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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

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 evaluating the safety and acceptability of two HIV prevention methods in pregnant and breastfeeding cisgender women, respectively – 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, which is being considered for regulatory approval. As Phase IIIb open-label studies, all women who enroll in these studies 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 taking place at four NIAID-funded clinical research sites (CRSs): the College of Medicine-Johns Hopkins University Research Project in Blantyre, Malawi; Wits Reproductive Health and HIV Institute (Wits RHI) Shandukani Research Centre in Johannesburg, South Africa; Makerere University–Johns Hopkins University (MU-JHU) Research Collaboration in Kampala, Uganda; and the University of Zimbabwe Clinical Trials Research Centre Zengeza CRS in Harare.

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, including, if not especially, during pregnancy and breastfeeding, when they are up to four-times more likely to acquire HIV. In sub-Saharan Africa, women and girls account for nearly 60 percent of all new HIV infections, and they are also likely to spend a significant portion of their reproductive years pregnant, breastfeeding or both – times of heightened risk. If a woman acquires HIV while pregnant or breastfeeding, there's a chance the virus could be transmitted to her baby as well. As such, protecting mothers against HIV would be protecting their babies, 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, but as is typically the case, women who were pregnant or breastfeeding were not included, and women who qualified for and enrolled in the study were required to use contraception and if they got pregnant, stop study product. As a result, information about the safety of these products when used during pregnancy and breastfeeding is somewhat limited, particularly for the dapivirine ring. While the information we have so far about their safety is encouraging, more safety data is needed so that national programs, health care providers and women themselves will be able to make informed decisions about the use of either Truvada as PrEP or the dapivirine ring during pregnancy and breastfeeding.

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Why is it important to know about a drug's safety during pregnancy and breastfeeding? What are the potential concerns?
Understanding the drug safety during pregnancy and breastfeeding helps women and their healthcare providers make good decisions about medication use. 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. While most drugs get passed into breastmilk at low levels, it's important to know how much and at what levels a particular drug might pose a risk for the baby.

What do we know so far about the safety of Truvada as PrEP in pregnant and breastfeeding women?
Truvada as PrEP is approved in many countries, and, in some settings, is being offered to pregnant and breastfeeding women. However, most of the information about the safety of Truvada during pregnancy and breastfeeding is from women living with HIV who used it in combination with other drugs as treatment, with several studies finding no harm. It's based primarily on this data that the World Health Organization (WHO) recommends women who are at risk of HIV use Truvada as daily oral PrEP during pregnancy and breastfeeding, while also acknowledging the need for safety data in these populations. Thus far, a growing body of evidence from observational studies has seen no cause for concern. Still, some national programs and healthcare providers remain hesitant about its use until there is additional safety data from a controlled trial.

DELIVER and B-PROTECTED, and another study called IMPAACT 2009, which is being conducted at the same sites among adolescent girls and young women ages 16-24, will provide more specific data about the safety of PrEP during pregnancy and breastfeeding. IMPAACT 2009 was also designed to provide information about the pharmacokinetics (drug absorption) of Truvada as PrEP during pregnancy, which is important because lower drug levels have been noted in pregnant women who are living with HIV and using Truvada as treatment. Indeed, results of the first phase of the study, which were reported early 2020, found the same to be true when Truvada is used as prevention, with drug levels that were 31 to 37 percent lower during pregnancy than in the postpartum period, indicating that full adherence to daily pill taking will be especially important during pregnancy.

What do we know so far about the safety of the dapivirine ring in pregnant and breastfeeding women?
Compared to Truvada as PrEP, much less is known about the safety of the monthly dapivirine ring in pregnant and breastfeeding women. The dapivirine ring is a new HIV prevention method, which in July 2020 received a positive opinion from the European Medicines Agency for its use among cisgender women ages 18 and older in developing countries, and soon after, was added to WHO's list of pre-qualified medicines. In addition, WHO's updated guidelines for HIV prevention, published in March 2021, recommend the ring as an additional HIV prevention choice for women at substantial risk of HIV. The ring's developer, the International Partnership for Microbicides (IPM), is seeking approval of the ring in eastern and southern Africa, with the first of these decisions possibly by mid-2021. IPM is also seeking regulatory approval from the US Food and Drug Administration. If approved, use of the ring during pregnancy or breastfeeding would be at the discretion of healthcare providers and women themselves – a decision that would have to be made based on very little data.

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 the Phase III trials and stopped using the ring as soon as learning 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 suggest ring use during conception and early pregnancy was not harmful, the DELIVER study will provide information about the ring when it is used for longer periods and at different stages during pregnancy. Results of a small study of women who had recently weaned their babies suggest the ring is safe for breastfeeding moms, and that a breastfed infant's exposure to drug would be minimal. B-PROTECTED will be important for confirming these results in women who are actively breastfeeding and using the ring.

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. Understanding 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. In both studies, multiple layers of safety monitoring are important features. 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.

What happens if a woman acquires HIV? And what will be done to protect her baby?
Women who take part in these studies are instructed to use their assigned study product consistently – daily for PrEP, and for the ring, to leave it in for a full month at a time – as well as receive free condoms, frequent HIV testing and HIV risk-reduction counseling, and routine testing and treatment for sexually transmitted infections. Despite these protective measures, a participant could still acquire HIV. Participants who test positive for HIV will be linked immediately to services providing treatment and to prevent transmission of HIV to her baby. Participants will stop using the study products, but they and their baby can still come for study visits.

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 could begin enrolling women into either study, approvals were 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.

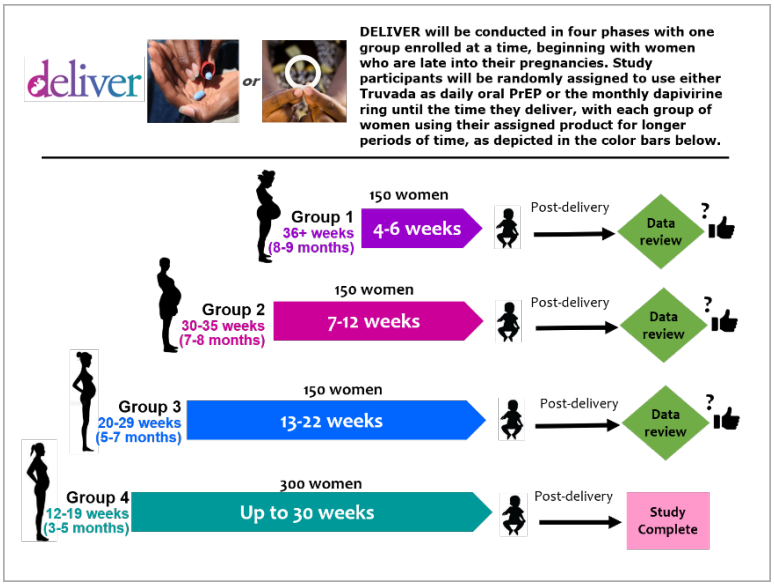
What are community views about the use of PrEP and the ring during pregnancy and breastfeeding?
To understand community attitudes and perceptions about the use the ring and PrEP during pregnancy and breastfeeding, researchers conducted the MTN-041 (MAMMA) study in the same communities in Malawi, South 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.

More about the DELIVER (MTN-042) Study

Who is leading the DELIVER (MTN-042) Study?
DELIVER is being led by Katherine Bunge, MD, MPH, 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.

When did DELIVER start and how long before it will have results?
DELIVER began in February 2020 and is anticipated to take three to four years to conduct. Because of the way it is designed, results will be available at specific intervals throughout the study.

How is the DELIVER study designed?



As currently 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 to 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 enrolling the next group. 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.

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.

Are changes in the study design being considered? If so, what's the rationale and what would be changed?
The need for safety data for the dapivirine ring in pregnant and breastfeeding women is more urgent than ever. With the EMA's positive opinion of the ring last year (2020), the ring's developer, the International Partnership for Microbicides (IPM), is now seeking its approval in several African countries, including those where DELIVER is being conducted. The first decisions could be as early as mid-2021, and in anticipation of the ring's approval, the WHO has already incorporated it into its HIV prevention guidelines.

As such, researchers are proposing modifications in DELIVER's design that would shorten the timeframe for the study's completion and therefore expedite the availability of its final results. Instead of enrolling four groups, the study would enroll three – with the third group being 250 women who are three to seven months pregnant, 200 of whom would be assigned to use the dapivirine ring. Importantly, these changes would not compromise the scientific integrity of the study nor have an impact on the many safety measures already in place. Pending in-country ethics and regulatory approvals, these modifications are anticipated to go into effect early 2022, after the study's completion of Cohort 2.

Who may enroll in DELIVER?
To be considered for the study, women must be HIV-negative, between the ages of 18-40, have normal pregnancy (at the gestational age currently enrolling) and be carrying one baby. Women must also plan to deliver at a hospital or health center and agree to enroll her baby.

How will the study determine whether these products are safe to use during pregnancy?
Though most pregnancies are "uneventful," pregnancy is not without risks, and, as such, it is expected that there will be participants in DELIVER who experience complications, some of which may be serious. The research team will document all pregnancy outcomes (whether it was a full-term live birth, premature birth or stillborn), the method of delivery (vaginal or Cesarean) and the infant's birth weight. The team will also assess the health of both babies and mothers, keeping track of certain complications. These include complications associated with high blood pressure, or so-called hypertensive disorders of pregnancy (gestational hypertension, eclampsia and

preeclampsia); postpartum endometritis, an infection in the uterus that develops after childbirth; chorioamnionitis, an infection in the uterus affecting the amniotic sac or its membranes; and postpartum hemorrhage, or excessive bleeding after childbirth.

Researchers will look to see if the complications and outcomes observed among women in the study are similar in frequency to what would be expected for women generally in the local community, or if they are being experienced more often, which would suggest use of either PrEP or the dapivirine ring as the reason. As a basis for comparison, the research team will use data collected through a special sub-study called MTN-042B as well as an extensive review of published reports and scientific literature for studies taking place in Malawi, South Africa, Uganda and Zimbabwe within the past 20 years.

What exactly was the MTN-042-B sub-study and why is it important?
MTN-042B involved a review of more than 10,000 medical records of women who had given birth within the past seven days that took place over a period of approximately eight weeks at nine healthcare facilities in Blantyre, Malawi; Kampala, Uganda; Johannesburg, South Africa; and in Harare and nearby Chitungwiza, Zimbabwe – the same hospitals and clinics where participants enrolling in DELIVER will be giving birth. As part of the review, researchers took note of the pregnancy outcome and whether the chart included a diagnosis for any of the complications being monitored in DELIVER. In this way, the research team was able to calculate the estimated background rates, or prevalence, of these outcomes and complications in the very same communities where DELIVER is being conducted – information that will be critical for assessing the safety of PrEP and the ring. The data collected in MTN-042B may also be of benefit to local health authorities and other research groups conducting studies in the same urban communities within Malawi, South Africa, Uganda and Zimbabwe. Because many of the complications documented in MTN-042-B are of the type not routinely monitored by national programs or included in comprehensive surveillance-like studies in these settings, the data collected through the medical chart review fills important gaps in information regarding the prevalence of these complications at the local level.

What is the role of the Interim Review Panel?
The Interim Review Panel (IRP) is an independent group of experts in the fields of pediatrics, obstetrics and gynecology, public health, statistics, and ethics from sub-Saharan Africa and North America that plays an important role in monitoring the safety of participants in the DELIVER study. After the last woman in each group has given birth, the IRP will review all of the safety data from that group and, based on this review, will make a recommendation whether the study should proceed with enrollment of the next group of women, who would be earlier in pregnancy and use the study products for longer; should be modified due to concerns about one of the products; or that the study stop altogether. The IRP will use as a basis for comparison the background rates of complications and outcomes provided through the medical records review (MTN-042B) as well as published rates of pregnancy outcomes for each trial-site country.

More about the B-PROTECTED (MTN-043) Study

Who is leading the B-PROTECTED (MTN-043) Study?
B-PROTECTED is being led by Maxensia Owor, MBChB, MMed (Paed), MPH, from MU-JHU in Kampala, Uganda, who 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.

When did B-PROTECTED start and how long before it will have results?
B-PROTECTED began in August 2020 and is expected to complete participant follow-up late 2021, with results anticipated by mid-2022.

How is the B-PROTECTED study designed?
B-PROTECTED will enroll up to 200 HIV-negative breastfeeding mothers together with 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 three times as many participants assigned to use the dapivirine ring. 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.

How will you determine the safety of Truvada as PrEP and the dapivirine ring during breastfeeding?
Researchers will assess how much drug from Truvada and the dapivirine ring passes into breast milk and how much (if any) passes to the baby after breastfeeding. At each study visit, clinic staff will also conduct interviews and physical exams to check for any new signs or symptoms in mothers and their infants and try to determine their cause.

Who may enroll? What are the requirements?
To enroll, women must be exclusively breastfeeding their babies, i.e., not providing their baby any food or drink other than breast milk, and agree to continue exclusive breastfeeding throughout the three months of the study. At the time of enrollment, participants must be using an effective method of contraception, and be willing to be assigned by chance to use either daily oral Truvada or the monthly dapivirine vaginal ring.

More about the dapivirine ring and oral PrEP

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 gets slowly released 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 or other HIV prevention options.

What is oral 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 yet been evaluated. The safety and efficacy of F/TAF among cisgender adolescent girls and women will be evaluated as part of a trial Gilead is planning in South Africa and Uganda.

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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.