

US study of dapivirine ring in lactating women finds little drug gets into breast milk

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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.

Provided by Microbicide Trials Network

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