10,000-plus medical charts provides comparator for HIV prevention study in pregnant women

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A detailed examination of more than 10,000 medical records at maternity clinics and hospitals in urban Malawi, South Africa, Uganda and Zimbabwe has yielded important insight about pregnancy and

neonatal outcomes in these communities as well as the frequency with which different complications occur. The findings, which were published in *PLOS ONE*, include data not often available or reported in much of eastern and southern Africa.

The medical chart review was undertaken by researchers from the National Institutes of Health-funded Microbicide Trials Network (MTN) in preparation for the DELIVER (MTN-042) study, now underway, that is evaluating the safety of two HIV prevention methods in pregnant women- a daily antiretroviral pill called Truvada, an approach known as oral PrEP (short for pre-exposure prophylaxis) and the monthly dapivirine vaginal ring.

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. Because there is no placebo group in DELIVER- all women will use an active product—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 would be expected for women in that region generally, or occurring more often, which would suggest the use of either PrEP or the dapivirine ring as the reason.

The medical chart review was conducted 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 confined their review to records of women who had delivered within the previous seven days, taking 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. Also documented was whether the record included a diagnosis for any of the complications to be monitored in DELIVER. Many of these are complications of the type not routinely monitored by national programs or included in comprehensive surveillance-like studies in these settings. As such, the data collected through the medical chart review fills important gaps in information regarding the prevalence of these complications at the local level, in particular, 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.

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.

"We now have a good idea of background rates for the specific pregnancy complications and outcomes that we are monitoring in DELIVER, and, importantly, in the very same communities where the study is being conducted, which will be extremely useful in our evaluation of the safety of the ring and PrEP during pregnancy. We hope this data can also be of benefit to local health authorities and other research groups who are evaluating novel interventions during pregnancy," said Jennifer Balkus, Ph.D., M.P.H., assistant professor, department of epidemiology, University of Washington in Seattle, and the paper's lead author.

The chart review, which was designed and conducted as a sub-study of

DELIVER (and called 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. In total, 10,138 medical records were examined. Research teams had no interaction with patients or the clinical staff caring for them.

MTN-042B began in August 2019 and was completed in March 2020, just one month after the first site started enrolling participants into the DELIVER study. To date, more than 140 participants have been enrolled.

DELIVER is being conducted in a step-wise, backward fashion, enrolling one group of women at a time, beginning with 150 women who are late in pregnancy (36-37 weeks, or about 8-9 months pregnant) when it is believed use of PrEP or the ring would pose the least risk. Interim reviews of study data by an independent panel of experts will take place after each group to determine whether it is safe to proceed to the next phase, using as a basis of comparison the background rates of complications and outcomes provided through the medical records review 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.

The first of these interim reviews is expected to take place in the coming months, after the last participant in group one has given birth.

DELIVER will provide the kind of information that national programs, health care providers and women themselves need to make informed decisions about whether to use Truvada as PrEP or the dapivirine ring during pregnancy, when a women's chances of acquiring HIV are up to three times greater than at any other time during their lives.

Both products have been found to be well tolerated and to reduce the risk of HIV in clinical trials involving nonpregnant women. PrEP is approved in several countries, and data thus far suggests it is safe to use during pregnancy, though more information about its safety is needed. The monthly dapivirine ring is a new HIV prevention method, which last year 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 the World Health Organization (WHO) 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. IPM is seeking approval of the ring in eastern and southern Africa, with the first of these decisions possibly by mid-year. IPM is also seeking regulatory approval from the US Food and Drug Administration. Compared with Truvada, much less is known about the ring's safety during pregnancy.

The clinical research sites (CRSs) conducting DELIVER also conducted the medical chart reviews for the MTN-042B sub-study. These are the College of Medicine-Johns Hopkins University Research Project in Blantyre, Malawi; Makerere University-Johns Hopkins University (MU-JHU) Research Collaboration in Kampala, Uganda; Wits Reproductive Health and HIV Institute (Wits RHI) Shandukani Research Centre in Johannesburg, South Africa; and the University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC) 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.

More information: *PLOS ONE* (2021). journals.plos.org/plosone/arti… journal.pone.0248423

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