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DELIVER: A Safety Study of a Dapivirine Vaginal Ring and Oral PrEP for the Prevention of HIV During Pregnancy

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Background: Pregnancy represents a period of high HIV acquisition risk. Safety data for the monthly dapivirine vaginal ring (DVR) during pregnancy are limited. Here, we report data from the first 2 cohorts of pregnant participants in MTN-042/DELIVER, a phase 3b, randomized, open-label safety trial of DVR and oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). MTN-042 is being conducted in 3 cohorts beginning with later gestational ages when risks of drug exposure are less.

Methods: Eligible pregnant individuals aged 18–40 years in Malawi, South Africa, Uganda, and Zimbabwe were randomized 2:1 to monthly DVR or daily TDF/FTC. Participants in cohort 1 initiated product use between 36 weeks 0 days (36 0/7 weeks) and 37 6/7 weeks gestation; participants in cohort 2 initiated product use between 30 0/7 and 35 6/7 weeks gestation. All participants continued product use until delivery or 41 6/7 weeks gestation. Pregnancy outcomes and complications were assessed and summarized using descriptive statistics and compared with local background rates obtained through a separate chart review.

Results: One-hundred and fifty participants were enrolled into cohort 1 with 101 randomized to DVR and 49 to TDF/FTC. One-hundred and fifty-seven participants were enrolled into cohort 2 with 106 randomized to DVR and 51 to TDF/FTC. In both cohorts, pregnancy complications were rare and similar to local background rates.

Conclusion: In this first study of a long-acting HIV prevention agent in pregnancy, adverse pregnancy outcomes and complications were uncommon when DVR and TDF/FTC were used in the third trimester of pregnancy, suggesting a favorable safety profile for both prevention products.

Key Words: HIV prevention, pregnancy, safety, pre-exposure prophylaxis, dapivirine vaginal ring

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INTRODUCTION

Pregnancy and postpartum are times of increased HIV acquisition risk.[1] One analysis of 2 HIV prevention trials found that the per-act probability of HIV acquisition was nearly 3 times higher for individuals in late pregnancy compared with their nonpregnant counterparts.[2] Biologically, hormonal changes are associated with increased innate immunity with associated inflammation and decreased adaptive immunity with fewer natural killer cells and reduced cytotoxic T-cell response.[3–7] The progesterone-dominant genital environment is associated with mucosal thinning and increased CCR5 coreceptor expression. Behaviorally, condoms may be used less frequently during pregnancy and sexual partners may seek partners outside of their relationships.[8] Effective HIV prevention methods

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are essential for pregnant people, not only for the pregnant person's health but also for the infant. Perinatal transmission is estimated to be as high as 18% with incident HIV infection during pregnancy.[9]

Oral daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as pre-exposure prophylaxis (PrEP) was the first regimen clinically shown to prevent HIV-1 acquisition. Among nonpregnant reproductive-aged cisgender women, the Partners PrEP trial demonstrated a 66% reduction in HIV-1 incidence compared with placebo.[10] Subsequent demonstration projects reported even higher reductions (>95%) and confirmed high adherence.[11] Efficacy trials of TDF/FTC did not include pregnant and breastfeeding individuals; however, substantial data from pregnant and lactating individuals using TDF/FTC as treatment for HIV and hepatitis B supported its safety.[12] When the US Food and Drug Administration approved TDF/FTC for HIV-1 prevention, it supported continuing or initiating use during pregnancy for women who might benefit[13] as did the World Health Organization.[14] Since 2012, more data have been generated from follow-up studies evaluating the safety and acceptability of TDF/FTC among HIV-negative pregnant persons and no safety concerns have been raised.[15–18]

The dapivirine vaginal ring (DVR) was demonstrated to reduce HIV acquisition in 2 large randomized placebo-controlled clinical trials, and in post hoc analyses, effectiveness was as high as 75% among women who had consistent use.[19–21] The DVR received a positive scientific opinion from the European Medicines Agency under the Article 58 procedure in July 2020 and was recommend by World Health Organization as an additional HIV prevention option in January 2021 as part of a combination prevention approach for "women at substantial HIV risk."[22] It has since been approved by national regulatory authorities in Zimbabwe, South Africa, and Uganda, among others, for women aged 18–45 years. Data available in pregnancy are limited to the periconception period from individuals participating in clinical trials who became pregnant[23] and were instructed to stop using the DVR. Furthermore, the DVRs' acceptability during pregnancy has not been assessed.

We implemented MTN-042/DELIVER, a phase 3b study of DVR and TDF/FTC to assess safety, adherence, and acceptability when used during pregnancy (MTN-042/DELIVER ClinicalTrials.gov Number: NCT03965923). The trial was designed to provide safety data to inform policy makers charged with making product use recommendations during pregnancy as well as pregnant people and clinicians faced with weighing risks and benefits. This study is being conducted in 3 sequential cohorts, with cohort 1 enrolling pregnant participants from 36 0/7 weeks to 37 6/7 weeks gestation, cohort 2 enrolling from 30 0/7 weeks to 35 6/7 weeks gestation, and cohort 3 from 12 0/7 weeks to 29 6/7 weeks gestation. Here, we present details on study design and safety data from cohorts 1 and 2. Maternal safety data from cohort 3 will be presented at a later date. The last maternal participant exited the study in June, 2023, and infant follow-up will continue through May, 2024.

METHODS

Community and Stakeholder Engagement

Given the complexity of conducting safety trials of investigational products during pregnancy, the Microbicide Trials Network (MTN), in partnership with AIDS Vaccine-Advocacy Coalition, held a regional stakeholders consultation in April 2018 to gauge support for advancing DVR in both pregnant and breastfeeding populations and, if supported by regional stakeholders, to solicit input into protocol design.[24] Attendees included Ethics Committee and Institutional Review Board Chairs, Ministry of Health representatives, National Drug Regulatory Authority representatives, Civil society and Non-Governmental Organization representatives, a World Health Organization representative, and other researchers with relevant expertise from Malawi, Uganda, South Africa, and Zimbabwe. Key recommendations are summarized in Table 1. Follow-up stakeholder consultations with additional support from local organizations took place in each of the 4 study countries between March 2019 and January 2020. Attendees included people who had used DVR and TDF/FTC, traditional leaders, representatives from faith-based organizations, male partners, representatives from maternal health and HIV NGOs, Ministry of Health, Institutional Review Board and Ethics Committee representatives, and midwives and physicians. The focus of these meetings was to discuss strategies for study implementation and to explore participants' attitudes about the study's relevance. Key recommendations included maximizing partner and family involvement, strengthening existing relationships with health care facilities, and providing community support and education around the protocol.

Study Overview

Healthy pregnant, HIV-negative people aged 18–-40 years were enrolled across 4 research sites: Blantyre, Malawi; Johannesburg, South Africa; Kampala, Uganda; and Chitungwiza, Zimbabwe (study protocol available at www.mtnstopshiv.org). The primary study objective was to describe maternal and infant safety profiles and pregnancy outcomes after study product use during pregnancy. The protocol was approved by the Prevention Sciences Review Committee of the National Institute of Allergy and Infectious Diseases of the US National Institutes of Health and ethics review committees at each study site.

Study Population

Written informed consent was obtained for maternal participants (subsequently referred to as "participants") and their infants. Eligibility criteria for both cohorts included HIV negative status and the intention to deliver at a health facility where adequate records could be obtained. Key exclusion criteria were current or prior pregnancy complication, genitourinary tract infection at enrollment, or significant laboratory or pelvic examination findings at enrollment. Cohort 1 required a viable singleton pregnancy between 36 0/7 and 37 6/7 weeks' gestation as confirmed by ultrasound; cohort 2

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TABLE 1. Stakeholder Consultation Recommendations for Changes to MTN-042/DELIVER Protocol

Recommendation	Activity	Outcome
Create valid comparator data	Collect background pregnancy outcome data from the participating hospitals	MTN-042B, chart review of 10,138 delivery records at facilities caring for the DELIVER study population[25]
Ensure Global South representation on the Interim Review Panel	Include African pediatrician, obstetrician/gynecologist, midwife, and public health experts on the Interim Review Panel	The Interim Review Panel of 7 experts included 4 African members
Mitigate nonstandardized reporting of pregnancy complications	Adopt standardized definitions for pregnancy complications	Standardized criteria derived from Brighton Collaboration[26] were applied to both DELIVER and MTN-042B
Increase infant follow-up beyond 6 mo	Extend infant follow-up to 1 yr	Protocol revised to extend infant follow-up
Consider mental health evaluation	Include mental health evaluation as part of the safety evaluation	Protocol revised to include mental health evaluation using Edinburgh Postpartum Depression Scale throughout study participation
Carefully describe causes of maternal and neonatal death	Facilitate autopsies	Developed study operations guidance at each site in the event of a maternal or infant death
Share interim study results with participants	Inform participants in later cohorts about the results from previous cohorts	Created communications materials for study participants after each cohort

required a viable singleton pregnancy between 30 0/7 and 35 6/7 weeks' gestation at enrollment as confirmed by ultrasound. Infants were enrolled at birth without set inclusion or exclusion criteria.

Randomization and Study Products

At enrollment, participants were randomized to monthly DVR or daily TDF/FTC assigned in a 2:1 ratio using a fixed-size block randomization, stratified by site. The DVR is an off-white, flexible silicone ring that contains 25 mg of dapivirine. The DVR is intended to be inserted monthly and provide a sustained release of drug over the month. Daily TDF/FTC is a fixed-dose oral tablet containing 300 mg TDF and 200 mg FTC. Participants randomized to DVR were taught how to insert and remove the ring and instructed to remove the ring on onset of labor (defined as the start of contractions or rupture of membranes) or 41 6/7 weeks gestation, whichever came first. Standards of obstetric care in all of the site countries recommend that women be induced by 42 0/7 weeks gestation to avoid pregnancy complications. Participants were provided an instruction card in the local language for health care providers should they present for care with the ring in place.

End points

Primary end points for this study were composite maternal safety, composite infant safety, and pregnancy outcomes. Composite safety for both mother and infant encompassed all serious adverse events (SAEs) and grade 3 or higher adverse events (AEs) as per Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[27,28] Pregnancy outcomes were classified as either full-term live birth (≥37 weeks), preterm live birth (<37 weeks), or intrauterine fetal demise ≥20 weeks. Secondary end points for this study included adherence, acceptability, infant drug levels, and pregnancy complications. Regarding pregnancy complications, each participant was assessed for hypertensive disorders of pregnancy, chorioamnionitis, puerperal sepsis and endometritis, preterm premature rupture of membranes, hemorrhage, and fever of unclear etiology.

Congenital Anomalies

Congenital anomalies were included in SAE reporting although for cohorts 1 and 2, study product would not be implicated given the advanced gestational age at enrollment. We report this information here for reference and comparison for cohort 3. All potential congenital anomalies (both minor and major) were reported by sites and reviewed by an independent consultant geneticist masked to study arm who confirmed a final determination after reviewing infant history and photographic survey (process previously described).[29] The European Surveillance of Congenital Anomalies Guide served as a reference for site clinicians.[30]

Study Visits and Procedures

Pregnant participants returned for in-person visits every 2 weeks and had either in-person or telephone visits on alternating weeks until delivery. Safety-related study procedures conducted in-person included HIV counseling and testing; medical history update; obstetric abdominal examination; and renal, hematologic, and hepatic laboratory evaluations. During telephone visits, clinicians assessed for adverse events (AEs) by history. A postpregnancy outcome visit was scheduled in the clinic for both maternal and infant participants within 2 weeks of delivery. At this visit, maternal laboratory evaluations were conducted as needed; and infant serum creatinine was assessed for all infants. A final safety assessment for the mother was performed 6 weeks after delivery. Infant safety follow-up occurred at 6 weeks, 6 months, and 12 months of life.

Safety Oversight

A Protocol Safety Review Team composed of protocol chairs, Division of AIDS and National Institute of Child Health and Human Development medical officers, MTN

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safety physicians, and International Partnership for Microbicides and Gilead representatives met monthly to review AE data. After all pregnancy outcomes were collected from cohort 1, an external Interim Review Panel (IRP) comprised of 7 members from both Africa and North America who are experts in pediatrics, obstetrics and gynecology, nursing, public health, statistics, and ethics reviewed the safety data and issued an opinion as to whether the study should proceed into the next cohort. This process was repeated after the completion of cohort 2.

Sample Size

The total sample size for all 3 cohorts is approximately 550 pregnant participants: 150 participants each in cohorts 1 and 2 with 2:1 randomization to DVR: TDF/FTC and 250 in cohort 3 with 4:1 randomization. The sample size was determined based on the estimated minimum number of person-years needed for regulatory agencies to assess the safety of the DVR. While data on the safety of TDF/FTC in pregnancy are currently available, the TDF/FTC group was included here for reference.

Statistical Analysis

Using an intent-to-treat analysis, descriptive statistics were used to summarize the frequency of primary safety end points, pregnancy outcomes, and complications by study arm. This report includes adverse event data ascertained through 6 weeks after the date of delivery for both participants and their infants in cohorts 1 and 2. Infant birth weight was also summarized using descriptive statistics. Potential congenital anomalies are reported for reference. Given that we expected some outcomes of interest to occur at low frequencies, no formal statistical testing by arm was performed. However, frequencies of outcomes were qualitatively compared with background rates ascertained as part of a formal multisite, cross-sectional chart review (MTN-042B) conducted at maternal obstetric units where individuals participating in the DELIVER study were expected to deliver.[25]

RESULTS

Study Participants

Between February 2020 and April 2021, 227 participants were screened for cohort 1 and 150 enrolled (101 DVR, 49 TDF/FTC; see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/C122). Enrollment paused briefly early in the COVID-19 pandemic (March–May 2020) until sites implemented risk mitigation plans. The most common reasons for ineligibility were urogenital infection (n = 10), no qualifying ultrasound (n = 8), and a pregnancy outside the gestational age range (n = 8). In cohort 2, of 218 participants screened, 157 were enrolled between September 2021 and March 2022 (106 DVR, 51 TDF/FTC; see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/C122). The most common reasons for cohort 2 ineligibility were no qualifying ultrasound (n = 18), hemoglobin ≥ Grade 2 (n = 9), and urogenital infection (n = 6). Select demographic characteristics, which were generally similar by cohort and arm, are presented in Table 2.

Pregnancy Outcomes

In cohort 1, pregnancy outcome data were available for 148 of 150 participants (99 of 101 in the DVR and 49 of 49 in the TDF/FTC arm). One participant was lost to follow-up, and 1 participant withdrew consent. Most pregnancies resulted in full-term live births (98%) with only 3 (2%) preterm births, 1 (1%) in the DVR arm and 2 (4%) in TDF/FTC (Table 3). There was 1 stillbirth in the TDF/FTC arm. Pregnancy outcome data were available for 154 of 157 participants in cohort 2. One participant withdrew because of family pressures, one withdrew because of relocation, and 1 participant was lost to follow-up. Despite singleton pregnancy being a requirement for inclusion, 1 participant was found to have twins after enrollment; as a result, there were 155 pregnancy outcomes in total. Most cohort 2 pregnancies resulted in full-term live births (94%) with 10 (6%) preterm births, 6 (6%) in the DVR arm and 4 (8%) in the TDF/FTC arm. There was 1 stillbirth in the DVR arm. Frequencies of pregnancy outcomes for both cohorts were similar to those observed in MTN-042B with the exception of stillbirth, which was lower in the DELIVER cohorts.

Maternal Safety

One percent of cohort 1 DVR users experienced 1 or more composite AEs while that percentage of DVR users in cohort 2 was 13.2%, similar to both TDF/FTC groups (Table 4). In cohort 1, there were 4 maternal SAEs reported (Table 4), 1 in DVR arm (urinary tract infection) and 3 in TDF/FTC arm (antepartum hemorrhage, preeclampsia, and perineal injury). In cohort 2, there were 11 maternal SAEs reported, 9 in the DVR arm (2 preeclampsia, 2 hemorrhage, and 1 each of the following: chorioamnionitis, gestational hypertension, oligohydramnios, COVID-19 infection, and postoperative wound infection) and 2 in the TDF/FTC arm (hemorrhage and gastroenteritis). No SAE in either cohort was deemed related to study product.

Infant Safety

In cohort 1, median birthweight was 3.2 kg (interquartile range 3.0–3.4 kg). In cohort 2, the median birthweight was 3.1 kg (interquartile range 2.8–3.4 kg). The percentage of infants with 1 or more composite AEs was similar across cohorts and study arms. In cohort 1, among 147 infants, there were 10 infant SAEs reported (7 in the DVR arm and 3 in the TDF/FTC arm). There was 1 infant death at day of life 2 in the TDF/FTC arm and 1 Grade 4 event for hypoxic ischemic encephalopathy in the same infant (Table 4). In cohort 2, among 152 infants, there were 17 infant SAEs reported (14 in the DVR arm and 3 in the TDF/FTC arm). There was 1 neonatal death in the DVR arm of a female infant delivered by cesarean section at 34 6/7 weeks (1540 grams) for fetal

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TABLE 2. Participants Characteristics at Enrollment by Study Arm and Cohort

Cohort 1	Dapivirine Arm (n = 101)	TDF/FTC Arm (n = 49)	Both Arms (n = 150)
Participant age (yr), mean (SD)	25.4 (5.4)	25.1 (5.4)	25.3 (5.4)
Study site (%)			
Blantyre, Malawi	18 (18)	9 (18)	27 (18)
Johannesburg, South Africa	28 (28)	14 (29)	42 (28)
Kampala, Uganda	30 (30)	14 (29)	44 (29)
Zengeza, Zimbabwe	25 (25)	12 (24)	27 (25)
Had a prior pregnancy (%)	66 (65)	38 (78)	104 (69)
Number of prior full-term live births, mean (SD)	1.7 (1.1)	1.5 (1.0)	1.6 (1.0)
Number of prior spontaneous abortions (<20 weeks), mean (SD)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)
Gestational age at enrollment (wk), mean (SD)	36.4 (0.4)	36.4 (0.6)	36.4 (0.5)
Cohort 2	**Dapivirine Arm (n = 106)**	**TDF/FTC Arm (n = 51)**	**Both Arms (n = 157)**
Participant age (yr), mean (SD)	26.2 (5.5)	26.7 (6.2)	26.4 (5.7)
Study site (%)			
Blantyre, Malawi	26 (25)	14 (27)	40 (25)
Shandukani, South Africa	20 (19)	8 (16)	28 (18)
Kampala, Uganda	28 (26)	14 (27)	42 (27)
Zengeza, Zimbabwe	32 (30)	15 (29)	47 (30)
Had a prior pregnancy (%)	84 (79)	35 (69)	119 (76)
Number of prior full-term live births, mean (SD)	1.6 (1.0)	1.7 (1.0)	1.7 (1.0)
Number of spontaneous abortions (<20 weeks), mean (SD)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)
Gestational age at enrollment (wk), mean (SD)	30.8 (1.1)	30.7 (1.1)	30.8 (1.1)

distress. On delivery, the infant was noted to have multiple dysmorphic features and clinical features of rubella and cytomegalovirus infection. She died on the first day of life.

Congenital Anomalies

In cohort 1, there were 4 congenital anomalies (3%) reported by site staff, 2 (2%) in the DVR arm (scrotal hernia and left foot anonychia) and 2 (4%) in the TDF/FTC arm (umbilical hernia and congenital diastasis recti), of which only 1 anomaly was confirmed after geneticist review (left foot anonychia). In cohort 2, there were 10 congenital anomalies (6%) reported by site staff, 7 (7%) in the DVR arm [ankyloglossia, cryptorchidism, postaxial polydactyly, umbilical hernia (n = 2), syndromic features, café au lait macule, and scrotal hernia] and 3 (6%) in the TDF/FTC arm [laryngomalacia and umbilical hernias (n = 2)]. Four (2.5%) were ultimately confirmed (cryptorchidism, syndromic features, laryngomalacia, and postaxial polydactyly).

Pregnancy Complications

The frequency of pregnancy complications by cohort and arm are summarized in Table 5 with available MTN-042B frequencies provided as a reference. Hypertensive disorders of pregnancy were the most commonly reported complication.

TABLE 3. Pregnancy Outcomes by Study Arm and Cohort

Cohort 1	Dapivirine Arm (n = 99)* n (%)	TDF/FTC Arm (n = 49) n (%)	Both Arms (n = 148) n (%)
Live births	99 (100)	48 (98)	147 (99)
Full term (≥37 weeks)	98 (99)	46 (96)	144 (98)
Premature (<37 weeks)	1 (1)	2 (4)	3 (2)
Stillbirth/intrauterine fetal demise	0 (0)	1 (2)	1 (1)
Cohort 2	**Dapivirine Arm (n = 104)* n (%)**	**TDF/FTC Arm (n = 50) n (%)**	**Both Arms (n = 154) n (%)**
Live births	103 (99)	51 (100)†	154 (99)
Full term (≥37 weeks)	97 (94)	47 (92)	144 (94)
Premature (<37 weeks)	6 (6)	4 (8)	10 (6)
Stillbirth/intrauterine fetal demise	1 (1)	0 (0)	1 (1)

*Number of participants with obtainable pregnancy outcomes.
†51 live births among 50 women as 1 woman had undiagnosed twins.

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TABLE 4. Maternal and Infant Serious Adverse Events and Grade 3 or Higher AEs by Study Arm and Cohort

Cohort 1 Maternal Adverse Events	Dapivirine Arm (n = 101) n (%)	TDF/FTC Arm (n = 49) n (%)	Both Arms (n = 150) n (%)
Participants with 1 or more composite AEs*	1 (1.0)	4 (8.2)	5 (3.3)
Nausea	0 (0)	1 (2.0)	1 (0.7)
Urinary tract infection	1 (1.0)	0 (0)	1 (0.7)
Perineal injury	0 (0)	1 (2.0)	1 (0.7)
Fetal distress syndrome	0 (0)	1 (2.0)	1 (0.7)
Hemorrhage in pregnancy	0 (0)	1 (2.0)	1 (0.7)
Preeclampsia	0 (0)	1 (2)	1 (0.7)
Cohort 1 Infant Adverse Events	**Dapivirine Arm (n = 99) n (%)**	**TDF/FTC Arm (n = 48) n (%)**	**Both Arms (n = 147) n (%)**
Participants with 1 or more composite AEs*	12 (12.1)	6 (12.5)	18 (12.2)
Trisomy 21	1 (1.0)	0 (0)	1 (0.7)
Pneumonia	1 (1.0)	1 (2.1)	2 (1.4)
Underweight	6 (6.1)	3 (6.3)	9 (6.1)
Rectus diastasis	0 (0)	1 (2.1)	1 (0.7)
Hypoxic–ischemic encephalopathy	0 (0)	1 (2.1)	1 (0.7)
Jaundice	1 (1.0)	0 (0)	1 (0.7)
Acute kidney injury	1 (1.0)	0 (0)	1 (0.7)
Meconium aspiration syndrome	0 (0)	1 (2.1)	1 (0.7)
Neonatal asphyxia	2 (2.0)	0 (0)	2 (1.4)
Neonatal respiratory distress syndrome	1 (1.0)	0 (0)	1 (0.7)
Respiratory distress	0 (0)	1 (2.1)	1 (0.7)
Transient tachypnoea of the newborn	1 (1.0)	0 (0)	1 (0.7)
Cohort 2 Maternal Adverse Events	**Dapivirine Arm (n = 106) n (%)**	**TDF/FTC Arm (n = 51) n (%)**	**Both Arms (n = 157) n (%)**
Participants with 1 or more composite AEs*	14 (13.2)	5 (9.8)	19 (12.1)
Anemia	0 (0)	1 (2.0)	1 (0.6)
Amniotic cavity infection	1 (0.9)	0 (0)	1 (0.6)
COVID-19	1 (0.9)	0 (0)	1 (0.6)
Gastroenteritis	0 (0)	1 (2.0)	1 (0.6)
Postoperative wound infection	1 (0.9)	0 (0)	1 (0.6)
Gestational hypertension	1 (0.9)	0 (0)	1 (0.6)
Hemorrhage in pregnancy	1 (0.9)	0 (0)	1 (0.6)
Oligohydramnios	1 (0.9)	0 (0)	1 (0.6)
Placenta previa hemorrhage	0 (0)	1 (2.0)	1 (0.6)
Postpartum hemorrhage	1 (0.9)	0 (0)	1 (0.6)
Preeclampsia	2 (1.9)	0 (0)	2 (1.3)
Premature labor	4 (3.8)	2 (3.9)	6 (3.8)
Preterm, premature rupture of membranes	1 (0.9)	0 (0)	1 (0.6)
Proteinuria	2 (1.9)	0 (0)	2 (1.3)
Cohort 2 Infant Adverse Events	**Dapivirine Arm (n = 102) n (%)**	**TDF/FTC Arm (n = 51) n (%)**	**Both Arms (n = 153) n (%)**
Participants with 1 or more composite AEs*	17 (16.7)	7 (13.7)	24 (15.7)
Dysmorphism	1 (1.0)	0 (0)	1 (0.7)
Facial edema	1 (1.0)	0 (0)	1 (0.7)
Multiple organ dysfunction syndrome	1 (1.0)	0 (0)	1 (0.7)
Bronchiolitis	2 (2.0)	1 (2.0)	3 (2.0)
Gastroenteritis	1 (1.0)	0 (0)	1 (0.7)
Pneumonia	1 (1.0)	1 (2.0)	2 (1.3)
Fetal distress syndrome	2 (2.0)	0 (0)	2 (1.3)
Jaundice	1 (1.0)	0 (0)	1 (0.7)
Small for dates	9 (8.8)	6 (11.8)	15 (9.8)
Neonatal asphyxia	2 (2.0)	0 (0)	2 (1.3)

*Composite safety for both mother and infant encompassed all SAEs and grade 3 or higher AEs as per Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[24,27]

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IRP Review

The IRP reviewed primary maternal end points through delivery and as available for the infants depending on the date of birth relative to the IRP review for each cohort. The IRP unanimously agreed on both occasions that there were no safety concerns and recommended that the study continue as planned. They noted that determining AE relationship to the study product was inherently challenging and recommended continued vigilance for associations.

DISCUSSION

In these first 2 cohorts of pregnant individuals using DVR or TDF/FTC in the third trimester, untoward pregnancy outcomes, adverse events, and pregnancy complications were uncommon, and outcomes were qualitatively similar to background rates in study communities.[25] As expected, the frequency of preterm birth for cohort 1 was lower than the estimated background rate because participants were enrolled at 36 weeks or beyond. Similarly, the rates of stillbirth were lower in both cohorts likely reflecting the inclusion criterion of a healthy singleton pregnancy. In the absence of safety concerns and with the support of the IRP, the third cohort of participants was enrolled and recently completed maternal follow-up. Taken together, data from DELIVER will provide critical safety data for pregnant individuals, clinicians, and regulators on use of DVR throughout pregnancy. This study provides the only human safety data of DVR beyond the periconception period of pregnancy. Makanani et al[23] compared the pregnancy incidence and outcomes by study arm in individuals participating in MTN-020 (ASPIRE) trial, where pregnancy tests were performed monthly and study product was withheld on pregnancy detection. During follow-up, there were 181 pregnancy outcomes in 179 women with no difference in pregnancy incidence, pregnancy outcomes, or frequency of congenital anomalies by study arm.

This study adds to the growing body of literature, demonstrating the safety of TDF/FTC during pregnancy.[31] In a systematic review, Davey et al[18] identified 5 completed and 9 pending studies investigating maternal and infant outcomes after TDF/FTC exposure during pregnancy. Of 5 completed studies including 1042 TDF/FTC-exposed pregnancies, 4 found no differences in pregnancy or infant outcomes in exposed versus unexposed. The Partners Demonstration Project found PrEP exposed infants had lower z-scores for length at 1 month, which resolved by 1 year of life.[32] Nine ongoing studies, including DELIVER, will provide data on >6200 additional TDF/FTC-exposed pregnancies and assess perinatal, infant growth and bone health outcomes.

Historically, pregnant individuals have been classified as a "vulnerable population" and have been excluded from clinical trials of investigational products.[33] Most pregnancy safety data are collected several years postlicensure.[34] The DELIVER study illustrates that conducting safety trials of an investigational product in a pregnant population is possible, and DELIVER's model of de-escalating risk through a cohort approach might serve as a valuable model for the study of other investigational products in pregnancy.

Reassuring animal data, sponsor support, and pharmaceutical company's willingness to advance a product in a pregnant population are all prerequisites to pregnancy trials; however, central to the success of this trial's launch were the series of stakeholder engagement meetings held during protocol development and before implementation. Often

TABLE 5. Maternal Pregnancy Complications by Study Arm and Cohort

	Cohort 1		Cohort 2		
Pregnancy Complication	**Dapivirine Arm (n = 99) n (%)**	**TDF/FTC Arm (n = 49) n (%)**	**Dapivirine Arm (n = 106) n (%)**	**TDF/FTC Arm (n = 51) n (%)**	**Local Background Frequencies (95% CI) of Pregnancy Complications (%)***
Any hypertensive disorder of pregnancy†	3 (3)	4 (8)	9 (8)	5 (10)	10.5 (10.0 to 11.3)
Gestational hypertension	3 (3)	2 (4)	6 (6)	5 (10)	4.4 (4.0 to 4.8)
Preeclampsia without severe features	0 (0)	1 (2)	1 (1)	0 (0)	2.2 (1.9 to 2.5)
Preeclampsia with severe features	0 (0)	1 (2)	2 (2)	0 (0)	2.1 (1.9 to 2.4)
Eclampsia	0 (0)	0 (0)	0 (0)	0 (0)	0.6 (0.5 to 0.8)
Peripartum/Antepartum hemorrhage	0 (0)	1 (2)	2 (2)	2 (4)	—
Postpartum hemorrhage	2 (2)	1 (2)	2 (2)	0 (0)	3.2 (2.9 to 3.6)
Fever of unclear etiology	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (0.1 to 0.2)
Chorioamnionitis	0 (0)	0 (0)	1 (1)	0 (0)	0.2 (0.1 to 0.3)
Postpartum endometritis	0 (0)	0 (0)	0 (0)	1 (2)	0.4 (0.3 to 0.5)
Puerperal sepsis	0 (0)	0 (0)	0 (0)	2 (4)	—
Other‡	1 (1)	1 (2)	4 (4)	0 (0)	—

*Data on background rates obtained as part of a published systematic chart review (MTN-042B).[30] Peripartum/antepartum hemorrhage and puerperal sepsis were not assessed in MTN-042B.

†Any hypertensive disorders is the total of the gestational hypertension, preeclampsia without severe features, preeclampsia with severe features, and eclampsia rows.

‡Others included placenta previa and postpartum anemia for cohort 1 and obstructed labor, oligohydramnios, placenta previa, and wound cellulitis for cohort 2.

CI, confidence interval.

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"stakeholders" are limited to Ethics Committee/IRBs, investigators, and sponsor. Expanding this list to include pregnant individuals, clinicians, faith-based organizations, NGOs, national drug authorities, and policy makers, among others, from protocol development onward leads to a better protocol and a smoother regulatory process. It also helped to lay the groundwork for study implementation as representatives from many sectors of the community contributed to the development process. Having engaged in discussion about utility, feasibility, and ethics of study conduct at stakeholder meetings, community leaders were exceptionally well-informed about the study's stepwise design with safety checks in place and were able to communicate this effectively to others in the community. The high retention rate, defined here as the proportion of participants participating in this study at the time of delivery, in both cohorts during the first 2 years of the COVID-19 pandemic highlights participants' high level of interest and support from their communities and providers.

One strength of this study was the availability of complete background rates for pregnancy outcomes and complications from the formal chart review conducted before study initiation as was recommended by the African stakeholders. A second strength was the use of standardized definitions for pregnancy complications, which minimized the challenges related to having variable definitions for common pregnancy complications.[35] Nonetheless, findings from DELIVER need to be interpreted in the context of several limitations. Only uncomplicated singleton pregnancies were included; furthermore, all study sites are in urban/peri urban settings. As a result, the findings may not be generalizable to more complicated pregnancies or to pregnant individuals living in more rural settings. Because cohorts 1 and 2 only enrolled third trimester pregnancies by design, drug exposure was short. Finally, the study population is too small to appreciate less common pregnancy and neonatal complications.

Cisgender women and other individuals with the capacity for pregnancy have the potential to spend a significant portion of their reproductive lives pregnant or breastfeeding.[36] Excluding pregnant and breastfeeding individuals from safety evaluations of new medications places them in a precarious position once the medication is licensed.[37–39] Together with their clinician, they must decide whether to use the medication without any available safety data in human pregnancy. Rather than releasing a medication to the market without safety data, pharmaceutical companies must evaluate the safety of medications during pregnancy with a safe and thoughtful approach. DELIVER is a valuable model, both for its centering of community stakeholders during study development and sequential approach to evaluating safety. The results from DELIVER suggest that the DVR and TDF/FTC are safe for use in late pregnancy—thus allowing patients and clinicians to effectively weigh risks and benefits of these HIV prevention options.

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