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QUESTIONS and ANSWERS

The DELIVER (MTN-042) and B-PROTECTED (MTN-043) Studies:
Meeting the HIV Prevention Needs of Pregnant and Breastfeeding Women

I. DELIVER and B-PROTECTED: Overview, Context and Need

What are the DELIVER and B-PROTECTED studies?
DELIVER (MTN-042) and B-PROTECTED (MTN-043) are Phase IIIb studies that are evaluating the safety and acceptability of two HIV prevention methods – daily use of an antiretroviral (ARV) pill called Truvada®, an approach known as PrEP (short for pre-exposure prophylaxis) and the monthly dapivirine vaginal ring – in pregnant and breastfeeding cisgender women, respectively. As Phase IIIb open-label studies, all women will use an active product – there is no placebo group. DELIVER is the first study of its kind of the dapivirine ring in pregnant women, and B-PROTECTED is the first study of the ring in women who are actively breastfeeding.

Who is conducting and funding these studies?
Both the DELIVER and B-PROTECTED studies are being conducted by the Microbicide Trials Network (MTN), which is funded by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and National Institute of Mental Health, all components of the U.S. National Institutes of Health.

Where are DELIVER and B-PROTECTED being conducted?
Both studies are being conducted at the same four MTN-affiliated clinical research sites (CRSs): College of Medicine-Johns Hopkins University Research Project in Blantyre, Malawi; Wits Reproductive Health and HIV Institute (Wits RHI) Shandukani Research Centre, Johannesburg, South Africa; Makerere University–Johns Hopkins University (MU-JHU) Research Collaboration, Kampala, Uganda; and the Zengeza CRS of the University of Zimbabwe College of Health Sciences Clinical Trials Research Centre in Harare.

When did DELIVER and B-PROTECTED start and how long will they take to be conducted?
DELIVER began in February 2020 and is anticipated to take up to four years to conduct. B-PROTECTED began in August 2020 and is expected to complete participant follow-up mid-2021.

Why are the DELIVER and B-PROTECTED studies important?
Women need safe and effective methods for HIV prevention they can use at all times of their lives, perhaps especially during pregnancy and breastfeeding, when they are up to four-times more likely to acquire HIV. Moreover, if a woman acquires HIV during pregnancy or breastfeeding, her baby is at greater risk of getting infected as well. Protecting mothers against HIV would mean their babies would be protected, too.

Both Truvada as daily oral PrEP and the dapivirine ring have been shown to be well tolerated and reduce the risk of HIV in clinical trials involving nonpregnant and non-breastfeeding women. Typical of most trials, however, women who were pregnant or breastfeeding were excluded from participation, and those who enrolled had to use contraception, and, if they became pregnant, stop using study product. Such measures primarily intend to protect the fetus and baby from potential harm but also mean that if a drug is approved there will be little or no information about its safety and use during pregnancy and breastfeeding. Truvada as PrEP is approved in many countries, and experience thus far suggests it is safe in pregnant and breastfeeding women, yet not all national programs are willing to offer it these populations until there is more data about its safety. The dapivirine ring is

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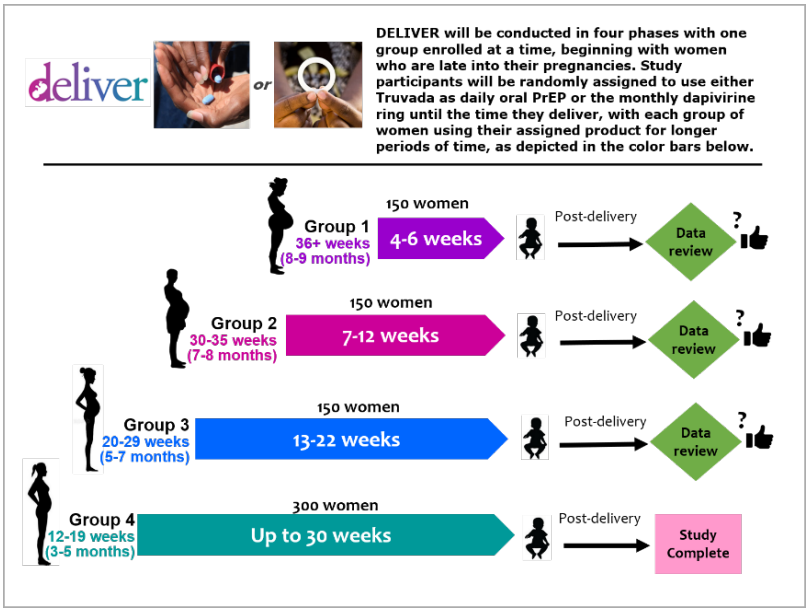
a new product being considered for approval in the same countries where the DELIVER and B-PROTECTED studies are being conducted. Very little is known about the ring when used during pregnancy and breastfeeding. DELIVER and B-PROTECTED aim to collect the kind of information needed for regulatory authorities and national programs to consider making the dapivirine ring available to pregnant and breastfeeding women as well as enable health care providers, and women themselves, to make informed choices about whether to use the ring or oral PrEP during pregnancy and breastfeeding.

How is a woman who is pregnant or breastfeeding any different? What are the potential concerns?
A woman's body undergoes many changes during pregnancy and breastfeeding that could affect how a drug gets absorbed and distributed – a drug may not work as well or its use may not be safe, causing harm to the mother, her pregnancy or baby. A drug could interfere with hormones necessary for the production of breastmilk or, quite likely, pass into the breastmilk itself, which at some point could potentially be harmful.

If clinical trials don't usually include pregnant and breastfeeding women how are these studies safe?
Since its inception in 2007, MTN's scientific portfolio has included a comprehensive research program purposefully designed to take incremental steps for determining whether HIV prevention products are safe to use by women during pregnancy and breastfeeding. Indeed, whether a drug is safe to use during pregnancy or breastfeeding is a question best answered in a controlled clinical trial setting with utmost attention to the safety of both mothers and their babies, rather than in the "real-world" after a drug is already widely available, when in practice, a drug may be used by pregnant and breastfeeding women without the benefit of knowing this is safe.

Both the DELIVER and B-PROTECTED studies are designed to learn about the safety of the dapivirine vaginal ring and Truvada as daily oral PrEP in the safest, most efficient way possible. For instance, DELIVER is being conducted in a step-wise, backward fashion, enrolling one group of women at a time, beginning with women who are late in pregnancy, when use of the ring or PrEP is likely to pose the least risk. In addition, reviews of study data will be conducted after each group to determine whether it is safe to continue. 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 either the dapivirine ring or oral PrEP does not pose additional risk or harm to the mother or her fetus. Multiple layers of safety monitoring are important features of both studies. Ensuring the safety of mothers and babies is what's most important, and site staff will stop a woman's use of PrEP or the ring if there are any concerns.

How is the DELIVER study designed?
DELIVER 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 enroll 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 with enrolling the next group.



Participants 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. Women will be followed for an additional six weeks after giving birth, and their babies will be in the study for one year.

How will you be able to determine whether these products are safe to use during pregnancy?
Though most pregnancies are "uneventful", pregnancy is not without risks. Different kinds of complications can occur, some of these serious. In DELIVER, the research team will document all pregnancy outcomes – whether the pregnancy resulted in a normal delivery with a fully developed baby, an earlier than expected delivery, an early pregnancy loss (miscarriage) or stillbirth. The team will also assess the health of both babies and mothers, keeping track of certain complications. These include high blood pressure or hypertensive disorders of pregnancy (eclampsia and preeclampsia), infection in the womb (chorioamnionitis or endometritis), infection in the blood, and heavy bleeding (hemorrhage). Researchers will take note of any differences that occur between women using the dapivirine ring and women using Truvada as daily PrEP. If the outcomes and complications observed in the study were similar in type and frequency to those considered "normal" for that region, this would suggest that use of these products during pregnancy would not pose additional risk.

Researchers will use as a basis for comparison data collected through a special sub-study called MTN-042B as well as an extensive review of published reports and scientific literature. MTN-042B involved reviewing more than 11,000 medical charts at the same centers and hospitals where DELIVER study participants are expected to have their babies and documenting the pregnancy and complications that occurred within a two-month period.

How is the B-PROTECTED study designed?
B-PROTECTED will enroll up to 200 breastfeeding mothers together with their 6- to 12-week-old babies they are breastfeeding. 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.

Who is leading each of these studies?
DELIVER is being led by Katherine Bunge, MD, of the University of Pittsburgh School of Medicine; and Bonus Makanani, MBBS, FCOG (SA), from the University of Malawi College of Medicine in Blantyre, who are the study's protocol chairs, along with Lee Fairlie, MBChB, FCPeds(SA), MMED (Paeds), from Wits RHI in Johannesburg, South Africa, who is the protocol co-chair. For B-PROTECTED, Maxensia Owor, MBChB, MMed (Paed), MPH, from MU-JHU in Kampala, Uganda, is protocol chair, with Lisa Noguchi, PhD, CNM, Johns Hopkins Bloomberg School of Public Health, Baltimore; and Jennifer Balkus, PhD, MPH, from the University of Washington School of Public Health in Seattle, serving as protocol co-chairs.

What kind of approvals were required to conduct these studies?
Both the DELIVER and B-PROTECTED studies underwent extensive and rigorous review by NIAID and the US Food and Drug Administration (FDA). Moreover, before any site can begin enrolling women into either study, approvals are required of national regulatory authorities in the trial site country and by the site's Institutional Review Board (IRB) or Ethics Committee (EC). IRBs and ECs ensure that studies are scientifically valid and ethically sound and provide oversight throughout the duration of the trial.

What are community views about the use of PrEP and the ring during pregnancy and breastfeeding?
To understand community attitudes and perceptions about the use the ring and PrEP during pregnancy and breastfeeding, researchers conducted the MTN-041 (MAMMA) study in the same communities in Malawi, South Africa, Uganda and Zimbabwe where DELIVER and B-PROTECTED studies would take place. MTN-041 involved group discussions with pregnant and breastfeeding women, male partners, mothers and mothers-in-law and interviews with community leaders, health care providers, midwives and traditional birth attendants, among others. Across all groups, there was an appreciation that women were at high risk of HV during pregnancy and breastfeeding and a need for different methods of protection such as the vaginal ring and oral PrEP. For these products to be accepted, many felt buy-in of healthcare providers would be key. The influence that male partners have over women's decision making and behavior was also emphasized, though in some settings, mothers and mothers-in-laws were deemed equally, if not more, influential.

II. About the Dapivirine Ring and Truvada as Oral PrEP

The Dapivirine Ring

What is the dapivirine vaginal ring?
The dapivirine vaginal ring is made of a flexible silicone material containing 25mg of the ARV dapivirine that when placed inside the vagina slowly releases directly to the site of potential infection during the month it is worn, with low absorption elsewhere in the body. Women can insert and replace the ring themselves each month. The ring was developed by the nonprofit International Partnership for Microbicides (IPM), which is seeking its regulatory approval for cisgender 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.

What is the regulatory status of the ring?
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, which is for products intended for use outside of the European Union and specifically address a disease of major public health interest in low- and middle-income countries. Applications reviewed under Article 58 are conducted according to the same standards as medicines intended for use in the European Union.

Through a collaborative process coordinated through WHO, IPM is now 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 also be seeking US FDA approval. 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.

What do we know about the dapivirine vaginal ring?
Multiple studies of the ring conducted in Africa, Europe and the US have shown it to be well tolerated in HIV-negative women, with no safety concerns. The largest of these were two Phase III clinical trials – ASPIRE (MTN-020), conducted by the MTN, and The Ring Study (IPM 027), led by IPM – involving more than 4,500 women ages 18-45 in Malawi, South Africa, Uganda and Zimbabwe. Results, reported in 2016, found the dapivirine ring reduced the risk of HIV by approximately 30 percent overall. Additional data provided during the EMA's review showed the dapivirine ring reduced women's HIV risk by 35 percent in The Ring Study. Across both studies, higher levels of protection were seen in women who used the ring most regularly. Results of the HOPE (MTN-025) open-label extension (OLE) study for former ASPIRE participants, and the DREAM (IPM 032) OLE for former Ring Study participants, which were first reported in 2019, showed increased ring use and suggested a greater reduction in HIV risk (about 50 percent) than in the Phase III trials.

What is known about the dapivirine ring in pregnant and breastfeeding women?
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, the DELIVER study will provide information about the ring when it used for longer periods and at different stages during pregnancy.

In a study called MTN-029/IPM 039, MTN researchers found dapivirine was absorbed at very low levels in breast milk and noted no safety concerns. MTN-029/IPM 039 enrolled 16 women in the United States who were no longer nursing their babies but still producing milk and who used the dapivirine ring for 14 consecutive days. The study was designed so that babies wouldn't be exposed to drug, but based on levels measured in maternal breast milk, researchers estimated an infant's daily exposure to drug would have been very low. B-PROTECTED will be important for confirming these results in women who are actively breastfeeding and using the ring.

Truvada as Oral PrEP

What is PrEP?
PrEP, which stands for pre-exposure prophylaxis, is an HIV prevention method in which people who don't have HIV take an ARV pill daily to reduce their risk of being infected. WHO recommends oral PrEP for anyone at significant HIV risk.

The ARV pill most commonly used as PrEP is Truvada, the brand name for a tablet containing the ARVs tenofovir disoproxil fumarate and emtricitabine that is marketed by Gilead Sciences of Foster City, California. Truvada was originally developed (and still used) for the treatment of HIV, in combination with other ARVs. Truvada was first approved for use as PrEP by the US FDA in 2012 and has since been approved in more than 50 countries. In 2019, Gilead obtained FDA approval of a second drug for PrEP called Descovy®, which contains emtricitabine and tenofovir alafenamide (F/TAF). Approval does not apply to people at risk of getting HIV through receptive vaginal sex, because effectiveness in this population has not been evaluated. Gilead is planning a trial to begin sometime in 2020 to collect data about the safety and efficacy of F/TAF among cisgender women in Africa.

What do we know about Truvada as oral PrEP in pregnant and breastfeeding women?
Most of the information about the safety of Truvada during pregnancy and breastfeeding is from women living with HIV and taking Truvada as part of a treatment. 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 using it as PrEP. 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 used during pregnancy and breastfeeding does not pose significant risk to the mother, her pregnancy or baby. As clinical studies, DELIVER and B-PROTECTED, and another study called IMPAACT 2009, will provide more specific data about the safety of PrEP during pregnancy and breastfeeding. IMPAACT 2009, which is being conducted among adolescent girls and young women ages 16-24 at the same sites as DELIVER and B-PROTECED, was designed to provide information about the pharmacokinetics (drug absorption) of Truvada during pregnancy as well.

Lower drug levels have been noted in pregnant women using Truvada as treatment, and indeed, IMPAACT 2009 found the same was true when Truvada was used as PrEP. Results of the first phase of the study, which looked specifically at this question and were reported early 2020, found drug levels were 31 to 37 percent lower during pregnancy than in the post-partum period, reinforcing the importance of maintaining daily adherence. In the second phase of the study, researchers will be using these data as a reference for accurately determining whether study participants are taking PrEP daily, and also assess the safety of PrEP in both mothers and their infants.

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More information about the MTN is available at www.mtnstopshiv.org/. To learn more about the DELIVER (MTN-042) and B-PROTECTED (MTN-043) go to https://mtnstopshiv.org/news/studies/mtn042 and https://mtnstopshiv.org/news/studies/mtn043. For more information about the dapivirine ring go to www.ipmglobal.org.

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