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The DELIVER and B-PROTECTED Studies:
Preventing HIV in Pregnant and Breastfeeding Women

In a nutshell

- 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. In addition, if a woman acquires HIV during pregnancy or breastfeeding, the more likely she is to transmit the virus to her baby as well. For many women, the amount of time they are pregnant, breastfeeding, or both, represents a significant portion of their reproductive years.
- Daily use of an antiretroviral (ARV) pill called Truvada®, an approach known as PrEP (short for pre-exposure prophylaxis), and a monthly vaginal ring containing the ARV dapivirine have been shown to be well tolerated and to reduce the risk of HIV in previous trials involving nonpregnant and non-breastfeeding women. While Truvada as PrEP is approved in many countries, not all are willing to offer it to pregnant and breastfeeding women until more is known about its safety. The dapivirine ring is a new product, which in July 2020 received a positive opinion by the European Medicines Agency (EMA), a significant step toward its potential approval in African countries. Much less is known about the ring when used during pregnancy and breastfeeding.
- The DELIVER (MTN-042) study for pregnant women and the B-PROTECTED (MTN-043) study for women who are breastfeeding aim to collect the kind of information needed for regulatory authorities and national programs to consider making the dapivirine ring available to pregnant and breastfeeding women as well as for helping health care providers, and women themselves, to make informed choices about whether to use the ring or oral PrEP during pregnancy and breastfeeding.
- Both the DELIVER and B-PROTECTED studies are being led by the US National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN) at four MTN-affiliated sites in Malawi, South Africa, Uganda and Zimbabwe.

Two Studies: Protecting Pregnant and Breastfeeding Women against HIV

Both DELIVER and B-PROTECTED are Phase IIIb open-label studies. This means that all women will use an active product – either Truvada as daily oral PrEP or the monthly dapivirine ring. Which product they will use is determined by randomization, or chance. Twice as many women will be randomly selected to use the ring because more safety data is needed about its use during pregnancy and breastfeeding.

Both studies are designed to learn about the safety of Truvada as PrEP and the dapivirine vaginal ring in the safest, most efficient way possible.

- **DELIVER** (MTN-042) will enroll 750 HIV-negative women at different times during pregnancy, who will use either the monthly dapivirine vaginal ring or Truvada as daily PrEP until the time they deliver. Of the 750 women who will be enrolled, 500 will be randomly assigned to use the vaginal ring. The study consists of four phases and will be conducted in a stepwise, backward fashion, 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. Women will be followed for an additional six weeks after giving birth and their babies will be in the study for one year.
- **B-PROTECTED** (MTN-043) will enroll up to 200 breastfeeding mothers and their 6- to 12-week-old babies. Participants will be randomly assigned to use either the monthly dapivirine ring or Truvada as daily oral PrEP, with more participants assigned to use the dapivirine ring than oral Truvada. Women will use their assigned product for three months and be followed for an additional two weeks. Babies will be in the study for the same amount of time. Researchers will assess how much drug from Truvada and the dapivirine ring passes into breast milk and how much passes to the baby after breastfeeding, and will measure the effects, if any, this may have on the health and safety of both mother and child.

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Why oral PrEP and the dapivirine ring?

- **Oral PrEP using Truvada,** which contains the ARVs emtricitabine and tenofovir disoproxil fumarate, is approved for HIV prevention in many countries, though a number of national programs have yet to decide whether to offer PrEP to pregnant and breastfeeding women. That's because most of the information about the safety of Truvada in these populations is among women who are living with HIV and using Truvada as part of a treatment regimen. It is based primarily on these data that the World Health Organization recommends Truvada as PrEP during pregnancy and breastfeeding, while also acknowledging the need for more information about its safety specifically in HIV-negative women. PrEP demonstration projects in which women who become pregnant may choose to continue using PrEP, are beginning to provide additional insight, with a growing body of evidence suggesting that PrEP use does not pose significant risk to the mother, her pregnancy or baby.

  Researchers have noted that when women who are taking Truvada as treatment become pregnant their bodies take up less drug than they would otherwise. In early 2020, results from the first component of the IMPAACT 2009 study confirmed the same was true for adolescent girls and young women using Truvada as PrEP, finding drug levels to be 31-37 percent lower during pregnancy compared to during the post-partum period. These results reinforce the importance of daily adherence to PrEP for pregnant adolescents and young women and don't necessarily indicate a lower PrEP efficacy for this group, say the researchers who are planning to proceed with the second part of the study that will enroll up to 350 participants who are HIV-negative and pregnant. IMPAACT 2009 is being conducted at the same sites as the DELIVER and B-PROTECTED studies.

- **The dapivirine vaginal ring** is made of a flexible silicone material containing 25mg of the ARV dapivirine that gets slowly released inside the vagina – the site of potential infection – during the month it is worn, with low absorption elsewhere in the body, Women can insert and replace the dapivirine ring themselves each month. The ring was developed by the nonprofit International Partnership for Microbicides (IPM), which is seeking its regulatory approval for women ages 18 and older. If approved, the dapivirine ring would be the first biomedical prevention method designed specifically for cisgender women and the first long-acting method. Importantly, the ring would represent another option for women who are unable or prefer not to use daily oral PrEP.

  In July 2020, the European Medicines Agency (EMA) adopted a positive opinion for the ring, a significant step toward its potential approval in African countries. The EMA's review was conducted in cooperation with the World Health Organization (WHO) through the Article 58 procedure. Now, through a collaborative process coordinated by the WHO, IPM is seeking regulatory approval of the dapivirine ring in Kenya, Malawi, Rwanda, South Africa, Tanzania, Uganda and Zimbabwe, where the public health need is great and previous studies of the dapivirine ring took place. The first of these approvals could be as early as mid-2021. IPM will be seeking approval from the U.S. Food and Drug Administration as well. In parallel, the WHO will review evidence on the ring as part of its treatment and prevention guidelines process and conduct an abbreviated review for the ring's prequalification, a quality assurance designation that would help facilitate decisions about ring access. Until data from the B-PROTECTED and DELIVER studies is available, however, national programs and health care providers are unlikely to recommend the ring's use by women who are pregnant or breastfeeding.

  Information about the safety of the dapivirine ring during pregnancy and breastfeeding is reassuring but 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. While these findings are important for understanding outcomes associated with exposure during conception and early pregnancy, more information is needed about the safety of the ring during the second and third trimesters. Likewise, safety data is needed among women who are actively breastfeeding and using the ring. Results of a study called MTN-029/IPM 039, which involved women in the U.S. who were no longer nursing but still producing milk, found dapivirine was absorbed at very low levels in breastmilk.

Pregnant and Breastfeeding Women: A History of Being Left Behind in Clinical Research

Pregnant and breastfeeding women are typically excluded from participating in clinical trials, especially from trials of new drugs. Though women of reproductive age may enroll, they often must use contraception throughout study participation, and if they become pregnant, stop using the study product immediately. Such measures are primarily intended to protect the fetus and baby from potential harm but also mean that if the drug is approved for use there will be little or no information about its safety during pregnancy or breastfeeding. As such, decisions about its use during these periods must therefore be made without the benefit of information regarding its safety and effectiveness. Having this information is vitally important. The body undergoes many changes during pregnancy that could affect how a drug gets absorbed and distributed -- a drug may not be as effective or its use may be harmful to the mother, her pregnancy or newborn baby. A baby being breastfeed could be exposed to drug that gets passed into breastmilk, which could be harmful.

Most of what is learned about the safety of a drug during pregnancy and breastfeeding emerges *after* a drug is approved, through post-marketing surveillance registries that keep track of pregnancy complications and adverse outcomes. Studies of a drug specifically involving pregnant or breastfeeding aren't typically conducted until years after approval, if at all.

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More information about the MTN and the DELIVER and B-PROTECTED studies involving pregnancy and breastfeeding women can be found at www.mtnstopshiv.org or click here to watch a short video. For more information about the dapivirine ring go to www.ipmglobal.org.

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