# Researchers launch study to assess safety of PrEP and dapivirine ring in pregnant women

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A woman who is eight-months pregnant is the first participant to be enrolled into a study evaluating the safety and acceptability of two different HIV prevention approaches when used during pregnancy—the monthly dapivirine vaginal ring, which is currently under regulatory review, and a daily antiretroviral (ARV) pill called Truvada, an approach already approved in several countries and commonly referred to as PrEP, short for pre-exposure prophylaxis.

The study, known as DELIVER, or MTN-042, is the first of its kind of the dapivirine ring in pregnant women and will also provide much needed information about the safety of Truvada as PrEP in this population.

DELIVER is being led by the National Institutes of Health-funded Microbicide Trials Network (MTN) and will be conducted at four clinical research sites in Malawi, South Africa, Uganda and Zimbabwe. A similar study involving breastfeeding mothers and their babies, called B-PROTECTED (MTN-043), is expected to launch in the coming months at these same sites. Both are Phase IIIb clinical trials.

Globally, more than half of all people living with HIV are cisgender women, and in sub-Saharan Africa, they are particularly vulnerable, especially during pregnancy and breastfeeding, when they are up to four times more likely to acquire HIV. For many women, the amount of time they are pregnant, breastfeeding, or both, represents a significant portion of their reproductive years. Ultimately, the goal of the DELIVER and B-PROTECTED studies is to ensure that women can have safe and effective HIV prevention options they can use throughout their lives, including during pregnancy and breastfeeding.

Both Truvada as PrEP and the dapivirine ring have been shown to reduce the risk of HIV in previous trials involving nonpregnant and non-breastfeeding women, with safety parameters indicating these methods were also well tolerated. Women who were pregnant or breastfeeding were excluded from participation in these trials, and those who enrolled had to use contraception, and, if they became pregnant, stop using study product. Such measures, which are typical in clinical trials, are primarily intended to protect the fetus and baby from potential harm but also mean that little or no information about the safety of a drug during pregnancy or breastfeeding will be available. In particular, during pregnancy, the body undergoes many changes that could affect how a drug gets absorbed and distributed such that the drug may not be as effective, or its use may be harmful to the mother, her pregnancy, fetus or baby.

Information thus far about the safety of Truvada as PrEP and the dapivirine ring during pregnancy is encouraging but still quite limited. While Truvada (which contains the ARVs emtricitabine and tenofovir disoproxil fumarate) is approved as PrEP in many countries, some national programs have yet to decide whether to offer it to pregnant women. The vaginal ring, which contains the ARV dapivirine, is a new product developed by the nonprofit International Partnership for Microbicides (IPM). IPM is seeking the ring's regulatory approval. If approved, the ring would be the first biomedical prevention option designed specifically for women—and the first long-acting method, but its use would not be recommended (contraindicated) for women who are pregnant or breastfeeding. Specific data on the ring's safety and use among pregnant and breastfeeding women is needed before regulators would consider expanded approval for these populations.

"There is no question of the need for more definitive

information about the safety of oral PrEP and the dapivirine vaginal ring during pregnancy and breastfeeding. National governments need it, clinicians need it, and, most of all, women need it so they can make informed decisions," said Bonus Makanani, M.B.B.S., F.C.O.G. (SA), associate professor of obstetrics and gynecology at the University of Malawi College of Medicine in Blantyre. Dr. Makanani is overseeing DELIVER at the Malawi site as well as leading the overall study with Katherine Bunge, M.P.H., M.D., an assistant professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine.

"Mothers—and their babies—deserve and need to be protected from HIV with methods they know are safe to use when they are pregnant or breastfeeding," Dr. Bunge added. "With DELIVER, it's all about safety. The purpose of the study is to assess the safety of two HIV prevention products—the ring and PrEP—during pregnancy, but also to do so in the safest way possible."

DELIVER will enroll 750 healthy, HIV-negative pregnant women ages 18-40 who will be randomly assigned to use either the monthly dapivirine ring or Truvada as daily PrEP. Of the 750 women who will be enrolled, 500 will be assigned to use the vaginal ring. All participants will be asked to use their assigned product until the time they deliver. Women will be followed for an additional six weeks, and their babies will remain in the study for one year.

The study will be conducted in four phases, enrolling one group of women at a time, beginning with women who are late in pregnancy, with each successive group of women at an earlier stage of pregnancy and using their assigned product longer. Interim reviews of study data by an independent panel of experts will take place after completion of each phase and before determining whether it is safe to proceed to the next phase.

One reason for this design is to be attentive to the potential risks and complications that can occur at different times during pregnancy and fetal development, and to ensure that use of the dapivirine ring or oral PrEP does not pose additional risk or harm to either the mother or her fetus.

The first group will consist of 150 women late in pregnancy, who are 36-37 or more weeks (8-9 months) pregnant, when it is believed use of PrEP or the ring would pose the least risk. The second and third groups will each enroll 150 women who are 30-35 weeks (7-8 months) and 20-28 weeks (5-7 months) pregnant, respectively; while the fourth group will comprise 300 women who will be 12-19 weeks (3-5 months) into their pregnancies.

Sites will work closely with nearby hospitals and health centers where women are receiving their primary care and are likely to deliver.

"The facilities that are collaborating with us have been quite receptive to this study, and the communities are fully supportive as well," commented Lee Fairlie, MBChB, FCPeds (SA), MMED (Paeds), who is the DELIVER protocol co-chair and also leading the study at the Wits Reproductive Health and HIV Institute (Wits RHI) Shandukani Research Centre in Johannesburg, South Africa, where the first participant was enrolled.

Pending in-country ethics and regulatory approvals, the study should to begin within the next few months at the three other sites: the College of Medicine-Johns Hopkins University Research Project in Blantyre, Malawi; Makerere University-Johns Hopkins Research Collaboration in Kampala, Uganda; and the University of Zimbabwe College of Health Sciences Clinical Trials Research Centre, Zengeza.

Participants in the study will be seen every two to four weeks and asked questions about their health and experience using the ring or PrEP and whether they are having any problems, such as headache, nausea, pain or discomfort. In addition, women will undergo physical exams, and laboratory tests will be conducted. All women will receive HIV risk-reduction counseling and testing, and, as needed, be referred for any medical or counseling services not provided through the study or at the site.

The dapivirine ring is made of flexible silicone that

slowly releases dapivirine in the vagina during the month that it is worn. Women can insert the ring themselves and replace it with a new one each month. In 2016, two large clinical trials - ASPIRE, conducted by the MTN, and The Ring Study, led by IPM, found the ring was well-tolerated and helped reduce the risk of HIV by approximately 30 percent. In 2019, results of two open-label extension studies - HOPE for former ASPIRE participants and DREAM for former Ring Study participants -suggested higher adherence—indicating women want and will use the ring—and safety findings consistent with the Phase III trials. Together, the results also suggest a greater reduction in HIV risk (about 50 percent) than seen in the Phase III studies.

Information about the use of the dapivirine vaginal ring during pregnancy and breastfeeding is still very limited. Though animal studies of dapivirine indicate no concerns related to pregnancy or fetal development, the only human data is from about 250 women who became pregnant while participating in ASPIRE and The Ring Study and stopped use of the ring as soon as it was known they were pregnant. Notably, there were no significant differences in pregnancy and infant outcomes between women assigned to use the dapivirine ring and those assigned to use a placebo. These findings are important for understanding outcomes associated with exposure during conception and early pregnancy and support moving forward with DELIVER, which will provide information about the safety of the ring during the second and third trimesters.

Most of the information about the safety of Truvada during pregnancy is in women living with HIV who are using Truvada as part of an HIV treatment regimen, with multiple studies showing it is not harmful. It is based primarily on these studies that the World Health Organization recommends Truvada as PrEP during pregnancy and breastfeeding, while also acknowledging the need for more data about the safety in HIV-negative women. Observational studies in which women who have become pregnant while using Truvada as PrEP and continued its use have thus far seen no cause for concern, but key questions about safety and outcomes remain unanswered.

The IMPAACT 2009 study, which is being conducted at the same sites as the DELIVER and B-PROTECTED studies, is evaluating the safety and drug absorption and distribution of Truvada when used as PrEP by pregnant adolescent girls and young women ages 16-24. Researchers have completed the first phase, which looked at how drug is taken up in the body during pregnancy and during the post-partum period. Pending results, the study will proceed to the next phase, enrolling up to 350 participants who are no more than 32 weeks into their pregnancies. Overall results are anticipated in 2022.

Complementing DELIVER and B-PROTECTED are two additional studies in MTN's research portfolio. MTN-041 assessed community and stakeholder's attitudes and beliefs about the use of daily PrEP and the monthly dapivirine ring by pregnant and breastfeeding women in each of the trial site communities where DELIVER and B-PROTECTED will be conducted. MTN-041 included focus groups with male partners, mothers and mothers-in-law, and women who were currently or recently pregnant or breastfeeding, as well as in-depth interviews with community and traditional leaders and service providers. Results are anticipated to be reported later this year. The other study, MTN-042B, has nearly completed recording data close to 8,000 medical records medical charts of pregnancy outcomes and complications occurring within a two-month period at centers and hospitals where DELIVER/MTN-042 study participants are expected to deliver. This data, together with data collected as part of an extensive review of published reports and scientific literature, will help serve as a basis for comparison of pregnancy and infant outcomes in DELIVER.

DELIVER is expected to take up to four years to complete, with results anticipated in 2024.

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