Safety outcomes among infants whose mothers used the dapivirine vaginal ring or oral PrEP during pregnancy (MTN-042/DELIVER): a randomised phase 3b study

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Summary

Background HIV acquisition risk during pregnancy remains high and additional data supporting pre-exposure prophylaxis (PrEP) in pregnancy are needed. The aim of the MTN-042/DELIVER study was to evaluate the dapivirine vaginal ring (DVR) and daily oral tenofovir disoproxil fumarate plus emtricitabine use as PrEP during pregnancy. We report infant outcomes following confirmed in-utero exposure.

Methods This randomised, controlled, open-label, phase 3b study was conducted in four clinical research sites in Malawi, South Africa, Uganda, and Zimbabwe. Pregnant, HIV-negative, healthy women aged 18–40 years were enrolled at 36–37 weeks' (cohort 1), 30–35 weeks' (cohort 2), and 12–29 weeks' (cohort 3) gestation and randomly assigned 2:1 (cohorts 1 and 2) and 4:1 (cohort 3) to receive the DVR (dapivirine 25 mg) or oral PrEP (tenofovir disoproxil fumarate 300 mg plus emtricitabine 200 mg). All infants born to maternal participants were enrolled and included in the primary infant analysis to evaluate infant safety with in-utero exposure to study product. Infant visits were conducted at less than 2 weeks, 6 weeks, 6 months, and 12 months of age. The primary infant composite safety outcome included serious adverse events and grade 3 or higher adverse events. Birth outcomes (livebirth or stillbirth, prematurity), adverse events (including frequency between each study visit), and growth up to 12 months were evaluated and collected. This study is registered with ClinicalTrials.gov (NCT03965923). The trial is completed and the database closed.

Findings The study was conducted between Feb 7, 2020, and May 13, 2024. In total, 545 infants were included: 147 in cohort 1, 154 in cohort 2, and 244 in cohort 3. Mean intrauterine exposure was 23·3, 59·7, and 113·8 days, respectively. Overall, 545 (99%) of 550 pregnancy outcomes were livebirths. Serious adverse events occurred in 66 (17%) of 398 infants in the DVR group and 15 (10%) of 147 in the oral PrEP group. Grade 3 or higher adverse events occurred in 95 (24%) of 398 and 29 (20%) of 147 infants, respectively, none related to product exposure. 41 (51%) of 81 new-onset serious adverse events occurred by age 6 weeks, and ten (91%) of 11 congenital anomalies were diagnosed by age 6 months. There were no maternal or infant HIV acquisitions.

Interpretation Over 12 months of follow-up of infants, the DVR and oral PrEP were generally safe, with no composite adverse events related to study product. Together with available maternal safety data, this supports use of the DVR and oral PrEP by pregnant women to prevent HIV.

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Introduction

Pregnancy and the postpartum period remain high-risk periods for maternal HIV infection, despite increased availability of HIV prevention options for pregnant women, treatment as prevention in discordant relationships, and rigorous implementation of vertical transmission prevention practices including HIV testing and antiretroviral therapy (ART) initiation during pregnancy.[1] HIV acquisition during pregnancy results in untreated or late treatment of maternal HIV and an associated increased viral load. Maternal acquisition of HIV increases risks of poorer outcomes in the mother and cumulative HIV transmission risk to the infant through pregnancy, delivery, and breastfeeding to as high as 40%.[2] Oral pre-exposure prophylaxis (PrEP), when used consistently, is more than 90% effective.[3] The dapivirine vaginal ring (DVR) has an efficacy of around 30%, increasing to 50% with good adherence, and up to 91% with near-perfect adherence as measured by residual ring dapivirine.[4,5] Use of PrEP products in pregnancy requires safety data including maternal and infant outcomes for registration and roll-out at country level and for user reassurance.

Substantial amounts of data are available for oral PrEP with tenofovir disoproxil fumarate plus emtricitabine in pregnancy, with no increased risk of prematurity,

Research in context

Evidence before this study

We searched PubMed for relevant articles published from inception to April 30, 2025. Search terms included "dapivirine vaginal ring", "oral pre-exposure prophylaxis", "oral tenofovir disoproxil fumarate/emtricitabine", "pregnancy and PrEP", "HIV prevention", "HIV acquisition", "adherence", "dapivirine and tenofovir disoproxil fumarate plus emtricitabine exposure", "common infant adverse events", and "infant growth and development". We included meta-analyses and systematic reviews with no language restrictions. While there are substantial data on oral pre-exposure prophylaxis with tenofovir disoproxil fumarate plus emtricitabine in pregnancy that show safety in infants exposed in utero, data including pregnant women using the dapivirine vaginal ring (DVR) and infant safety are scarce. In the placebo-controlled MTN-020/ASPIRE trial, women tested monthly for pregnancy and DVR use was discontinued if pregnancy occurred. The MTN-016 study evaluated outcomes among infants whose mothers became pregnant on ASPIRE and found no difference in maternal and infant outcomes between the placebo and DVR groups. Maternal safety results for MTN-042, where DVR or tenofovir disoproxil fumarate plus emtricitabine was used in pregnancy, from cohorts 1 (≥36 weeks' gestation) and 2 (30–35 weeks' gestation) have been published, with no DVR-related adverse maternal safety events reported and high acceptability of the product. This was a randomised controlled study and the quality of evidence is high. The recently published MTN-043 study evaluated DVR exposure in breastfeeding women and their infants and found no safety concerns and low dapivirine concentrations in breastfed infants.

Added value of this study

This study provides new data on infant safety when maternal DVR is initiated during the second trimester and used continuously through delivery. This study also reports on maternal adherence to study product. This study provides additional evidence to the growing body of data regarding safety of HIV prevention modalities in pregnancy, strengthened in this study by providing evidence of adherence, and therefore product exposure in infants. Adverse events, none of which were related to study product, were common, and we also report that a large proportion of these events occur by age 6 months, suggesting that this might be an appropriate length of infant follow-up for studies evaluating antiretroviral use during pregnancy.

Implications of all the available evidence

Infant safety data from this phase 3 trial support the use of the DVR during pregnancy. Women who are using DVR for prevention can be advised that it is safe to continue use throughout pregnancy. Pregnant women who want to use an HIV prevention method can consider starting this method during pregnancy. Infant exposure to dapivirine in utero is minimal based on the low dapivirine concentrations detected in infant plasma. In this study, adherence to the DVR was high and it was a feasible option for women to prevent acquisition of HIV and potential infection of their neonate. Studies of antiretrovirals in pregnant women, which include infant safety follow-up, could consider 6 months of follow-up, instead of 12 months, given that most adverse events are detected by 6 months of life.

small-for-gestational age (SGA), low birthweight, stillbirth, or congenital anomalies noted compared with regimens not containing tenofovir disoproxil fumarate, demonstrating its safety.[6–8] Overall infant growth appeared similar in infants exposed and not exposed to tenofovir disoproxil fumarate, and no differences were seen in laboratory evaluations of infant renal function or bone mineral density.[9] Since 2016, WHO has supported use of oral PrEP containing tenofovir disoproxil fumarate by pregnant and breastfeeding women at high risk of HIV infection as part of a comprehensive vertical transmission prevention package.[10]

Data on pregnancy outcomes among women using the DVR are scarce. The safety of DVR use in the periconceptual period in a small number of participants was reported in MTN-020/ASPIRE, a placebo-controlled phase 3 efficacy study of the DVR.[5,11] In MTN-020/ASPIRE, 169 women became pregnant on study, resulting in 179 pregnancies, with no difference in pregnancy outcomes between the placebo and DVR groups. Study product was discontinued when pregnancy was diagnosed.[11] MTN-042/DELIVER was designed to assess the safety of DVR use in pregnancies intentionally exposed to DVR in the second and third trimesters in a stepwise fashion across three cohorts, each at an earlier gestational age. Maternal results from cohorts 1 and 2 of MTN-042/DELIVER reported no safety concerns.[12] Results from the MTN-043/B-PROTECTED study, which evaluated the DVR and oral tenofovir disoproxil fumarate plus emtricitabine in breastfeeding women and their infants, are available and report no safety concerns for either the mother or infant.[13] Pharmacokinetic data from mothers and infants from that study showed very low infant exposures to plasma dapivirine or accumulation of intraerythrocytic tenofovir diphosphate.[13] Additional safety data on infants exposed in utero to newer products such as the DVR are important.

In this analysis, we report results from infants whose mothers were enrolled on the MTN-042/DELIVER study, a randomised, open-label clinical trial conducted in four clinical trial sites in Malawi, South Africa, Uganda, and Zimbabwe, to evaluate the safety of the DVR and oral PrEP (tenofovir disoproxil fumarate plus emtricitabine) in pregnant women not living with HIV and their infants. Herein, we describe composite safety results (grade 3 and higher adverse events, serious adverse events) as a primary

objective in infants exposed in utero to tenofovir disoproxil fumarate plus emtricitabine and to dapivirine through maternal use of the DVR, discontinued at birth outcome, up to 12 months of life. We also evaluate the frequency with which adverse events occur in children. Because evaluation of safety outcomes during pregnancy and after birth for the mother and infant requires an understanding of adherence and exposure to product to reach meaningful conclusions, as a secondary objective, we present maternal adherence data and infant drug exposures at different timepoints throughout study participation.

Methods

Study design and participants

MTN-042/DELIVER was a randomised, controlled, open-label, phase 3b study to evaluate safety and acceptability of the DVR and oral PrEP (tenofovir disoproxil fumarate plus emtricitabine) in pregnant women and their infants. Details regarding the study design have been described previously.[12]

In MTN-042/DELIVER, pregnant, HIV-negative, healthy women aged 18–40 years from Malawi, South Africa, Uganda, and Zimbabwe were enrolled in a stepwise manner, with those at the most advanced gestational age of 36 weeks and 0 days (36^{+0} weeks) to 37^{+6} weeks enrolling first (cohort 1), then 30^{+0} weeks to 35^{+6} weeks (cohort 2), and finally 12^{+0} weeks to 29^{+6} weeks (cohort 3). Maternal participants were screened after signing informed consent and exclusion criteria for maternal participation included risk factors for adverse birth outcomes from their current pregnancy (multiple gestation, placenta previa, cervical cerclage, abnormal fetal anatomy, intrauterine growth restriction [IUGR], diabetes, hypertensive disorder of pregnancy, severe malaria, treatment for preterm labour, or oligohydramnios or polyhydramnios) or previous pregnancy (IUGR, hypertensive disorder of pregnancy, intrauterine fetal demise, or preterm delivery) or if they had any laboratory results that could compromise safety, to ensure no increased risks of adverse outcomes on study. In the maternal cohorts, enrolment into each subsequent cohort proceeded after interim safety review from the previous cohort.

Infants were enrolled at birth without set inclusion or exclusion criteria.

Ethics board approval was obtained at each site through the relevant local institutional review board or ethics committee, as well as through relevant national bodies as required. Malawi: University of Malawi College of Medicine Research and Ethics Committee (P.08/19/2765); Johns Hopkins Bloomberg School of Public Health Institutional Review Board (9656); Pharmacy and Medicines Regulatory Authority (PMRA/CTRC/IIIB/10012020119); South Africa: University of the Witwatersrand, Johannesburg Human Research Ethics Committee (190701B); South African Health Products Regulatory Authority (20190814); Uganda: Joint Clinical Research Center (JC1719); Johns Hopkins Medicine Institutional Review Board (IRB00227240); Uganda National Council for Science and Technology (HS 2699); National Drug Authority (CTC-1-0121); Zimbabwe: Medical Research Council of Zimbabwe (MRCZ/A/2523); Joint Research Ethics Committee for the University of Zimbabwe, College of Health Sciences and Parirenyatwa Group of Hospitals (JREC/212/19); Medical Control Authority of Zimbabwe (B/279/5/181/2020). All maternal participants provided written informed consent for themselves and their infants before initiation of study procedures. This study is registered with ClinicalTrials.gov (NCT03965923). The trial is completed and the database closed. The protocol and statistical analysis plan are available online.

For the **protocol** see https://cdn.clinicaltrials.gov/large-docs/23/NCT03965923/Prot_000.pdf

For the **statistical analysis plan** see https://cdn.clinicaltrials.gov/large-docs/23/NCT03965923/SAP_002.pdf

Randomisation and masking

Maternal participants were randomly assigned using a permuted block randomisation schedule, 2:1 (cohorts 1 and 2) and 4:1 (cohort 3), to receive the DVR (dapivirine 25 mg) or oral PrEP (tenofovir disoproxil fumarate 300 mg plus emtricitabine 200 mg). Infants were not randomly assigned on study but were allocated to the maternal randomisation group; all were followed up according to study visits described above. Those assessing safety outcomes or conducting the analysis were not masked to randomisation data.

Procedures

Infant visits were conducted at each study site by study staff at less than 2 weeks (post-pregnancy outcome [PPO] visit), 6 weeks, 6 months, and 12 months of age. At each visit, infant health and feeding history was collected. At the PPO visit, a thorough surface examination was conducted in all participants. At subsequent visits, general examination including vitals, anthropometry, and fontanelle closure was conducted, along with targeted clinical examination as required, and information about concomitant medications and adverse events was recorded through maternal verbal report as well as record review, such as the infant road-to-health card. Infant congenital anomalies were reviewed by a study-assigned clinical geneticist.

Birth outcomes and adverse events were defined and graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July, 2017.[14] Composite safety outcomes were the primary outcomes (grade ≥3 adverse events and serious adverse events). Growth parameters (weight, length, and head circumference) were collected at each visit and evaluated according to the following standards: at delivery, weight was plotted against Intergrowth-21 charts, to evaluate fetal growth at gestational age, which was calculated by the most accurate means (ultrasound, last menstrual period, or fundal height).[15] At birth and in infants younger than 28 days, growth was evaluated using WHO weight-for-age tables and weight was graded according to the DAIDS Female Genital Grading Table.[16] Mild SGA was

categorised between the 3rd and 10th percentile, and severe SGA below the 3rd percentile; there is no "moderate" classification in this table. For infants aged 28 days or older, WHO weight-for-length Z scores were used to grade weight-for-length using DAIDS grading tables.[14] Poor growth was considered moderate if the weight-for-length Z score was between –2 and –3, and severe if –3 or below. Development was assessed using the Ages and Stages Questionnaire, a screening tool to detect gross developmental abnormalities by interviewing a parent or caregiver at the age 6-month and 12-month visits across communication, gross motor, fine motor, problem solving, and personal–social domains.[17] All adverse events were collected throughout the study.

In infants, blood for creatinine was collected at the PPO visit and again at subsequent visits if any abnormalities were detected in the PPO sample or if clinically indicated, to monitor any potential renal complications with exposure to tenofovir disoproxil fumarate plus emtricitabine. Infants had samples taken at the PPO visit (within 2 weeks of birth) to evaluate exposure to dapivirine and tenofovir disoproxil fumarate plus emtricitabine.

To evaluate maternal adherence and infant exposure to study product, maternal blood samples were collected at enrolment, and then subsequent in-clinic visits during pregnancy (every 2–4 weeks) and at the PPO visit.

In the DVR group, plasma was collected to analyse dapivirine concentrations and residual product was measured in the dapivirine rings for participants assigned to this group.

A random subset of maternal plasma samples (50% of DVR group participants) were tested to characterise exposure to dapivirine. All infant samples were tested. Plasma dapivirine concentrations were determined using previously described liquid chromatography–tandem mass spectrometry (LC-MS/MS) analysis; the assay lower limit of quantification (LLOQ) was 20 pg/mL.[18] All bioanalytical assays were validated in accordance with recommended bioanalytical guidelines.[19]

Residual dapivirine concentrations in returned rings were measured. All used rings were collected during follow-up, with the final ring being collected at the PPO visit. As previously described, DVR use was estimated based on residual drug concentrations in returned rings, determined by acetone extraction and high-pressure liquid chromatography.[20] The dapivirine release rate was calculated by subtracting the amount of residual dapivirine in returned rings from the amount in control rings from the same lot divided by the duration of time that the participant had the ring. For rings returned at the PPO visit, the date of delivery was used to approximate duration of ring use. Dapivirine residual drug analysis in used rings was performed at FARMOVS (Bloemfontein, Free State, South Africa) using an LLOQ of 18 mg/ring. Residual drug rates above 0·9 mg/28 days were considered to reflect at least some use over the month.[4,17] All returned rings were tested.

In the oral PrEP group, dried blood spots were collected to evaluate intraerythrocytic tenofovir diphosphate drug concentrations. A random subset of samples from 30% of maternal participants in the oral PrEP group from cohort 1, and 100% of participants in the oral PrEP group from cohorts 2 and 3, were analysed. Intraerythrocytic tenofovir diphosphate was quantified via LC-MS/MS analysis as previously described, with an LLOQ of 31·3 fmol/punch for tenofovir diphosphate.[20] An updated methanol–water solution was used to extract tenofovir diphosphate and emtricitabine triphosphate, resulting in higher drug recoveries. LLOQ was based on previous studies in non-pregnant adults.

Recognising the ethics of conducting PrEP studies with new products in pregnant women, where risk–benefit balance might differ from HIV treatment studies, the MTN 042/DELIVER team held a number of stakeholder consultations, which preceded protocol finalisation and study initiation. Recommendations from stakeholders (regulators, ethicists, clinicians, community representatives and advisory boards, and advocates) included extending follow-up duration from the originally planned 6 months to 12 months, aligning with previous US Food and Drug Administration (FDA) guidance;[21] standardised definitions based on Global Alignment on Immunization Safety Assessment (GAIA) network definitions; and use of tools such as the Ages and Stages Questionnaire, designed to screen for developmental progress at set timepoints.[17,22] These recommendations were included in the study design.

Outcomes

The primary outcomes for this report include infant safety data, measured primarily using a composite safety measure which included all serious adverse events and all grade 3 or higher adverse events (including growth and development).[14] The primary maternal and pregnancy safety data have been published for cohorts 1 and 2,[12] and the data for cohort 3 will be published separately. The secondary outcomes included acceptability (previously published[23]), measurement of infant in-utero exposure to study product (infant plasma dapivirine and intraerythrocytic tenofovir diphosphate concentrations), and adherence (maternal plasma dapivirine concentrations, residual dapivirine concentrations in returned rings, and intraerythrocytic tenofovir diphosphate concentrations). Exploratory analyses include the genital microenvironment and will be published separately.

Systematic infant outcome and safety data were collected at each study visit. Safety measures included adverse events, growth parameters collected at each visit, and development evaluated at age 6 months and 12 months. We assessed the proportion of new-onset adverse events occurring by 6 weeks, between 6 weeks and 6 months, and between 6 months and 12 months of age.

DVR adherence was categorised according to cutoffs for release rate (high use, >4·0 mg/28 days; some use, 0·9–4·0 mg/28 days; little to no use, <0·9 mg/28 days) and plasma dapivirine concentration (high use, >95 pg/mL; some use, 20–95 pg/mL; little to no use, <LLOQ [20 pg/mL]). Oral PrEP adherence was categorised according to cutoffs for tenofovir diphosphate, based on whether the drug had been taken for up to 6 weeks (high use, ≥600 fmol/punch; some use, 150–599 fmol/punch; low use, <150 fmol/punch) or for more than 6 weeks (high use, ≥650 fmol/punch; some use, 200–649 fmol/punch; low use, <200 fmol/punch).

Statistical analysis

The sample size for this study was selected to have a minimum of 100 person-years of maternal safety data on the DVR. This number is typically required by the US FDA for product safety evaluation, to support use as an HIV prevention method among pregnant women. This was approximately 550 participants across three cohorts (150 each in cohorts 1 and 2 and 250 in cohort 3). The confidence intervals (CIs) are provided in the protocol. Data from all enrolled infants were included in the intention-to-treat analysis for the three cohorts, with group determined by the randomisation of the infant's mother.

For the primary infant composite safety endpoint, the number and percentage of infants experiencing at least one adverse event, either a serious adverse event or grade 3 or higher adverse event, and the exact binomial 95% CIs were calculated by group and by cohort.

Mothers' adherence was summarised as either having evidence of exposure or not based on whether the participant had at least one sample above a threshold for the following measures: plasma dapivirine (above LLOQ) or residual dapivirine release rate (>0·9 mg/28 days) for participants in the DVR group; and intraerythrocytic tenofovir diphosphate (>200 fmol/punch, or >150 fmol/punch if sample was

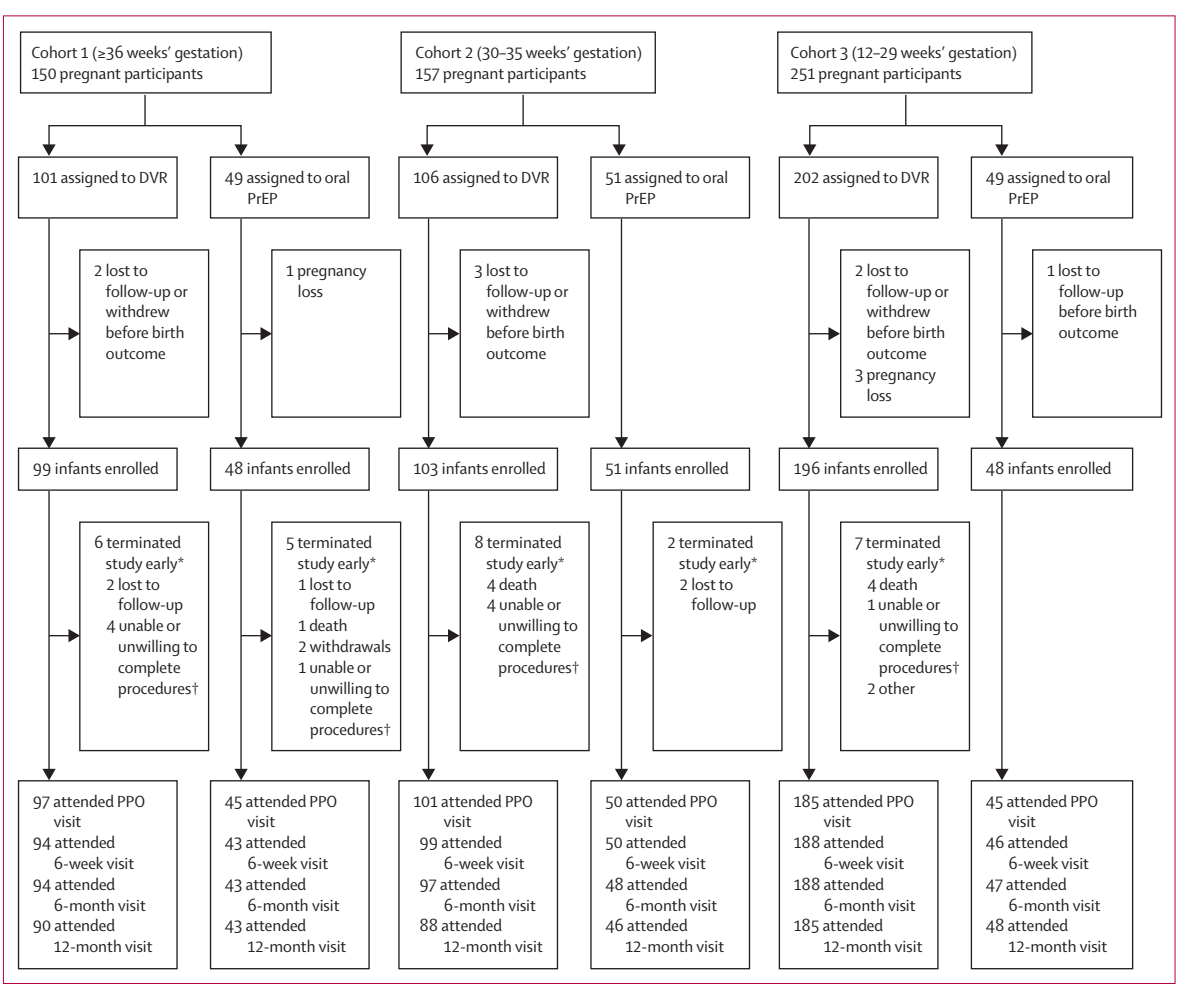

Figure 1: **Trial profile**
DVR=dapivirine vaginal ring. PPO=post-pregnancy outcome. PrEP=pre-exposure prophylaxis (tenofovir disoproxil fumarate plus emtricitabine). *Children did not need to attend the final study visit to be considered to have terminated at the scheduled exit visit. †The infants' parents or caregivers were unable or unwilling to complete study procedures.

collected within 6 weeks of randomisation) for participants in the oral PrEP group.

The secondary infant drug measurement endpoint was analysed descriptively by calculating the number and percentage of infants who had quantifiable intraerythrocytic blood tenofovir diphosphate (among infants whose mothers were randomly assigned to receive oral PrEP) or plasma dapivirine (among infants whose mothers were randomly assigned to receive the DVR) concentrations at the PPO visit. Quantifiable samples were those above the LLOQ for each assay. Infant drug concentrations were also summarised descriptively; for these summaries, samples below the LLOQ were imputed to have a value of half the LLOQ. Statistical analyses were conducted in SAS version 9.4 and R version 4.0.4.

Role of the funding source

US National Institutes of Health (NIH) employees contributed to study design, interpretation of data, manuscript development, and decision to publish, as well as safety oversight during study conduct, but had no role in data collection or analysis.

Results

The study was conducted between Feb 7, 2020, and May 13, 2024. Across all cohorts and groups of the study,

	Cohort 1		Cohort 2		Cohort 3		Total	
	DVR (n=99)	Oral PrEP (n=48)	DVR (n=103)	Oral PrEP (n=51)	DVR (n=196)	Oral PrEP (n=48)	DVR (n=399)	Oral PrEP (n=147)
Sex at birth								
Female	48 (48%)	24 (50%)	62 (60%)	24 (47%)	104 (53%)	25 (52%)	214 (54%)	73 (50%)
Male	51 (52%)	24 (50%)	41 (40%)	27 (53%)	93 (47%)	23 (48%)	185 (46%)	74 (50%)
Gestational age at birth; median (IQR)	40·1 (39·0–41·0)	39·4 (38·3–41·0)	39·7 (38·7–40·7)	39·6 (38·3–40·7)	39·9 (39·1–40·8)	39·6 (38·4–40·5)	39·9 (39·0–40·9)	39·6 (38·4–40·7)
Length of intrauterine product exposure, days*; mean (SD)	24·3 (10·4)	21·1 (11·8)	60·3 (13·8)	58·5 (16·7)	114·6 (29·5)	110·3 (26·6)	78·2 (44·4)	63·3 (41·2)
Preterm births†	1 (1%)	3 (6%)	6 (6%)	4 (8%)	8 (4%)	3 (6%)	15 (4%)	10 (7%)
Available birthweights, n	94	47	101	50	192	48	387	145
Birthweight, kg; mean (SD)	3·19 (0·39)	3·14 (0·42)	3·06 (0·44)	3·12 (0·45)	3·13 (0·47)	3·04 (0·42)	3·13 (0·45)	3·10 (0·43)
Low birthweight (<2·5 kg)‡	2/94 (2%)	3/47 (6%)	6/101 (6%)	3/50 (6%)	12/192 (6%)	3/48 (6%)	20/387 (5%)	9/145 (6%)
Intergrowth-21 weight-for-age severity grade‡								
Mild (≥3rd to 10th percentile)	5/94 (5%)	3/47 (6%)	12/101 (12%)	6/50 (12%)	28/192 (15%)	5/48 (10%)	45/387 (12%)	14/145 (10%)
Severe (<3rd percentile)§	4/94 (4%)	4/47 (8·5%)	8/101 (8%)	2/50 (4%)	11/192 (6%)	2/48 (4%)	23/387 (6%)	8/145 (5%)
Normal	85/94 (90%)	40/47 (85%)	81/101 (80%)	42/50 (84%)	153/192 (80%)	41/48 (85%)	319/387 (82%)	123/145 (85%)

Data are n (%) or n/N (%) unless otherwise indicated. DVR=dapivirine vaginal ring. PrEP=pre-exposure prophylaxis (tenofovir disoproxil fumarate plus emtricitabine). *Time from maternal randomisation to product discontinuation. †Born at less than 37 completed weeks. ‡Percentages are based on the number of available birthweights. §In the Division of AIDS Female Genital Grading Table, no "moderate" grading category exists.

Table 1: **Birth characteristics including gestational age, birthweight, and product exposure for infants enrolled in cohorts 1–3**

	Cohort 1		Cohort 2		Cohort 3		Total	
	DVR (n=99)	Oral PrEP (n=48)	DVR (n=103)	Oral PrEP (n=51)	DVR (n=196)	Oral PrEP (n=48)	DVR (n=399)	Oral PrEP (n=147)
Grade 1	18 (18%)	6 (13%)	9 (9%)	4 (8%)	21 (11%)	8 (17%)	48 (12%)	18 (12%)
Grade 2	51 (52%)	19 (40%)	59 (57%)	30 (59%)	112 (57%)	30 (63%)	222 (56%)	79 (54%)
Grade 3	23 (23%)	11 (23%)	21 (20%)	8 (16%)	39 (20%)	5 (10%)	83 (21%)	24 (16%)
Grade 4	0	2 (4%)	1 (1%)	2 (4%)	3 (2%)	0	4 (1%)	4 (3%)
Grade 5 (death)	0	1 (2%)	4 (4%)	0	4 (2%)	0	8 (2%)	1 (<1%)
Neonatal death (<28 days)	0	1 (2%)	1 (1%)	0	2 (1%)	0	3 (<1%)	1 (<1%)
Death >28 days (infant mortality)	0	0	3 (3%)	0	2 (1%)	0	5 (1%)	0
Number of infants with ≥1 composite adverse event (%; 95% CI)	23 (23%; 15–33)	15 (31%; 19–46)	30 (29%; 21–39)	10 (29%; 10–33)	48 (24%; 19–31)	6 (13%; 5–25)	101 (25%; 21–30)	31 (21%; 15–29)
Congenital anomalies	2 (2%)	0	4 (4%)	1 (2%)	3 (2%)	1 (2%)	9 (2%)	2 (1%)

Data are n (%), where n refers to numbers of infants with at least one adverse event. Participants with multiple adverse events are only counted for their most severe event. Composite safety encompassed all serious adverse events and grade 3 or higher adverse events as per Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events through 12 months. DVR=dapivirine vaginal ring. PrEP=pre-exposure prophylaxis (tenofovir disoproxil fumarate plus emtricitabine).

Table 2: **Infant safety during study follow-up including composite safety outcomes stratified by enrolment cohort**

545 infants were enrolled: 147 in cohort 1 (DVR 99, oral PrEP 48), 154 in cohort 2 (DVR 103, oral PrEP 51), and 244 in cohort 3 (DVR 196, oral PrEP 48; figure 1). The final visit was attended by 133 (90%) of 147 infants in cohort 1, 134 (87%) of 154 in cohort 2, and 233 (95%) of 244 in cohort 3, with reasons for early infant termination from study including death, loss to follow-up, inability to adhere to study visits or procedures, and withdrawal of consent.

214 (54%) of 398 infants in the DVR group and 73 (50%) of 147 in the oral PrEP group were female; the median gestational age at birth was 39·9 weeks (IQR 39·0–40·9) in the DVR group and 39·6 weeks (38·4–40·7) in the oral PrEP group; mean duration of exposure to study product was 78·2 days (SD 44·4) for the DVR and 63·3 days (41·2) for oral PrEP (table 1). Overall, 545 (99%) of 550 pregnancy outcomes (one twin pregnancy) were livebirths. There were five stillbirths or intrauterine deaths (four [1%] DVR-exposed, one [<1%] oral PrEP-exposed). Across all three cohorts, 15 (4%) of 402 pregnancy outcomes in the DVR group were infants born at less than 37 weeks' gestation, compared with ten (7%) of 147 in the oral PrEP group. Birthweights across cohorts and groups were similar, with a mean birthweight of 3·13 kg (SD 0·45) in the DVR group and 3·10 kg (0·43) in the oral PrEP group, with 20 (5%) infants in the DVR group and nine (6%) in the oral PrEP group having a low birthweight (<2·5 kg). At birth, Intergrowth-21 weight-for-age percentiles showed that 45 (12%) and 14 (10%) infants in the DVR and oral PrEP groups, respectively, had mild (3rd to 10th percentile) SGA, while 23 (6%) and eight (5%) infants had severe (<3rd percentile) SGA.

83 (21%), four (1%), and eight (2%) of 399 infants in the DVR group, and 24 (16%), four (3%), and one (<1%) of 147 infants in the oral PrEP group, had their highest severity adverse events be grade 3, 4, or 5 adverse events, respectively, according to the DAIDS Toxicity tables (table 2). Serious adverse events occurred in 66 (17%) of 398 infants in the DVR group and 15 (10%) of 147 in the oral PrEP group. Grade 3 or higher adverse events occurred in 95 (24%) of 398 and 29 (20%) of 147 infants, respectively, none related to product exposure. There were nine deaths, including four neonatal deaths; three were in the DVR group (one child with prematurity; one with meconium aspiration syndrome; and one with dysmorphic features, multiorgan failure, and presumed congenital cytomegalovirus infection [cytomegalovirus IgM positive]) and one was in the oral PrEP group (hypoxic ischaemic encephalopathy). An additional five infants, all DVR-exposed, died after 28 days; causes included severe pneumonia (n=1), blunt head injury (n=1), acute gastroenteritis (n=2), and sudden infant death syndrome (n=1). No deaths were considered related to study product exposure. Congenital anomalies, reviewed and confirmed by the study geneticist, were reported in 11 infants, of whom nine were in the DVR group (major: trisomy 21 [n=1], dysmorphic features [n=1], and biliary atresia [n=1]; minor: polydactyly [n=1], pectus excavatum [n=1], missing toenails [n=1], undescended testes [n=2], and tongue tie [n=1]) and two were in the oral PrEP group (both minor: laryngomalacia [n=1] and undescended testes [n=1]). None of these were considered related to study product.[24]

Infant adverse events were typical for their communities (appendix pp 4–33), and none were considered to be related to study product by the site investigators or the protocol safety review team. A full list of adverse events is shown in the appendix (pp 4–33).

See Online for appendix

The mean creatinine concentration across all visits and all cohorts was 0·31 µmol/L. Creatinine was elevated in 11 children: eight had grade 1 (mild) elevation (1·1–1·3 times the upper limit of normal [ULN]); two grade 2 (moderate) elevation (1·3–1·8 times ULN); and one grade 3 (severe) elevation (1·8 to <3·5 times ULN). All resolved on study. No maternal or infant participants acquired HIV infection in this study.

Infant growth was similar across all cohorts and by study product at the 6-week, 6-month, and 12-month study visits (appendix p 2). Severe (WHO weight-for-length Z score –2 to –3) poor weight gain was observed in seven (2%) of 380 children in the DVR group and two (1%) of 139 in the oral PrEP group at the 6-week visit, no children at the 6-month visit, and one (<1%) of 362 in the DVR group and two (1%) of 137 in the oral PrEP group at the 12-month visit.

In the study, seven (1%) of 518 children assessed for developmental abnormalities fell below the threshold cutoff score at 6 months and 12 months (appendix p 3). Scores were similar in the DVR and oral PrEP groups. Seven infants had eight developmental abnormalities, which varied across domains, and were referred onward for further management.

Most new-onset serious adverse events and growth failure reported on study were reported at the infant 6-week visit (25 [49%] of 51 cases of grade 2 and nine [75%] of 12 of grade 3 weight-for-length Z scores; 41 [51%] of

	≤6 weeks	>6 weeks to 6 months	≥6 months to 12 months
Weight-for-length Z score grade ≥2 (moderate) (n=51)	25 (49%)	10 (20%)	16 (31%)
Weight-for-length Z score grade ≥3 (severe) (n=12)	9 (75%)	0	3 (25%)
Serious adverse events (n=81)	41 (51%)	22 (27%)	18 (22%)
Death* (n=9)	4 (44%)	2 (22%)	3 (33%)
Hospitalisations (n=71)	38 (54%)	18 (25%)	15 (21%)
Congenital anomalies† (n=11)	7 (64%)	3 (27%)	1 (9%)
Developmental delay (n=7)	0	2 (29%)	5 (71%)

Data are n (%). *Infant deaths: hypoxic ischaemic encephalopathy (n=1); prematurity (n=1); meconium aspiration syndrome (n=1); severe pneumonia (n=1); blunt head injury (n=1); dysmorphic features, cytomegalovirus infection, and multiorgan failure (n=1); acute gastroenteritis (n=2); sudden infant death syndrome (n=1). †Congenital anomalies (reviewed by study geneticist): missing toenails (n=1), trisomy 21 (n=1), laryngomalacia (n=1), polydactyly (n=1), undescended testes (n=3), dysmorphic features (n=1), biliary atresia (n=1), pectus excavatum (n=1), tongue tie (n=1).

Table 3: **New-onset adverse events by study visit up to 6 weeks, between 6 weeks and 6 months, and between 6 months and 1 year**

81 serious adverse events, including four [44%] of nine cases of death and 38 [54%] of 71 hospitalisations; and seven [64%] of 11 congenital anomalies; table 3). Proportions of new-onset serious adverse events reported between 6 weeks and 6 months, and between 6 months and 12 months, were similar. Almost all (ten [91%] of 11) congenital anomalies were diagnosed by 6 months. Among seven children with developmental delay, two (29%) were diagnosed at the 6-month visit and five (71%) at the 12-month visit.

Using plasma dapivirine measurements, 192 (96%) of 200 women had evidence of exposure to product. Mean plasma dapivirine concentration in women at the last study visit before delivery was 219 pg/mL (SD 117·2), and 157 (84%) of 187 women were above the 95 pg/mL threshold associated with continued product use; notably, maternal plasma dapivirine concentrations declined steadily by the PPO visit (figure 2A). Adherence to the DVR was observed in 199 (90%) of 222 samples at 12–29 weeks' gestation, 336 (87%) of 385 samples at 30–35 weeks' gestation, and 254 (84%) of 301 samples at 36 weeks' or later gestation across the three cohorts based on DVR residual ring measurements (figure 3A).

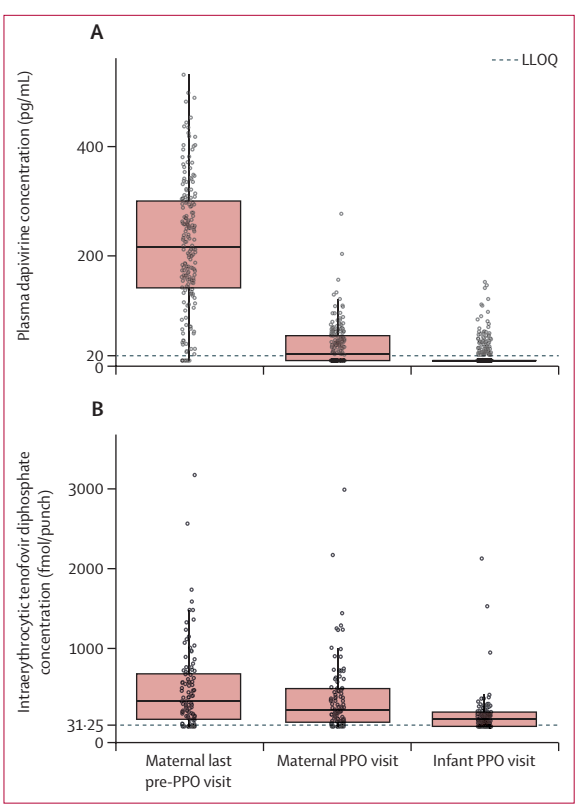

Figure 2: **Maternal and infant plasma dapivirine concentrations and intraerythrocytic tenofovir diphosphate concentrations during pregnancy and postpartum**

(A) Maternal dapivirine concentrations at the last visit before delivery, while still pregnant; maternal dapivirine concentrations at the PPO visit conducted within 2 weeks post-delivery; and infant dapivirine concentrations at the PPO visit. (B) Maternal tenofovir diphosphate concentrations at the last visit before delivery, while still pregnant; maternal tenofovir diphosphate concentrations at the PPO visit conducted within 2 weeks post-delivery; and infant tenofovir diphosphate concentrations at the PPO visit. LLOQ=lower limit of quantification. PPO=post-pregnancy outcome.

Plasma dapivirine concentrations were low in infants born of mothers assigned to the DVR group. Among infants with available samples, plasma dapivirine was quantifiable in only 22 (23%) of 94 infants in cohort 1, 31 (32%) of 97 infants in cohort 2, and 30 (16%) of 182 infants in cohort 3 (figure 2A). In infants, median dapivirine concentrations were at or near the LLOQ, with median concentrations of 10·0 pg/mL (IQR 10·0–10·0), 10·0 pg/mL (10·0–24·7), and 10·0 pg/mL (10·0–10·0) across cohorts 1, 2, and 3, respectively, at the PPO visit.

In the oral PrEP group, 86 (75%) of 115 women had any evidence of tenofovir disoproxil fumarate plus emtricitabine use during pregnancy while 29 (25%) of 115 women had no evidence of use, based on intraerythrocytic tenofovir diphosphate concentrations. Concentrations above the threshold to indicate maternal adherence were observed in 71 (49%) of 146 samples at 12–29 weeks' gestation, 115 (53%) of 217 samples at 30–35 weeks' gestation, and 105 (58%) of 181 samples at 36 weeks' or later gestation (figure 3B). Mean maternal intraerythrocytic tenofovir diphosphate concentration at the last study visit before delivery was 586·8 fmol/punch (SD 973·6) and decreased further at the PPO visit (figure 2B).

Tenofovir diphosphate was quantifiable in 30 (68%) of 44 infants in cohort 1, 35 (70%) of 50 infants in cohort 2, and 30 (70%) of 43 infants in cohort 3. Infant tenofovir diphosphate concentrations were low, with a median of 58·5 fmol/punch (IQR 15·6–141·5), 102·5 fmol/punch (15·6–176·0), and 89·2 fmol/punch (15·6–210·0), for cohorts 1, 2, and 3, respectively.

Mean maternal intraerythrocytic emtricitabine triphosphate concentration at the last study visit before delivery was 0·26 pmol/punch (SD 0·20) and decreased further at the postpartum visit. Emtricitabine triphosphate was quantifiable in seven (16%) of 44 infants in cohort 1, six (12%) of 50 infants in cohort 2, and one (2%) of 43 infants in cohort 3. Infant emtricitabine triphosphate concentrations were low, with a median of 0·05 pmol/punch (IQR 0·05–0·05), 0·06 pmol/punch (0·06–0·06), and 0·06 pmol/punch (0·06–0·06), for cohorts 1, 2, and 3, respectively.

Discussion

In the MTN-042/DELIVER study, we report that in-utero exposure to the DVR and tenofovir disoproxil fumarate plus emtricitabine is safe for infants, similar to our previous observations in mothers during the pregnant period.[12] In this study, no reported composite safety outcomes (serious adverse events as well as grade 3 or higher adverse events as the primary endpoints), including infant growth, development, and congenital anomalies, or adverse events in infants were considered

related to study product. All observed adverse events commonly occur in children in the countries where the study was conducted.[25] Although a growing body of evidence exists for exposure to tenofovir disoproxil fumarate plus emtricitabine during pregnancy and infant safety, this is the first study evaluating the impact of the DVR on infants when used in pregnancy from 12 weeks' gestation up to 1 year of life. Makanani and colleagues[11] have previously reported on infant safety from women who conceived while using a DVR, but discontinued product upon diagnosis of pregnancy, with no difference in safety between the groups including congenital anomalies (eight overall, four in each group). At birth, adverse infant outcomes were lower than that reported in the MTN 042B study, which was a precursor study to MTN-042/DELIVER to ensure accurate comparator data when these results were analysed.[26] In MTN 042B, which included data for 10 180 (97·6%) pregnancies in the same facilities where participants for MTN-042/DELIVER were recruited, 4·1% of infants were stillborn, 13·1% were delivered preterm, 15·5% had low birthweight, 2·0% died during the neonatal period, and 1·2% had congenital anomalies; by comparison, these percentages in MTN-042/DELIVER were 1% and 0·7% (stillbirth or intrauterine death), 4% and 7% (preterm), 5% and 6% (low birthweight), and 0·8% and 0·7% (neonatal death) for the DVR and oral PrEP, respectively. In MTN-042/DELIVER, only two congenital anomalies were considered major, and none was considered to be related to product exposure. Median birthweight in MTN-042/DELIVER was similar to MTN 042B.[26] Infant creatinine concentrations were in the normal range among most infants, with 11 having elevations (mostly grade 1 [mild]) which subsequently resolved. About one in seven infants in this study were SGA, which is slightly lower than global data from 2012 reporting that 19·3% of infants were SGA.[27] In low-income and middle-income countries, SGA is associated with substantial morbidity and is linked to 21·9% of neonatal deaths.[27] Ongoing evaluation of SGA and modifiable factors is important, given the persistent burden of short and long term morbidities in SGA infants.

Safety data for any prevention product are only valid if there is documented use of the study product and biological evidence that infants were exposed to the study drugs. In this study, good adherence to study product was observed, particularly to the DVR. Infant concentrations of intraerythrocytic tenofovir diphosphate and plasma dapivirine were measured to evaluate study product transfer to infants. 96% of women had evidence of DVR use based on plasma dapivirine concentrations. High acceptability of the DVR in pregnancy has already been reported and since DVR efficacy is, as expected, directly related to adherence, high levels of adherence and protection against HIV infection are achievable with near-perfect use in pregnancy.[4,23] Further reassurance in our study was provided by low observed concentrations

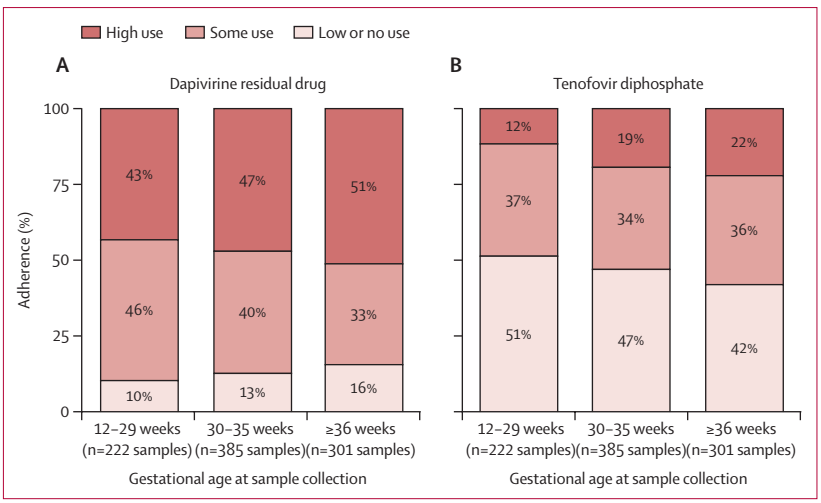

Figure 3: **Maternal adherence to the DVR and oral PrEP measured by residual ring dapivirine and intraerythrocytic tenofovir diphosphate**

(A) Residual ring measurements demonstrated that maternal adherence to the DVR was 89%, 87%, and 84% at 12–29 weeks', 30–35 weeks', and ≥36 weeks' gestation, respectively, based on definitions of "some use" and "high use" being considered as consistent use, providing evidence of infant in-utero exposure to product. The figure is represented as whole numbers, which has resulted in the adherence measure of 89% at 12–29 weeks. Decimal places added would give a result of 90% adherence. (B) Intraerythrocytic tenofovir diphosphate concentrations demonstrated that maternal adherence to oral PrEP was 49%, 53%, and 58% at 12–29 weeks', 30–35 weeks', and ≥36 weeks' gestation, respectively. DVR=dapivirine vaginal ring. PrEP=pre-exposure prophylaxis (tenofovir disoproxil fumarate plus emtricitabine).

of plasma dapivirine and intraerythrocytic tenofovir diphosphate concentrations in infant plasma. This might be advantageous for use in pregnancy where concerns regarding fetal exposure to drugs and potential toxicity exist.

Adherence to daily oral PrEP was lower than for the DVR, with one in four women having no evidence of having used oral PrEP as measured by tenofovir diphosphate from dried blood spots. Findings from the recently published PURPOSE-1 study, which reported 100% efficacy with 6-monthly lenacapavir, showed similar HIV incidence in women randomly assigned to oral PrEP groups to background HIV incidence in the community from where participants were recruited, and was attributed to poor adherence to oral PrEP.[28] Although with perfect oral PrEP adherence, efficacy is around 96%, this drops rapidly with suboptimal adherence and these data support that choices for PrEP, made with consideration for lifestyle, life stage, and perceived risk, are important in ensuring adequate adherence to the chosen PrEP method.[3,29]

Our study initially planned to follow up infants up to 6 months of life. However, stakeholders recommended that we follow up infants up to 1 year of life to ensure that all adverse events plausibly related to drug exposure could be captured and to document all congenital anomalies. In our study we observed that the highest proportion of infant adverse events occurred by the 6-week visit. Similar proportions of adverse events occurred between the 6-week and 6-month visits, and the 6-month and 12-month visits, and almost all (91%)

congenital anomalies were diagnosed by the 6-month visit. Common adverse events that occurred in the study included gastroenteritis, respiratory tract infections, neonatal jaundice, dermatitis, and malaria, and almost all infants had an adverse event during the study, but none were related to study product. Childhood illnesses and comorbidities are common, especially in low-income and middle-income environments such as sub-Saharan Africa, and could complicate interpretation of outcomes related to exposure to a study product.[25] Malnutrition, including stunting, wasting, and being overweight, is common in sub-Saharan Africa in children younger than 5 years, with increased mortality risk in children affected by stunting and wasting together.[30,31] Furthermore, in sub-Saharan Africa, 50·4% of children experience common childhood illnesses including respiratory tract infections, gastroenteritis, and fever.[25] Up to a third of children in low-income and middle-income countries might have cognitive or socioemotional developmental delay, which is associated with infectious disease, HIV exposure, stunting, poverty, male sex, low maternal and infant haemoglobin (greatest impact in the first 15 months of life), and maternal malaria.[32] We did not find a benefit to extending clinical follow-up in infants to 12 months of age. Given that adverse events occur commonly and are not related to study product exposure, and that most occur early in life (before 6 weeks of age), consideration for shortening the duration of follow-up in infants exposed to maternal product to 6 months is reasonable. Increased cost of longer follow-up time in infants might deter development of studies including pregnant individuals, resulting in a paucity of data in maternal and infant populations, where the study drug could be beneficial. Surveillance is essential to add to safety data, particularly for less common or rare anomalies.

A limitation of this study was that the sample size was not sufficient to evaluate rarer outcomes such as birth defects; however, the sample size required would exceed 10 000 participants, which was not feasible in this study.[33] In addition, the study excluded any maternal participants at risk for adverse outcomes, for safety reasons, based on the current or previous pregnancy, which might limit generalisability of the findings.

Over 6-month and 12-month follow-up of infants in the MTN-042/DELIVER study, no safety concerns were observed following demonstrated maternal use of the DVR or oral tenofovir disoproxil fumarate plus emtricitabine. No composite safety or adverse events were related to either DVR or oral PrEP and most events occurred by the 6-week visit, with most congenital anomalies diagnosed by 6 months. Combined with previously reported maternal safety findings, this analysis supports use of the DVR and oral tenofovir disoproxil fumarate plus emtricitabine by pregnant women to prevent HIV. Together with data on DVR use in breastfeeding individuals, and accumulating pregnancy and infant follow-up data with maternal cabotegravir and lenacapavir use, the increasing choice of products available for PrEP in pregnant and lactating women is very encouraging given the ongoing high risk of HIV acquisition during these time periods.

Contributors

LF, DWS, AM, KB, JP, CC, RS, and SLH contributed to study design. LF, KB, FM, CC, and JP contributed to safety monitoring. LF, DWS, AM, KB, JP, and SLH contributed to supervision of trial conduct. DWS contributed to analysis of the data. DWS, JP, LF, and AM directly accessed and verified the data. LF, DWS, AM, FM, KB, JP, CC, RS, MAM, PLA, and SLH contributed to interpretation of the data. LF, DWS, AM, KB, JP, FM, and SLH contributed to writing. All authors contributed to review and editing, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests

LF reports grant funding and payments for data monitoring committee participation from Gilead to her institution. SLH reports grant funding from the NIH, consulting fees from Merck and Freya Biosciences, and serving as a board member (unpaid) for the CROI Foundation Board. MAM reports NIH grant payments to his institution; payments from ViiV and Gilead made to his institution; serving as Co-Editor of Contemporary Practice in Clinical Chemistry, 4th Edition (published by Elsevier); and travel support for presenting at the annual meeting of the Association for Diagnostics and Laboratory Medicine. CC reports grant funding through her institution from Gilead Sciences, Merck, and Organon; and consulting fees from serving on a Gilead advisory board. PLA reports NIH funding to his institution; and Gilead payments to his institution. All other authors declare no competing interests.

Data sharing

The data from this manuscript will be available for sharing and use by other parties on request. Data are available for researchers who provide a methodologically sound proposal in accordance with the policies of the Microbicide Trials Network. Study-related documents (eg, protocol, statistical analysis plan, and informed consent form) can be made available with a signed data use agreement. Data will include those collected for the study, including individual participant data and a data dictionary defining each field in the set. Data will include de-identified participant data. For data access requests, contact sc.mtn-data-access@scharp.org, DWS at szydlo@fredhutch.org, and LF at lfairlie@wrhi.ac.za. Each analysis request will be considered, and will include study investigator involvement and review and approval of a proposal. A signed data access agreement will be signed between relevant parties.

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