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U.S. study of dapivirine ring in lactating women finds little drug gets into breast milk
Results presented at IAS 2017 support additional studies in breastfeeding and pregnant women

PARIS, July 24, 2017 – The antiretroviral (ARV) drug dapivirine that is released from an experimental vaginal ring to protect against HIV is absorbed in very low concentrations into breastmilk, according to a U.S. study of the dapivirine ring among women who were no longer nursing their babies but still producing milk.

Use of the ring for 14 consecutive days was also associated with low levels of dapivirine in women’s plasma, and posed few safety concerns, researchers from the National Institutes of Health (NIH)-funded Microbicide Trials Network ([MTN](#)) reported today at the 9th IAS Conference on HIV Science (IAS 2017) in Paris. The Phase I study, known as MTN-029/IPM 039, is the first study of the dapivirine ring in lactating women, following two Phase III trials – ASPIRE and The Ring Study – that found the ring was safe and helped protect against HIV among more than 4,500 women in sub-Saharan Africa.

Encouraged by these results, MTN investigators are planning additional studies that will explore whether the dapivirine ring is safe to use by women who are actively breastfeeding, and therefore safe for their infants; and, also evaluate the safety of the ring during pregnancy. These studies would be conducted at trial sites in Africa, and women would use the ring for a month at a time, as directed for HIV prevention.

The monthly dapivirine ring was developed by the International Partnership for Microbicides ([IPM](#)), a non-profit organization. When in place inside the vagina, the ring slowly releases dapivirine over the course of a month. The ring is made of a flexible plastic material, and women insert and replace the ring themselves each month. IPM is [seeking regulatory](#) approval of the dapivirine ring for women ages 18-45 based on results of [ASPIRE](#), which was conducted by MTN, and [The Ring Study](#), led by IPM.

Because the effects dapivirine could have on the developing fetus and breast-fed infants are unknown, women who participate in studies of the ring cannot be pregnant or breastfeeding, and are required to use effective contraception. Participants who become pregnant immediately stop use of the ring. Such precautions are standard in any clinical trial testing a new drug product in women of reproductive age. Consequently, a drug that may receive regulatory approval is often contraindicated in women who are pregnant or breastfeeding, yet, might be used by some anyway – without the benefit of knowing it is safe to do so. If approved, the same would be true of the dapivirine ring.

Many women remain sexually active during pregnancy and breastfeeding, when there may be greater risk of acquiring HIV, and may be especially difficult for women to negotiate the use of condoms with their

partners. Moreover, in regions where HIV incidence is high, such as sub-Saharan Africa, the percentage of women of reproductive age who are either pregnant, breastfeeding or both is also high.

Taken together, it is hoped that the results of the MTN-029/IPM 039 study and those of planned studies of the dapivirine ring among pregnant and breastfeeding women will demonstrate the product's safety in this population.

"There is little doubt that safe and effective HIV prevention methods are needed for women during all times of their lives," commented Sharon Hillier, Ph.D., principal investigator of the MTN, and professor and vice chair of the department of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine. "With the dapivirine ring, conducting this study was an important first step. If the ring is approved, we'd want it to ultimately be made available to all women, including those who are breastfeeding."

"Understanding the safe use of drugs in pregnancy and breastfeeding is a high priority across women's health. Eventually, we hope that we can assure women that using the dapivirine ring during breastfeeding – and pregnancy – is safe, with minimal exposure of the drug to their infants. However, understanding a product's safety during pregnancy and breastfeeding requires carefully designed trials that can obtain critical safety information while also ensuring the well-being of this special population. In this first study of dapivirine and breast milk, we were able to gather initial data without exposing infants to drug," said Lisa M. Noguchi, CNM, Ph.D., research associate in the department of epidemiology at the Johns Hopkins Bloomberg School of Public Health, and MTN's scientific director for pregnancy research, who reported the study results at IAS 2017.

MTN-029/IPM 039 enrolled 16 participants – women who had stopped breastfeeding their babies but could still pump breast milk – at the University of Pittsburgh-affiliated Magee-Womens Hospital and the University of Alabama at Birmingham. Women were asked to leave the vaginal ring in place for 14 days. Researchers collected milk and blood plasma samples prior to the ring being inserted, and then after three hours, six hours, 24 hours, seven days and 14 days, when the ring was removed. Samples were collected again two days later.

All participants had detectable drug in milk and plasma, beginning at three hours with concentrations gradually increasing until reaching a steady state between seven and 14 days. (Peak concentration for milk and plasma were 676 pg/mL and 327 pg/mL, respectively.) Two days after the ring was removed, drug levels had decreased by 60 percent.

Based on levels measured in maternal breast milk, researchers estimated that an infant's daily exposure to drug would be very low. For instance, a 6-month old baby weighing 8 kg (about 18 lbs) would probably take in about 600 ng (or 6/10,000 of a milligram) of dapivirine on a daily basis. By comparison, said researchers, a similar weight baby being breastfed by a mother taking the combination ARV Truvada would be exposed to about 4,000 ng of tenofovir and 300,000 ng of emtricitabine each day, levels that so far have not been seen to pose a health risk for breastfed infants.

Dr. Noguchi led the MTN-029/IPM 039 study with Richard Beigi, MD, MSc, an associate professor of reproductive health sciences at the University of Pittsburgh.

Three new studies are being planned as a follow-up to MTN-029/IPM 039 that will be conducted at four MTN-affiliated trial sites in Malawi, Uganda, South Africa and Zimbabwe. The first, MTN-041, is a qualitative study that will explore attitudes about use of a vaginal ring and oral PrEP during pregnancy and breastfeeding among women who are themselves pregnant and/or breastfeeding, male partners and key community gatekeepers, such as health care providers, traditional healers and religious and traditional leaders. Pending ethics and in-country approvals, the study is expected to start early 2018.

In MTN-042, researchers are proposing to evaluate the safety of the ring as well as oral PrEP in approximately 750 pregnant women, while MTN-043 would involve approximately 100 women who are breastfeeding as well as their infants.

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[Breast milk dapivirine pharmacokinetics and estimated infant exposure during dapivirine intravaginal ring use among lactating women](#) (Abstract MOPDC0106LB) will be presented during the poster discussion session, Antivirals and Pregnancy, 1-2 pm CEST, Monday 24 July.

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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 whose work is focused on the rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at <http://www.mtnstopshiv.org>.

About the dapivirine ring

The dapivirine ring is made of a flexible material, and women can insert and remove it themselves. It sits high inside the vagina where it slowly releases the active drug over the course of a month. The ring was developed by the International Partnership for Microbicides (IPM), a nonprofit with offices in the United States, South Africa and Europe. IPM holds an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, part of the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen), which is designed to ensure that women in low-resource settings have affordable access to any dapivirine-based microbicide. Dapivirine, also known as TMC-120, belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors that bind to and disable HIV's reverse transcriptase enzyme, a key protein needed for HIV replication.

Results of ASPIRE and The Ring Study, which were reported in February 2016, found the ring reduced women's risk of acquiring HIV by about 30 percent overall (by 27 percent in ASPIRE and by 31 percent in The Ring Study). Higher levels of protection were seen in women 21 and older, who used the ring regularly. Results of an exploratory analysis of ASPIRE data reported at AIDS 2016 found the level of HIV protection was at least 56 percent with consistent use and as high as 75 percent or more with near perfect use.

IPM is seeking regulatory approval of the dapivirine ring for women ages 18-45, the same age group in the ASPIRE and The Ring Study Phase III safety and efficacy trials. IPM is hopeful that the first regulatory approvals in African countries could be received as soon as early 2019.

For more information about the dapivirine ring, go to www.ipmglobal.org.

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