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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 use 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 without there being 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.

Though animal studies of dapivirine indicate no concerns related to pregnancy or fetal development, before DELIVER, the only human data was 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. Indeed, the study has already contributed greater understanding of the ring's safety in late pregnancy with interim results from the first cohort of participants finding no concerns.

While 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 are to 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. 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 oral 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. Participants also 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 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 protocol chairs Katherine Bunge, MD, MPH, of the University of Pittsburgh School of Medicine; and up until his death in July 2021, also Bonus Makanani, MBBS, FCOG (SA), from the University of Malawi College of Medicine in Blantyre, along with Lee Fairlie, MBChB, FCPeds (SA), MMED (Paeds), from Wits RHI in Johannesburg, South Africa, who is the protocol co-chair.

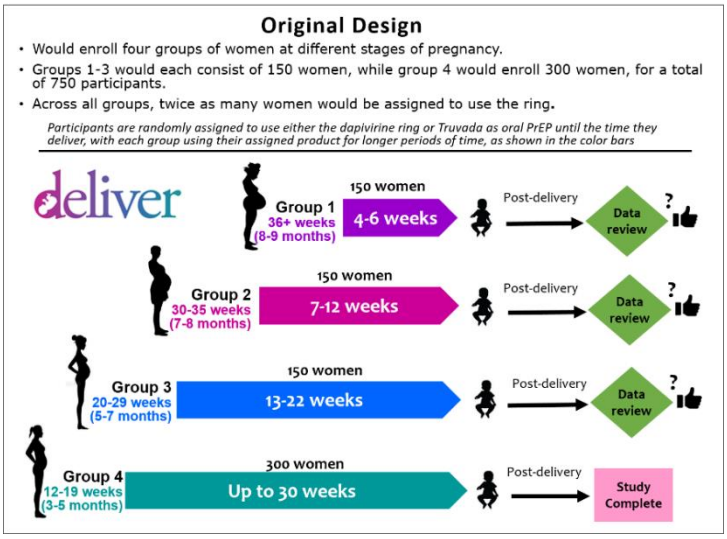
Who may enroll in DELIVER?
To be considered for the study, women must be HIV-negative, between the ages of 18-40, have a normal pregnancy (at the gestational age currently enrolling) and be carrying one baby. Women must also plan to deliver at a hospital or health center and agree to enroll her baby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

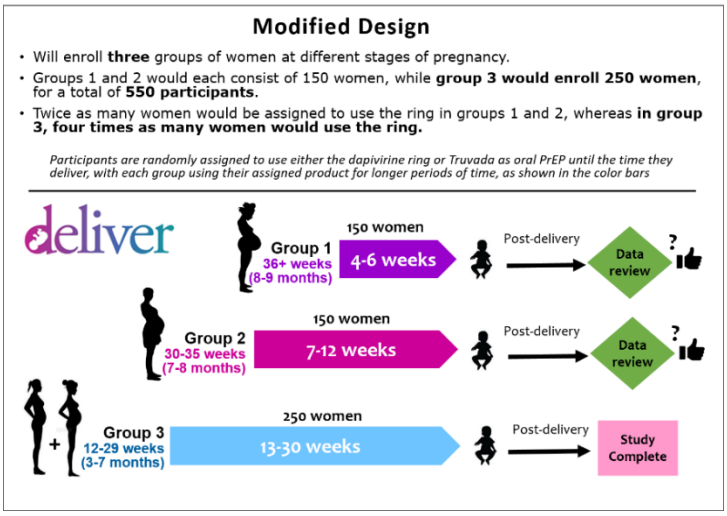
How is the DELIVER study designed?
DELIVER is designed to be conducted in step-wise fashion, enrolling one group of women at a time, beginning with women late in pregnancy, with participants randomly assigned to use either the dapivirine ring or Truvada as oral PrEP until the time they deliver. Interim reviews of study data by an independent panel of experts,

referred to as the Interim Review Board, or IRP, is to take place after completion of each group. Only if the IRP deems it safe to do so does the study then proceed to enroll the next group of women who would be earlier in pregnancy and use their assigned product longer.

While in the study, participants are seen by clinic staff every two to four weeks and asked 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 undergo physical exams, and laboratory tests are conducted. Women are to be followed for an additional six weeks after giving birth, and their babies will be in the study for one year.

As originally designed, DELIVER was to enroll 750 women across four groups, or cohorts, 500 of whom would be assigned to use the ring. In May 2021, researchers modified the design so that the study will instead enroll a total of 550 women across three groups. As before, groups one and two include 150 women each, the first being women who are 36-37 weeks (8-9 months) into their pregnancies at enrollment and the second cohort being women slightly earlier in pregnancy – about 30-35 weeks gestation, or 7-8 months. The third group will be 250 women who are between 12 and 29 weeks gestation (3 -7 months pregnant), 200 of whom will be assigned to use the dapivirine ring.





Why did researchers change the study's design?
The need for safety data for the dapivirine ring in pregnant and breastfeeding women is more urgent than ever. With the European Medicines Agency (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. In July 2021, the ring received its first approval, from the Medicines Control Authority in Zimbabwe. In anticipation of the ring being approved, the WHO has already incorporated it into its HIV prevention guidelines. Where approved, use of the ring during pregnancy or breastfeeding would be at the discretion of healthcare providers and women themselves, yet with very little data on which to base such a decision. The modifications in DELIVER's design would shorten the timeframe for the study's completion and therefore expedite the availability of its final results. Importantly, these changes would not compromise the scientific integrity of the study nor have an impact on the many safety measures already in place.

What is the status of the DELIVER study at this time and when is it expected to be completed?
DELIVER began in February 2020 and in May 2021 completed the first cohort of women who were 8-9 months pregnant when they enrolled. In June 2021, the IRP conducted its review of Cohort 1 safety data and finding no safety concerns, recommended that the study proceed to enroll the next cohort of participants (who are between 7-8 months pregnant), which is anticipated to begin at some sites in July (2021). Researchers anticipate completing Cohort 2 in early 2022. Provided the ensuing IRP review finds no safety concerns, and pending ethics and regulatory approvals of the study's design modification, enrollment of the last cohort of participants would begin soon after (Q1 or Q2 2021) and the study be completed about one year later in Q2 2023.

How is the safety of the dapivirine ring and Truvada as PrEP being assessed? What determines whether or not the study proceeds?
Though most pregnancies are "uneventful," pregnancy is not without risks, and, as such, it is expected there will be participants in DELIVER who experience complications, some that may be serious. The research team documents 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 also assesses 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.

Finding that the outcomes and complications experienced by women in the study are similar in frequency to what would be expected for women generally in the local community would suggest the use of the ring or Truvada as PrEP do not pose safety concerns. If, on the other hand, certain outcomes or complications occurred with greater frequency, this would be cause for concern and the interim review panel would likely pause or stop the study.

How do you know what the outcomes and complications are in each community?
Researchers conducted a special sub-study called MTN-042B that involved a review of more than 10,000 medical records at the same hospitals and clinics where DELIVER study participants give birth, taking 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 needed for assessing the safety of PrEP and the ring in DELIVER.

What were the findings from Cohort 1?
Interim results from the first cohort of participants, which were presented at IAS 2021 – the 11th IAS Conference on HIV Science, in July 2021, found that among the 150 participants, who were between 37 and 38 weeks pregnant at the time they started using either the dapivirine ring (101 participants) or oral PrEP (49 participants), there were relatively few adverse pregnancy outcomes, pregnancy complications and adverse infant outcomes. Furthermore, these occurred at rates that were similar to or lower than rates expected for women in the same communities where DELIVER is being conducted (based on estimates from the MTN-042B sub-study).

Hypertensive disorder of pregnancy, which would be expected to occur in about 10.6 percent of pregnancies, was the most common complication reported, yet in only seven participants, or 5 percent of the women in cohort 1. Of the seven participants, three were in the dapivirine ring group and four were using Truvada as oral PrEP. The majority of pregnancies resulted in live births (147, or 99 percent) and full-term (144, or 98 percent). Three participants (2 percent) gave birth prematurely – one in the dapivirine ring arm and two in the oral PrEP arm. The estimated preterm birth rate at the community level is estimated to be 12.7 percent. There was one stillbirth experienced by a participant in the Truvada arm, and .no cause could be identified. The frequency of stillbirth in the Truvada arm (2 percent) and the cohort as a whole (0.7 percent) is lower than the 4 percent observed in MTN-042B. Nausea experienced by a participant in the Truvada arm was thought to be related to her use of the product. No adverse events in infants were related to the mother's product use.

Who are the members of the Interim Review Panel?
The Interim Review Panel (IRP) is comprised of seven members from both Africa and North America whose collective expertise are in the areas of pediatrics, obstetrics and gynecology, nursing, public health, statistics, and ethics. Importantly, members are independent of the study team, the product developers and the study's funder.

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 the first biomedical HIV prevention product designed specifically for women. The ring is made of a flexible silicone material containing 25mg of the ARV drug dapivirine, about 4 mg of which is released into the vagina when used continuously for 28 days 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 approval in eastern and southern Africa, including in countries where DELIVER is being conducted. In July 2021, the ring received its first approval, from the Medicines Control Authority of Zimbabwe. IPM is also seeking regulatory approval from the US Food and Drug Administration. In anticipation of its approval, 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.

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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The MTN is supported by U.S. National Institutes of Health grants UM1AI068633, UM1AI068615 and UM1AI106707.
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.
21-July-2021