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A Time to Deliver:
Preventing HIV in Pregnant and Breastfeeding Women

Pregnant and Breastfeeding Women: Orphans of Clinical Research

Pregnant and breastfeeding women are typically excluded from participating in clinical trials, especially from trials of new pharmaceutical products. 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 ascertained in this population. Because women are required to stop the drug as soon it is known they are pregnant, researchers can only know about its safety when used at the time of conception and early pregnancy. As a result, a drug that receives regulatory approval will be contraindicated in women during pregnancy and lactation yet may still be prescribed (off-label) to women during pregnancy and breastfeeding anyway – without the benefit of knowing it is safe to do so.

The body undergoes many changes during pregnancy that could affect the bioavailability and distribution of drugs; they may work differently or not be as effective as they were in a clinical trial with non-pregnant women. 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. As such, most of what is learned about the safety of a drug during pregnancy (as well as during 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.

Protecting Pregnant and Breastfeeding Women Against HIV

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 the risk of infection is estimated to be three to four times greater than when not pregnant or nursing. As a global priority, women need safe and effective biomedical HIV prevention strategies for use throughout their lifespan. Indeed, their babies deserve to be protected, too.

For its part, the Microbicide Trials Network (MTN) is planning two studies that will take place at trial sites in Malawi, Uganda, South Africa and Zimbabwe.

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A Study of PrEP and the Dapivirine Ring in Pregnant Women

- **MTN-042,** or the **DELIVER** study, will evaluate the dapivirine vaginal ring and Truvada as daily PrEP (pre-exposure prophylaxis) in pregnant women to determine whether use of these products is safe for both women and their infants. 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.
- **MTN-043** 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. The MTN has already conducted a study (MTN-029/IPM 039) that involved U.S. women who were no longer nursing their babies but still producing milk, which found dapivirine was absorbed at very low concentrations in breastmilk.

Pending ethics and in-country approvals, MTN-042 is expected to start by mid-2019, and MTN-043 could begin soon after. In preparation for these trials, a qualitative study called **MTN-041** is being conducted to understand community belief systems and attitudes that may affect women's perceptions about and potential interest in using the ring or PrEP during pregnancy and breastfeeding. The study involves group discussions with women, male partners and mothers and mothers-in-law of pregnant and breastfeeding women and interviews with community leaders, healthcare providers, midwives and traditional birth attendants, among others.

All three studies are funded by the National Institute of Allergy and Infectious Diseases (NIAID); the *Eunice Shriver Kennedy* National Institute of Child Health and Human Development (NICHD) and National Institute of Mental Health, all components of the U.S. National Institutes of Health.

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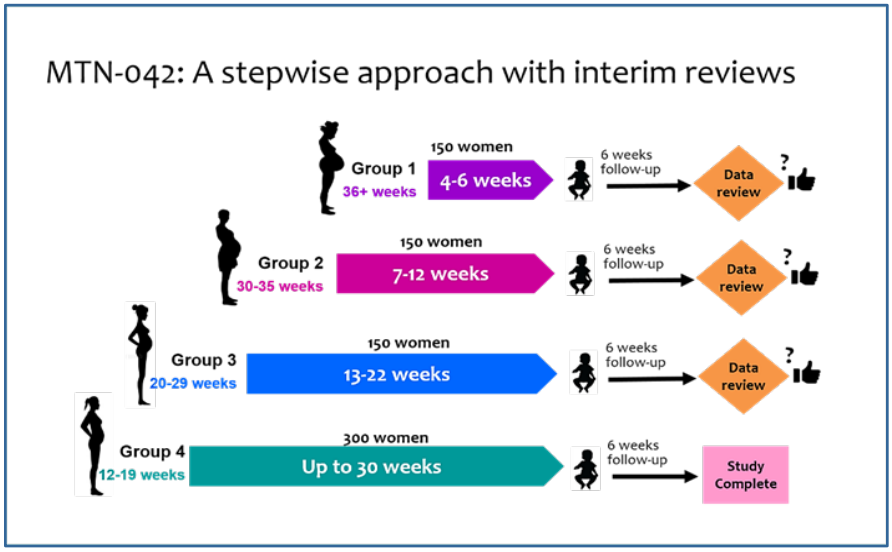
How is DELIVER (MTN-042) designed?

DELIVER is a Phase IIIb open-label study that will evaluate two different HIV prevention approaches in pregnant women — the monthly dapivirine vaginal ring and daily use of Truvada® as PrEP. Both approaches have been found to be safe and effective in trials involving non-pregnant women. The study will enroll 750 HIV-uninfected women at different stages of pregnancy. All participants will use an active product – there is no placebo group. Women will be randomly assigned to use either the dapivirine ring or PrEP until the time they deliver. For each woman assigned to use PrEP, two will use the ring.



Text within each colored arrow indicates the estimated time participants in each cohort would use their assigned product (daily PrEP or a monthly vaginal ring) before delivering.

The primary objective of the study is to understand whether PrEP and the ring are safe and well-tolerated when used during pregnancy — safe for the mother, her pregnancy and her baby. The study consists of four discreet phases defined by the gestational age of the women to be enrolled and will be conducted in a stepwise, backward fashion, beginning with women late in pregnancy (about 36 weeks) who would use either the ring or PrEP for about four to six weeks. Each subsequent group would use their assigned product longer. The fourth and last group of women will be 12-19 weeks pregnant and use either PrEP or the ring the longest – up to 30 weeks. Women will be followed for six weeks after delivery and infants will be followed for one year.

Interim reviews of study data will take place after completion of each phase, and the study will proceed to the next phase only if the review from the previous cohort indicates it is safe to do so. One reason for this design is to be attentive to the potential risks and complications that can occur at different times in pregnancy and fetal development and to ensure that the use of the dapivirine ring or oral PrEP does not pose additional risk or undue harm to either the mother or her fetus.

Why a study of oral PrEP and the dapivirine ring?

- **Oral PrEP**, which involves daily use of the antiretroviral (ARV) Truvada, is approved for HIV prevention in many countries, but guidelines on its use in pregnant 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, such as South Africa, PrEP is contraindicated because relatively little is known about Truvada's safety in HIV uninfected pregnant women. Most information about its safety during pregnancy is in HIV-infected women using Truvada as part of treatment. Observational data, though limited, suggests PrEP is safe in HIV negative women. PrEP demonstration projects in which women who become pregnant choose to continue using PrEP, should provide additional insight. Only DELIVER and another study called IMPAACT 2009 are designed specifically to evaluate safety of PrEP during pregnancy. IMPAACT 2009, taking place in the same countries as DELIVER, 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 International Partnership for Microbicides (IPM), which developed the dapivirine ring, is in the process of seeking regulatory approval for its use by women ages 18-45 based primarily on the ASPIRE and The Ring Study Phase III clinical trials. Should the ring be approved, 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. Data in pregnant women is quite limited, but reassuring. 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.

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More information about the MTN and studies involving pregnancy and breastfeeding can be found at www.mtnstopshiv.org.

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