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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, women are especially vulnerable. While the development of safe and effective prevention methods for women has long been a priority, much less attention has been paid to women's HIV prevention needs during periods of pregnancy or breastfeeding, when women are at greatest risk.
- It is estimated that women are 2-3 times more likely acquire HIV during pregnancy and 4 times more likely during periods of breastfeeding. For many women, the amount of time spent pregnant, breastfeeding, or both, represents a significant portion of their reproductive years when they are at heightened risk. Because HIV can infect babies during pregnancy, childbirth or breastfeeding, protecting moms means protecting their babies, too.
- Daily use of an antiretroviral (ARV) tablet called Truvada®, an approach often referred to as PrEP (short for pre-exposure prophylaxis), is approved for HIV prevention in many countries, but information about its safety in pregnant and breastfeeding women is limited. A monthly vaginal ring containing the ARV dapivirine is a new product under regulatory review – much less is known about its safety in these populations.
- Knowing whether daily PrEP and the monthly dapivirine ring are safe during pregnancy and breastfeeding is vitally important. The Microbicide Trials Network (MTN) is planning two studies, DELIVER (MTN-042), for pregnant women, and B-PROTECTED (MTN-043), for women who are breastfeeding, so that regulatory authorities and national programs have the kind of information they need to consider making these HIV prevention methods available to pregnant and breastfeeding women.
- Both studies are funded by the US National Institutes of Health and will be conducted at trial sites in Malawi, South Africa, Uganda and Zimbabwe. DELIVER enrolled its first participant in February 2020. Pending in-country ethics and regulatory approvals, B-PROTECTED is expected to start at some sites in April or May 2020.

Two Studies: Protecting Pregnant and Breastfeeding Women Against HIV

Both DELIVER and B-PROTECTED are Phase IIIb open-label studies. Phase IIIb studies are conducted after a product has already been shown to be safe and effective in Phase III trials. In Phase III trials, participants are randomly assigned to use either the active product or a placebo, which looks the same but contains no drug. There is no placebo in a Phase IIIb study. This means that all women in the DELIVER and B-PROTECTED studies will use an active product – either Truvada as daily PrEP or the monthly dapivirine ring.

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A Study of PrEP and the Dapivirine Ring in Pregnant Women

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 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. Their babies will be followed for one year after birth. The study will be conducted in a stepwise, backward fashion, beginning with women late in pregnancy. Of the 750 women who will be enrolled, 500 will use the vaginal ring. The study is the first to be conducted of the dapivirine ring during pregnancy.
- **B-PROTECTED** (MTN-043) will evaluate whether the dapivirine ring and PrEP are safe to use by women who are breastfeeding, and will enroll up to 200 mothers and their breastfed babies between 6-12 weeks of age. Women will use their assigned product – PrEP or the dapivirine ring – for three months and be followed for an additional two weeks.

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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. 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 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. Observational data from these studies, though limited, suggest no safety concerns. Only DELIVER and another study called IMPAACT 2009 are designed specifically to evaluate safety of PrEP during pregnancy. IMPAACT 2009 is taking place in the same countries and trial sites as DELIVER and will enroll up to 350 pregnant adolescents and young women ages 16-24.

- **The dapivirine ring,** which is used for a month at a time, contains the ARV dapivirine. Unlike Truvada, dapivirine is a new drug entity not used in the treatment of HIV. The dapivirine ring is made of flexible silicone that slowly releases dapivirine during the month that it is worn. Women can insert and replace the ring themselves. In 2016, two large clinical trials — ASPIRE, conducted by the MTN, and The Ring Study, led by the International Partnership for Microbicides (IPM), a non-profit organization that developed the dapivirine ring — found the ring was well-tolerated and helped reduce the risk of HIV by approximately 30 percent. More recently, 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, results also suggest greater reduction in HIV risk (about 50 percent) compared with the Phase III studies.

  IPM is seeking regulatory approval for the ring's use by women 18 and older. 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.

  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. 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. Likewise, results of a study called MTN-029/IPM 039 support moving forward B-PROTECTED. MTN-029/IPM 039, which involved U.S. women who were no longer nursing their babies 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, must stop using the study product immediately. Such measures 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. As a result, a drug that receives regulatory approval will be contraindicated for women during pregnancy and breastfeeding, and decisions about its use during these periods must therefore be made without the benefit of information regarding its safety and effectiveness.

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 newborn baby. With breastfeeding, the concern is that the drug could pass into breastmilk and have an effect on the health of a baby.

As such, most of what has been 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 women, if conducted at all, are typically years after its approval.

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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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