrEP implementation."

The composite is based on 517 women in Uganda and Zimbabwe, who were an average of 29 years of age when they entered VOICE B, an observational study within the HIV prevention trial VOICE – Vaginal and Oral Interventions to Control the Epidemic. According to the data, women with lower bone mineral density are most likely to have used the injectable contraceptive Depo-Provera (DMPA); have a lower body mass or lead a more sedentary lifestyle. Interestingly, at baseline, Ugandan women had lower bone density than women from Zimbabwe. The women in VOICE B represent a subset of the VOICE participants who were randomly assigned to one of trial's oral tablet regimens (tenofovir, Truvada or placebo tablet). The study involves bone density measurements every 6 months throughout the time they are using their study drug and for one year after the study medication is stopped. Researchers expect to complete VOICE B by August 2013 and be able to report its results later that same year.

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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. More information about the MTN is available at www.mtnstopshiv.org.