

Fact Sheet

The MTN-042B Sub-study of DELIVER (MTN-042)

Background and Context

- ▶ While the development of safe and effective prevention methods for women has long been a priority, less attention has been paid to women's HIV prevention needs during periods of pregnancy or breastfeeding, when they are up to three to four times more likely to acquire HIV. 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.
- ▶ Two HIV prevention methods – daily use of an antiretroviral (ARV) tablet called Truvada®, an approach called PrEP (short for pre- exposure prophylaxis), and a monthly vaginal ring containing the ARV dapivirine – were found in Phase III trials to reduce the risk of HIV with no safety concerns. Typical of most clinical trials, however, pregnant women were excluded from participation, and women who enrolled were required to use contraception, and, if they became pregnant, stop using study product immediately. As such, information about the safety of these products in pregnant women is somewhat limited, especially for the dapivirine ring, which is a new HIV prevention method under regulatory review.
- ▶ The only human data about the safety of the dapivirine ring during pregnancy is from about 250 women who, despite using contraception, became pregnant while participating in ASPIRE and The Ring Study and stopped use of the ring as soon as learning they were pregnant but continued to be followed by researchers. Of note, there were no significant differences in outcomes between women assigned to use the dapivirine ring and those assigned to use a placebo, but more information is needed about the ring's use for longer periods and at different stages of pregnancy. Most of the information about the safety of Truvada during pregnancy is based on its use as part of HIV treatment, with multiple studies showing no harm. Now that Truvada as PrEP is approved in many countries, some settings are also offering it to women during pregnancy. Thus far, outcomes have indicated no cause for concern, but some national programs are hesitant to provide PrEP to pregnant women until there is data from a controlled study.
- ▶ The DELIVER (MTN-042) study aims to collect the kind of safety data needed about Truvada as PrEP and the dapivirine ring during pregnancy so that national programs, health care providers and women themselves will be able to make informed decisions about their use. Knowing they are safe for both mother and baby is vitally important. After all, protecting moms against HIV would be protecting their babies, too. DELIVER is being conducted by the National-Institutes of Health-funded Microbicide Trials Network at four sites in Malawi, South Africa, Uganda and Zimbabwe.
- ▶ As a Phase IIIb open-label study, all women enrolling in DELIVER will use either PrEP or the ring. The study is being conducted in step-wise fashion, enrolling one group of women at a time, beginning with women late in pregnancy when it's thought the use of these products will pose the least risk. Moreover, reviews of study data will be conducted after each group to determine whether it is safe to continue enrolling the next group of women.
- ▶ Though most pregnancies are "uneventful," pregnancy is not without risks, and, as such, it's expected there will be participants in DELIVER who experience complications, some of which may be serious. With no placebo group, researchers needed a frame of reference for determining whether the particular complications or adverse events observed among women in the study are occurring with similar frequency to what can be expected for women locally, or more often, which would suggest use of either PrEP or the dapivirine ring as the reason.

Researchers designed and conducted MTN-042B as a sub-study of DELIVER to provide the basis for comparison needed to evaluate the safety of PrEP and the dapivirine ring during pregnancy.

MTN-042B in a nutshell

- MTN-042B involved a review of more than 10,000 medical records of women who had given birth in the previous seven days. The review took place over a period of approximately eight weeks at nine healthcare facilities – the same hospitals and clinics where participants enrolling in DELIVER would plan to give birth – in Blantyre, Malawi; Kampala, Uganda; Johannesburg, South Africa; and in Harare and nearby Chitungwiza, Zimbabwe.
- Researchers took note of the pregnancy outcome (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, as well as documented whether the record included a diagnosis for any of the complications to be monitored in DELIVER.

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- The complications being monitored in DELIVER and that were documented in MTN-042B are:
 - **complications associated with high blood pressure, or so-called hypertensive disorders of pregnancy**, which includes 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;
 - **postpartum hemorrhage**, or excessive bleeding after childbirth
- MTN-042B was approved by local ethics committees responsible for research oversight. Each of the research sites also obtained the permission of the participating hospitals and clinics to access medical records. Research teams had no interaction with patients or the clinical staff caring for them.
- MTN-042-B began in August 2019 and was completed in March 2020, just one month after the first site started enrolling participants into the DELIVER study.

What did MTN-042B find?

The full results of MTN-042B were published in [PLOS ONE](#) on 31 March 2021. Some of the key findings include the following:

- Of the 10,138 medical records examined, 13.6 percent included a diagnosis of HIV. Overall, most pregnancies (97 percent) resulted in single births, and 73 percent were vaginal deliveries.
- Most pregnancies (81 percent) resulted in the birth of a full-term baby; 13 percent of infants were born prematurely (before 37 weeks gestation) and 4.1 percent were stillborn, with rates that ranged from 3.1 to 5.5 percent across the four sites – all higher than the national stillborn birth rates for each country of about 2 percent. Likewise, while the lowest pre-term birth rate was in Kampala at 10.7 percent, and the highest was in Johannesburg, at 21.6 percent – both are rates that are higher than the 6.6 and 12.4 percent national estimates for Uganda and South Africa, respectively.
- Of the 9,767 live births (both full and pre-term births), 15.5 percent (1,539) were infants of low birthweight, weighing 2500 grams or less. Two percent of infants (192) died after birth.
- Gestational hypertension – a form of high blood pressure that develops later in pregnancy – was the most common pregnancy complication, which was noted in 4.4 percent of the charts reviewed, though rates varied by site. The lowest prevalence was seen in Kampala, Uganda (about 1 percent) and the highest prevalence was in Chitungwiza and Harare, Zimbabwe (9.3 percent). Preeclampsia and eclampsia, which are more serious hypertension-related complications, occurred in 4.3 percent and 0.6 percent of pregnancies, respectively. The second most common pregnancy complication was postpartum hemorrhage, reported in 3.2 percent of pregnancies. Other complications of interest to the research team – unexplained fever, chorioamnionitis and postpartum endometritis – each were reported in less than 1 percent of records.
- There were seven instances of maternal death, all of which occurred in Blantyre, accounting for less than 1 percent of pregnancies.

How will this information be used? How is it important?

MTN-042B provides researchers with estimated background rates for the specific pregnancy complications and outcomes that are being monitored in DELIVER, and, importantly, in the very same communities where the study is being conducted, which will be extremely useful for evaluating the safety of the ring and PrEP during pregnancy. After the last woman in each group has given birth, an independent panel of experts will review all of the safety data from that group. They will use the data collected through MTN-042B as a basis for comparison in order to make a determination whether to proceed enrolling the next group of women, who would be earlier in pregnancy and therefore be using their assigned product – PrEP or the dapivirine ring – longer. The Interim Review Panel will also base its assessment 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.

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. In addition, while national data exists for pregnancy outcomes generally, some of the findings from the chart review suggest these may not necessarily reflect what is happening at the local level. At some sites, for example, rates of premature births and stillbirths were found to be higher than what would be expected according to the national data.

The clinical research sites (CRSs) that conducted the medical chart reviews for the MTN-042B sub-study are also conducting DELIVER. These are the College of Medicine-Johns Hopkins University Research Project in Blantyre, Malawi; Makerere University-Johns Hopkins University Research Collaboration in Kampala, Uganda; Wits Reproductive Health and HIV Institute) Shandukani Research Centre in Johannesburg, South Africa; and the University of Zimbabwe Clinical Trials Research Centre Zengeza CRS in Harare. A similar study involving breastfeeding mothers and their babies, called B-PROTECTED (MTN-043), is also being conducted at these sites.

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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.

About the Microbicide Trials Network

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners whose work is focused on the rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at www.mtnstopshiv.org/.

31 March 2021