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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 women, and in sub-Saharan Africa, women are especially at high risk. 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 now approved 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.
- The DELIVER and B-PROTECTED studies are funded by the US National Institutes of Health and will be conducted at trial sites in Malawi, Uganda, South Africa and Zimbabwe. Pending in-country ethics and regulatory approvals DELIVER could begin in December 2019 and B-PROTECTED sometime early 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 oral PrEP or the dapivirine ring.

deliver
A Study of PrEP and the Dapivirine Ring in Pregnant Women

Both studies are designed to learn about the safety of 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-0430) 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 addition two weeks.

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Why oral PrEP and the dapivirine ring?

- **Oral PrEP** is approved for HIV prevention in many countries, but guidelines on its use in pregnant and breastfeeding women differ. The World Health Organization, while recognizing the need for more safety data, recommends PrEP during pregnancy and breastfeeding based on the view that the benefits of preventing HIV outweigh any potential risks. But in some countries, PrEP is contraindicated (not recommended) because relatively little is known about the safety of Truvada, the ARV used most often as PrEP, in HIV uninfected pregnant and breastfeeding women. Most information about its safety during pregnancy is in HIV- infected women using Truvada as part of treatment.

  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 PrEP is safe in HIV negative women. 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 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 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, conducted 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 (OLE) studies -- HOPE for former ASPIRE participants and DREAM for former Ring Study participants -- showed high adherence to the ring – indicating women want and will use the ring – and a strong safety profile consistent with the Phase III trials. 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 specifically for women – and the first long-acting method. However, regulatory authorities would need specific data on the ring's safety and use among pregnant and breastfeeding women before considering whether to expand approval to include this population.

  Information about the safety of the dapivirine ring during pregnancy and breastfeeding is reassuring but still very limited. Animal studies indicate no concerns related to pregnancy, and among the approximately 250 women in ASPIRE and The Ring Study who became pregnant, 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. Because women stopped using the ring as soon as they learned they were pregnant, the information is useful for understanding outcomes associated with exposure during conception and early development only. A study called MTN-029/IPM 039 that 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 participation, and if they become pregnant, must stop using the study product immediately. Such measures are intended to protect the fetus and baby from potential harm, but they also make certain that a drug's safety cannot be determined in this population. As a result, a drug that receives regulatory approval will be contraindicated in women during pregnancy and lactation. Drugs are often used during pregnancy and breastfeeding anyway – without knowing if the drug will be safe or effective.

The body undergoes many changes during pregnancy that could affect how the drug gets absorbed and distributed; they may work differently or not be as effective as they were in a clinical trial with non-pregnant women or women not breastfeeding. Of great concern is that drug could pass to the placenta and cause harm to the developing fetus – the very reason for excluding pregnant women from participating in research in the first place; or that the drug that passes into breastmilk could affect 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, may be years after its approval.

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For more information about the dapivirine ring go to www.ipmglobal.org. For more information about the MTN and the DELIVER and B-PROTECTED studies involving pregnancy and breastfeeding women can be found at www.mtnstopshiv.org. For more information about the dapivirine ring go to www.ipmglobal.org.

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