HIV acquisitions, safety, and pharmacokinetics of lenacapavir for HIV pre-exposure prophylaxis in pregnant and lactating women (PURPOSE 1): a substudy of a phase 3, randomised controlled trial

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Summary

Background Lenacapavir demonstrated high efficacy and safety as pre-exposure prophylaxis (PrEP) in cisgender women, but its use during pregnancy and lactation when women are disproportionately vulnerable to HIV acquisition has not previously been described. We aimed to evaluate HIV acquisition, safety, and pharmacokinetics of lenacapavir for PrEP in pregnant and lactating women.

Methods The randomised, double-blind, multicentre, active-controlled, phase 3 PURPOSE 1 study compared twice-yearly subcutaneous lenacapavir with daily oral emtricitabine–tenofovir alafenamide or emtricitabine–tenofovir disoproxil fumarate in women who were not pregnant at enrolment. Cisgender adolescent girls and young women aged 16–25 years were randomly assigned (2:2:1) to receive subcutaneous lenacapavir (927 mg, in two 1·5 mL injections) every 26 weeks following a 600 mg oral loading dose on days 1 and 2, daily oral emtricitabine (200 mg)–tenofovir alafenamide (25 mg), or daily oral emtricitabine (200 mg)–tenofovir disoproxil fumarate (300 mg). Participants who became pregnant could continue study drug in a planned substudy after providing additional written informed consent. We describe HIV infections, pregnancy outcomes, and adverse events during pregnancy and postpartum, and observed and model-derived lenacapavir plasma concentrations by pregnancy trimester and postpartum period. Pregnancy outcomes and infant congenital anomalies were determined by participant report and medical record review. Lenacapavir concentrations were measured in maternal plasma, breastmilk, and breastfed infant plasma.

Findings Among 5345 women enrolled between Sept 28, 2021, and Sept 15, 2023, 487 participants (184 allocated to lenacapavir, 208 allocated to emtricitabine–tenofovir alafenamide, and 95 allocated to emtricitabine–tenofovir disoproxil fumarate) had one or more pregnancies, resulting in 509 total pregnancies with 512 pregnancy outcomes, including three sets of twins. Median age was 21 years (IQR 19–23). Most pregnancies resulted in livebirths (128 [66%] of 195 on lenacapavir, 119 [54%] of 219 on emtricitabine–tenofovir alafenamide, and 56 [57%] of 98 on emtricitabine–tenofovir disoproxil fumarate). Numbers of pregnancy losses were similar across groups (60 [31%] of 195 on lenacapavir, 89 [41%] of 219 on emtricitabine–tenofovir alafenamide, 41 [42%] of 98 on emtricitabine–tenofovir disoproxil fumarate). Adverse events during pregnancy and postpartum were balanced across groups, with 44 (33%) of 132 reporting injection site reactions on lenacapavir; all were grade 1 or 2 and none led to discontinuation. Population pharmacokinetic analysis showed no statistically significant differences in lenacapavir exposure by pregnancy trimester or postpartum versus non-pregnant participants. Lenacapavir was present in breastmilk (median breastmilk-to-plasma ratio 0·52 [IQR 0·38–0·77] in 102 mother–infant pairs); however, exposure in infant plasma was minimal (median breastfed-infant-to-maternal plasma ratio: 0·02 [IQR 0·01–0·05] in 98 pairs).

Interpretation These data support accelerated access for lenacapavir in pregnant and lactating women.

Funding Gilead Sciences.

Introduction

More than half of people living with HIV worldwide are women, with the highest burden among those of reproductive age in sub-Saharan Africa.[1] Pregnancy and postpartum are periods of heightened vulnerability, with HIV incidence more than twice that of non-pregnant women.[2] This elevated risk threatens maternal health and increases the likelihood of vertical transmission to as

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Research in context

Evidence before this study

We searched PubMed and ClinicalTrials.gov for studies published from database inception up to Nov 30, 2025, using the terms "HIV prevention", "PrEP", "pregnancy", "lactation", "breastfeeding", AND "lenacapavir". Excluding the parent study of this analysis, no previous studies of lenacapavir in pregnant and lactating women were identified. Preclinical reproductive toxicology studies in rats that were referenced in the product label found no effects on fertility or early embryonic development when lenacapavir was administered at systemic exposures eight times the exposure to humans at recommended doses. Pregnant and postpartum women face increased biological and social vulnerability to HIV acquisition. Acute HIV infection during pregnancy or breastfeeding substantially raises the risk of vertical transmission, underscoring the need for safe and effective HIV prevention options during these periods. Daily oral emtricitabine–tenofovir disoproxil fumarate pre-exposure prophylaxis (PrEP) is recommended in pregnancy and is safe and highly effective when used as directed, but adherence, persistence, and tolerability challenges—particularly during pregnancy and postpartum—have restricted its overall impact. Longer-acting PrEP options might overcome these barriers by removing the need for adherence to daily pills. Twice-yearly subcutaneous lenacapavir was found to be highly efficacious at preventing HIV in cisgender women and presents a potential option for pregnant and lactating women. Due to long-standing concerns regarding fetal safety and uncertainty about drug-specific risks during pregnancy, many phase 3 PrEP studies have historically required participants who become pregnant to discontinue the study drug, although contemporary ethical and regulatory guidance increasingly emphasises structured assessment of inclusion and retention of pregnant people in clinical research and specific justification for instances where they are excluded. The field of HIV prevention has long sought to generate data on PrEP options in pregnancy, frequently initiating dedicated pregnancy studies soon after the efficacy studies have completed, albeit with inherent delays. In more recent years, advocacy for the earlier inclusion of pregnant participants in drug development research has spanned multiple fields of research. Within HIV prevention research, advocates have highlighted the scientific and ethical bases for inclusion and increasingly sought to acknowledge the agency of women to make reproductive health decisions when participating in clinical studies. For longer-acting PrEP options, discontinuing medication at the time of pregnancy is not feasible, presenting both a potential risk and an opportunity to understand use in pregnancy. Building on this foundation, the initial studies of lenacapavir for PrEP leveraged preclinical pregnancy safety data and the drug's long-acting nature to evaluate lenacapavir through the duration of pregnancy and lactation and to allow study participants to remain on study after becoming pregnant, while breastfeeding, or both.

Added value of this study

This study provides new data on lenacapavir for PrEP, with no HIV acquisitions observed, no concerning safety findings, and favourable tolerability in pregnant, postpartum, or lactating women. This study also provides evidence of no clinically significant differences in lenacapavir exposure during pregnancy and postpartum, with minimal exposure in breastfed infants, and adds pharmacokinetic data to support PrEP use in pregnancy and lactation.

Implications of all the available evidence

Our findings support the use of lenacapavir for pregnant and lactating women who want or need PrEP without the need for dose adjustment. These data have been included in regulatory approvals and used to inform WHO guidelines. With preclinical pregnancy safety data and a multidisciplinary assessment of the risks, benefits, and ethics of inclusion, it is feasible to allow pregnant and breastfeeding participants to remain in phase 3 PrEP studies and, in doing so, to potentially accelerate their access to biomedical PrEP options.

high as 40% without intervention.[3] These realities underscore the urgent need for effective prevention strategies during these crucial life stages.

WHO has previously recommended several pre-exposure prophylaxis (PrEP) options for pregnant and breastfeeding women, including daily oral emtricitabine–tenofovir disoproxil fumarate, the dapivirine vaginal ring, and intramuscular cabotegravir.[4] However, HIV infections during pregnancy and postpartum persist, highlighting the need to expand the HIV prevention toolkit. Lenacapavir, a first-in-class, multistage HIV-1 capsid inhibitor administered twice a year by subcutaneous injection,[5] is a promising PrEP option that might overcome adherence and persistence challenges associated with existing agents.

Lenacapavir demonstrated 100% efficacy and superiority to daily oral emtricitabine–tenofovir disoproxil fumarate in preventing HIV infection in PURPOSE 1, a randomised controlled trial of cisgender women.[5] Although the phase 3 study excluded pregnant and breastfeeding women at enrolment, it intentionally did not include a contraception requirement and allowed participants who subsequently became pregnant to remain in the study. This was supported not only by preclinical reproductive toxicology studies that showed no harmful effects,[6,7] but also by a growing body of evidence supporting biomedical HIV prevention in pregnancy and evolving ethical and pragmatic calls for earlier inclusion of pregnant participants in clinical trials.[8–16]

Here we report HIV infections, pregnancy outcomes, maternal and infant safety, and lenacapavir pharmacokinetics among participants who became pregnant during the randomised, masked phase of the study.

Methods

Study design and participants

We conducted a randomised, double-blind, active-controlled phase 3 study (PURPOSE 1; NCT04994509) at 28 clinical research sites in South Africa and Uganda (appendix pp 2–3). We enrolled cisgender adolescent girls and young women aged 16–25 years who were sexually active with cisgender male partners, not pregnant or breastfeeding a child at baseline, not currently using PrEP, and who reported no HIV testing within the previous 3 months. Participants were confirmed to be HIV negative using a previously published testing algorithm.[5] Participants were randomly allocated (2:2:1) to receive subcutaneous lenacapavir, daily oral emtricitabine–tenofovir alafenamide, or daily oral emtricitabine–tenofovir disoproxil fumarate. Both oral regimens are well studied and guideline-recommended for HIV treatment during pregnancy.[6,17]

Participants who became pregnant after random allocation were allowed to remain in the study following a reconsent process. Before study initiation, we developed the study's pregnancy and lactation approach through a deliberate, multiyear process grounded in Good Participatory Practice Guidelines.[18] We engaged community representatives, advocacy organisations, regulatory agencies, ethics committees, institutional review boards, maternal and paediatric health experts, and site investigators to guide the safe and responsible inclusion of pregnant and lactating women.[15,19–21] We worked closely with a Global Community Advisory and Accountability Group—including individuals with lived experience of navigating pregnancy, lactation, and HIV prevention—who played a central role in shaping the study's design and conduct. Ethical guidance from the Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) project was foundational, and we implemented relevant WHO and International Maternal Pediatric Adolescent AIDS Clinical Trials Network toolkit recommendations during the study.[15,22]

Pregnancy-related study procedures were aligned with routine study visits to minimise participant burden. During the study, in response to investigators' requests, a pregnancy support package for antenatal care visits and procedures, food assistance, delivery supplies, and transport reimbursement for postnatal visits was implemented for participants not receiving such support through government programmes or insurance. Local institutional review boards approved all support measures.

All participants provided written informed consent. The study was approved by South African, Ugandan, and US drug regulatory authorities and the institutional review board or ethics committee at each site and was conducted in compliance with Good Clinical Practice and Good Participatory Practice Guidelines.[18] The study was registered at ClinicalTrials.gov (NCT04994509) and is closed to enrolment and in follow-up.

Procedures

We have previously published the detailed study procedures.[5] At screening and random allocation, we confirmed participants were not pregnant or breastfeeding. Family planning and contraception counselling was provided at each study visit, per local standard of care. We conducted pregnancy testing at all scheduled visits. Participants were randomly assigned to receive subcutaneous lenacapavir (927 mg, in two 1·5 mL injections) every 26 weeks following a 600 mg oral loading dose on days 1 and 2; daily oral emtricitabine (200 mg)–tenofovir alafenamide (25 mg); or daily oral emtricitabine (200 mg)–tenofovir disoproxil fumarate (300 mg) with the corresponding oral or subcutaneous placebo. Participants who became pregnant could choose to continue their randomly allocated study drug, to switch to open-label emtricitabine–tenofovir disoproxil fumarate and be followed up for up to 78 weeks, or to withdraw from the study. Pregnancy outcomes and infant congenital anomalies were determined by participant report and medical record review.

See Online for appendix

We aligned maternal pharmacokinetic sampling with prespecified study visits to reduce participant burden. We collected blood and breastmilk samples from participants who opted to remain on the study drug, and blood samples from their infants in matched pairs at the first two scheduled visits after delivery, irrespective of time since last injection. An illustrative example of the potential pharmacokinetic sampling windows for maternal, infant, and breastmilk samples for four theoretical participants are shown (appendix p 4). If abdominal injections were determined to not be possible due to pregnancy, the thigh could be used as an alternative injection site. Lenacapavir concentrations in maternal plasma, breastmilk, and infant plasma were measured using validated high-performance liquid chromatography–tandem mass spectrometry methods (appendix p 4).[23]

Outcomes

We summarised pregnancy incidence, HIV infections during pregnancy, and pregnancy outcomes by each randomly allocated group. We included all pregnancies confirmed by the primary analysis date (May 8, 2024) and followed up pregnancy outcomes until March 26, 2025.[5] This main data cutoff includes our prespecified safety endpoints, allowing for detailed maternal safety data to be presented. Pregnancy incidence rate was calculated as the number of confirmed pregnancies divided by person-years of follow-up. Person-years of follow-up were defined as the sum of all participants' total time accrued in the randomised masked phase for the primary analysis. As such, this measure reflects the overall incidence of confirmed pregnancies per follow-up time during the randomised masked phase.

In addition, we present supplemental outcomes for all pregnancies diagnosed through the end of the randomised masked phase. Participants who completed

the end of the randomised masked phase visits could choose to enter a lenacapavir open-label extension study on a rolling basis through to Oct 21, 2024, and pregnancy outcomes were followed up through to Oct 6, 2025.

We quantified the number of women who experienced one or more pregnancies, the total number of unique pregnancies, and the total number of pregnancy outcomes to account for twin pregnancies. Pregnancy outcomes were classified as livebirths or pregnancy losses. Pregnancy losses included induced abortions, spontaneous abortions (<20 weeks' gestation), and stillbirths or intrauterine fetal demise (≥20 weeks' gestation).[24] We calculated estimated gestational age from the first day of the last menstrual period to the date of pregnancy outcome. If the last menstrual period date was unavailable, investigator-reported gestational age based on clinical assessment was used instead. When records were available, infant weight, length, and head circumference were compared with standardised WHO Z scores.

Safety outcomes included adverse events or injection site reactions associated with injections occurring during the pregnancy and postpartum period, defined as the time from the last menstrual period up to 6 weeks after the pregnancy outcome.

Pharmacokinetic outcomes included comparisons of lenacapavir plasma concentrations during each trimester, postpartum, and non-pregnant periods in participants who became pregnant versus those who did not, using population pharmacokinetic analysis. We summarised model-derived lenacapavir plasma maximum concentrations (C_{max}) and trough concentrations (C_{trough}) by pregnancy group.[25] We also compared lenacapavir concentrations for participants who received thigh injections to those who received abdominal injections, stratified by pregnancy. We calculated breastmilk-to-plasma ratios and breastfed-infant-to-maternal plasma ratios.

Statistical analysis

We summarised pregnancy outcomes, adverse events, and lenacapavir pharmacokinetic parameters using descriptive statistics within groups.

Pregnancy analyses were restricted to pregnancies that began (or were confirmed) during the randomised, masked phase of the study. Pregnancy-related outcomes were attributed according to the randomly allocated masked treatment received at the time of pregnancy onset, regardless of subsequent changes in treatment after pregnancy recognition.

Population pharmacokinetic analysis was done with non-linear mixed effects modelling (NONMEM) software version 7.5 (ICON Development Solutions, Dublin, Ireland), with statistical comparisons made within the population pharmacokinetic model (appendix p 4). Data handling, post-processing, and plotting were done in R

	Became pregnant			Overall became pregnant (n=487)	Overall did not become pregnant (n=4858)
	Lenacapavir (n=184)	F–TAF (n=208)	F–TDF (n=95)		
Age, years	21 (19–23)	22 (19–23)	21 (19–23)	21 (19–23)	21 (19–23)
Race					
Black	184 (100%)	207 (100%)	95 (100%)	486 (100%)	4853 (100%)
Education*					
No primary school	1 (1%)	4 (2%)	0	5 (1%)	34/4852 (<1%)
Some or completed primary education	56 (30%)	50 (24%)	27 (28%)	133 (27%)	431/4852 (9%)
Some or completed secondary education	115 (63%)	135 (65%)	63 (66%)	313 (64%)	3933/4852 (81%)
College or university	12 (7%)	19 (9%)	5 (5%)	36 (7%)	454/4852 (9%)
Never married	167 (91%)	189 (91%)	88 (93%)	444 (91%)	4730/4852 (97%)
Living with primary partner	21 (11%)	13 (6%)	5 (5%)	39 (8%)	314/4851 (6%)
Alcohol use in the past 3 months	130/183 (71%)	160 (77%)	74 (78%)	365/486 (75%)	3721/4834 (77%)
Cigarette use in past 3 months	31 (17%)	27/207 (13%)	13 (14%)	71/486 (15%)	738/4823 (15%)
Partner provides financial or material support	106/183 (58%)	120 (58%)	52 (55%)	278/486 (57%)	3047/4822 (63%)
Partner has sex with other partners	50/182 (27%)	60/199 (30%)	30/94 (32%)	140/475 (29%)	1304/4766 (27%)
Any chlamydia, gonorrhoea, *Trichomonas vaginalis*, or syphilis	63 (34%)	72 (35%)	40 (42%)	175 (36%)	1699/4857 (35%)
Male sex partners in past 3 months*	2 (1–5)	2 (1–10)	3 (1–8)	2 (1–6)	2 (1–3)
Transactional sex in past 3 months	76/182 (42%)	79/205 (39%)	44/93 (47%)	199/480 (41%)	1048/4791 (22%)

Data presented as median (IQR), n (%), or n/N (%) where participants had missing data or chose not to answer. Missing data and participants who responded prefer not to answer are excluded for calculation of percentage. F–TAF=emtricitabine–tenofovir alafenamide. F–TDF=emtricitabine–tenofovir disoproxil fumarate. *Participants with data missing or chose the option prefer not to answer: lenacapavir pregnancy (n=7), F–TAF pregnancy (n=14), F–TDF pregnancy (n=4), and no pregnancy (n=316).

Table 1: **Demographics and baseline characteristics**

(version 4.2 or later). We conducted all analyses using SAS (version 9.4).

Role of the funding source

The funder, Gilead Sciences (Foster City, CA, USA), was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

5345 women enrolled between Sept 28, 2021, and Sept 15, 2023, 487 of whom had one or more pregnancies. Median age was 21 years (IQR 19–23) in both participants who became pregnant and those who did not (table 1). Baseline characteristics were similar between participants who became pregnant and those who did not (table 1), with the exceptions that participants who became pregnant had lower levels of education than those who did not become pregnant (28% *vs* 10%, respectively, had at most completed primary education) and had higher rates of transactional sex (41% *vs* 22%, respectively; table 1).

509 total pregnancies resulted in 512 pregnancy outcomes, including three sets of twins (table 2). Pregnancy incidence was 10·5 per 100 person-years overall, and was similar across the three groups: 10·0 per 100 person-years for lenacapavir, 11·2 per 100 person-years for emtricitabine–tenofovir alafenamide, and 10·2 per 100 person-years for emtricitabine–tenofovir disoproxil fumarate (table 2). 344 (71%) of 487 who became pregnant opted to complete the randomised and masked phase study drug (figure 1).

We observed no HIV acquisitions during pregnancy among participants receiving lenacapavir. In total, five HIV infections occurred during pregnancy: four in the emtricitabine–tenofovir alafenamide group, and one in the emtricitabine–tenofovir disoproxil fumarate group. No cases of vertical HIV transmission were observed.

In the lenacapavir group, there were 193 pregnancies with 195 outcomes (two sets of twins) among 184 participants (table 2). 195 pregnancy outcomes comprised 128 (66%) livebirths (including one set of twins), 60 (31%) pregnancy losses, and seven (4%) unknown outcomes due to study discontinuation. Pregnancy losses comprised 35 (18%) induced or elective abortions, 20 (10%) spontaneous abortions, and five (3%) stillbirths (including one set of twins). Stillbirth rates were similar in the other randomly allocated groups (table 2).

In all randomly allocated groups, the majority of liveborn infants were born at term (table 2). Among infants born to participants receiving lenacapavir, six (5%) of 127 had congenital anomalies reported (two umbilical hernias, two ventricular septal defects, one polydactyly, and one infantile haemangioma); congenital anomaly rates were four (3%) of 117 in participants allocated to emtricitabine–tenofovir alafenamide and none in those allocated to emtricitabine–tenofovir disoproxil fumarate (table 2, appendix p 6). Of ten congenital anomalies, nine were assessed as unrelated to study drug, and one case of ventricular septal defect in an infant born to a participant receiving lenacapavir (in whom no genetic predisposition, maternal risk factors, or maternal exposures were identified) was assessed as related to the study drug. Small for gestational age was diagnosed in 11 (9%) of 128, 12 (10%) of 119, and nine (16%) of 56 infants in the lenacapavir, emtricitabine–tenofovir alafenamide, and emtricitabine–tenofovir disoproxil fumarate groups, respectively (table 2). Infant birth length, weight, and head circumference WHO Z scores did not differ by allocation group (figure 2). Data on supplemental outcomes from all pregnancies diagnosed through to the end of the randomised masked phase were similar, and

	Lenacapavir	F–TAF	F–TDF	Total
Pregnancy incidence				
Participants with confirmed pregnancies	184	208	95	487
Number of confirmed pregnancies	193	218	98	509
Pregnancy incidence rate per 100 person-years*	10·0	11·2	10·2	10·5
Pregnancy outcomes				
Total pregnancy outcomes†	195	219	98	512
Livebirths	128/195 (66%)	119/219 (54%)	56/98 (57%)	303/512 (59%)
Pregnancy losses	60/195 (31%)	89/219 (41%)	41/98 (42%)	190/512 (37%)
Stillbirths‡	5/195 (3%)	6/219 (3%)	3/98 (3%)	14/512 (3%)
Induced or elective abortions	35/195 (18%)	50/219 (23%)	23/98 (23%)	108/512 (21%)
Spontaneous abortions§	20/195 (10%)	33/219 (15%)	15/98 (15%)	68/512 (13%)
Pregnancies with unknown outcome¶	7/195 (4%)	11/219 (5%)	1/98 (1%)	19/512 (4%)
Livebirth outcomes				
At term (≥37 to ≤42 weeks' gestation)	105/128 (82%)	93/119 (78%)	40/56 (71%)	238/303 (79%)
Preterm (<37 weeks' gestation)	14/128 (11%)	19/119 (16%)	11/56 (20%)	44/303 (15%)
Post-term (>42 weeks' gestation)	9/128 (7%)	7/119 (6%)	5/56 (9%)	21/303 (7%)
Congenital abnormality‖	6/127 (5%)	4/117 (3%)	0	10/300 (3%)
Small for gestational age**	11/128 (9%)	12/119 (10%)	9/56 (16%)	32/303 (11%)

Data are presented as n, n (%), or n/N (%) unless otherwise stated. F–TDF=emtricitabine–tenofovir disoproxil fumarate. F–TAF=emtricitabine–tenofovir alafenamide. *Pregnancy incidence rate is the number of confirmed pregnancies divided by person-years of follow-up; person-years of follow-up are the sum of all participants' total number of years (365·25 days) in the randomised, masked phase for the primary analysis (lenacapavir 1934·1 years, F–TAF 1943·5 years, F–TDF 956·7, and total 4834·4). †Total pregnancy outcomes includes the number of livebirths, pregnancy losses, and pregnancies with unknown outcome; one pregnancy can include multiple outcomes or births (three sets of twins: two sets in participants randomly allocated to lenacapavir [one set of stillborn twins and one set of liveborn healthy twins] and one set in participants randomly allocated to F–TAF [liveborn and premature]); birth outcomes are reported for each individual infant. ‡Stillbirth or intrauterine fetal demise defined as occurring at 20 weeks' gestation or longer. There was one set of stillbirth twins in the lenacapavir group. §Spontaneous abortion defined as occurring at less than 20 weeks' gestation; estimated gestational age data are missing for one infant in the F–TAF group. ¶Unknown due to participant discontinuation for the following reasons: pregnancy (lenacapavir [two]; F–TAF [two]); investigator's discretion (F–TAF [one]); withdrawal of consent (lenacapavir [five] and F–TAF [four]); and loss to follow-up (F–TAF [four]; F–TDF [one]). ‖Includes one infant reported to have had a healthy outcome at birth whose congenital abnormality of umbilical hernia was first detected at approximately 4 months of age. **Small for gestational age was defined as a weight under the 10th percentile by sex and gestational age.

Table 2: **Pregnancy incidence and birth outcomes in participants with one or more pregnancies**

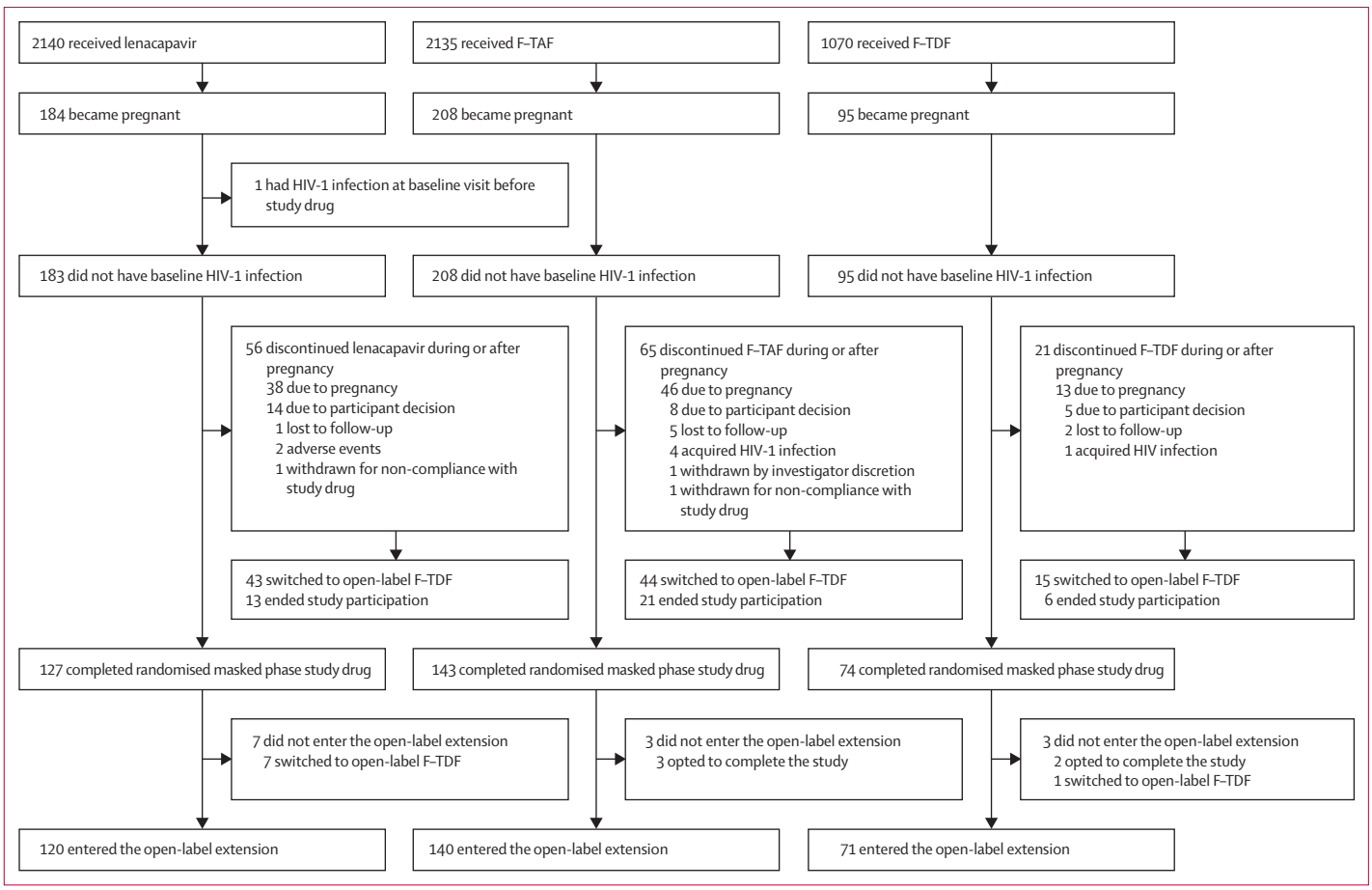

Figure 1: **Participant randomisation and pregnancy disposition**
F–TAF=emtricitabine–tenofovir alafenamide. F–TDF=emtricitabine–tenofovir disoproxil fumarate.

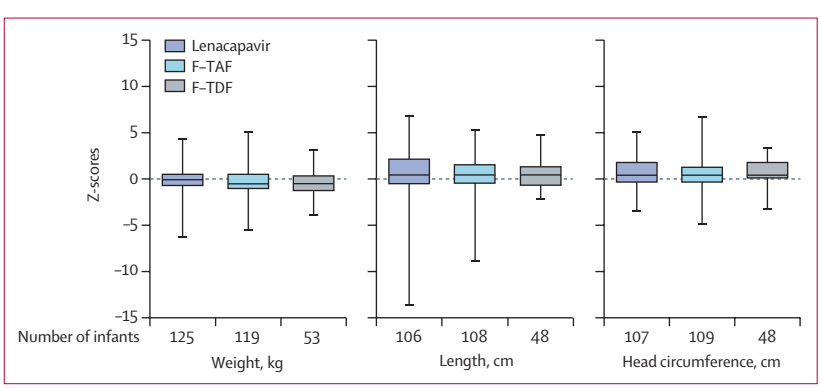

Figure 2: **Infant WHO Z scores at birth**
Box plots depict median (IQR) and range. This figure includes liveborn infants with available measurements at birth. Data are missing for the following number of infants: weight (three lenacapavir, zero F–TAF, and three F–TDF), length (22 lenacapavir, 11 F–TAF, and eight F–TDF), and head circumference (21 lenacapavir, ten F–TAF, and eight F–TDF). F–TAF=emtricitabine–tenofovir alafenamide. F–TDF=emtricitabine–tenofovir disoproxil fumarate.

include a total of 712 pregnancies, 269 of which were on lenacapavir (appendix p 7).

Maternal adverse events during pregnancy and postpartum were generally similar between study groups (table 3). The most common adverse events overall, excluding injection site reactions and spontaneous abortions, were urinary tract infections and vulvovaginal candidiasis. Injection site reactions associated with injections that occurred during pregnancy and postpartum were reported in 33% of participants who received lenacapavir and 12% of participants who received placebo injections in the emtricitabine–tenofovir alafenamide and emtricitabine–tenofovir disoproxil fumarate groups combined (table 4). Injection-site nodules were reported in 35 (27%) of 132 participants receiving lenacapavir and seven (4%) of 185 participants receiving placebo. In total, 74 injection-site nodules were reported from 338 lenacapavir injections (22%). At the time of analysis, 26 (35%) of 74 were ongoing and 48 (65%) of 74 had resolved over a median of 254 days (IQR 88–325). All reactions were grade 1 or 2 and there were no discontinuations due to injection site reactions. A lower percentage of participants who received lenacapavir injections in the thigh experienced injection site reactions (20%), compared with the abdomen (34%; table 4).

No apparent trimester-related trends were observed in lenacapavir concentrations across pregnancy trimesters and the postpartum period (figure 3). Consistent with these observations, model-derived lenacapavir C_{max} and C_{trough} concentrations (appendix pp 8, 10) were similar across pregnancy trimesters, postpartum, and non-pregnant periods. Formal evaluation within the population pharmacokinetic model found no statistically significant effect of pregnancy trimester or postpartum status on lenacapavir concentrations (appendix pp 11–13). In 102 mother–infant pairs (range 10–187 days postpartum), the median breastmilk-to-plasma ratio for lenacapavir was 0·52 (IQR 0·38–0·77). In 98 pairs (range 10–190 days postpartum), median breastfed-infant-to-maternal plasma ratio for lenacapavir was 0·02 (IQR 0·01–0·05; appendix p 9).

Among 62 participants who received subcutaneous thigh injections during pregnancy and had pharmacokinetic data available, plasma lenacapavir concentrations were similar to those of participants who had abdominal injections (appendix p 14).

	Lenacapavir (n=184)	F-TAF (n=208)	F-TDF (n=95)
Adverse events†	135 (73%)	142 (68%)	68 (72%)
Grade ≥2	112 (61%)	112 (54%)	55 (58%)
Grade ≥3	36 (20%)	39 (19%)	22 (23%)
Serious adverse events†	41 (22%)	50 (24%)	22 (23%)
Adverse events leading to discontinuation of study drug†	1 (1%)‡	0	0
Adverse events occurring in ≥5% of participants in any randomised group§			
Urinary tract infection	39 (21%)	34 (16%)	27 (28%)
Upper respiratory infection	20 (11%)	16 (8%)	6 (6%)
Vulvovaginal candidiasis	17 (9%)	22 (11%)	8 (8%)
Genitourinary chlamydia infection	16 (9%)	10 (5%)	8 (8%)
Vaginal discharge	13 (7%)	6 (3%)	6 (6%)
Vomiting	10 (5%)	16 (8%)	9 (9%)
Headache	10 (5%)	15 (7%)	4 (4%)
Malaria	10 (5%)	6 (3%)	4 (4%)
Nausea	7 (4%)	10 (5%)	8 (8%)
Morning sickness	3 (2%)	5 (2%)	6 (6%)
Death	0	0	0

Data presented as number (%). F-TAF=emtricitabine–tenofovir alafenamide. F-TDF=emtricitabine–tenofovir disoproxil fumarate. *Adverse events and laboratory abnormalities that are reported here were those that occurred in participants who had received at least one dose of a study drug or placebo. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 27.1) and graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events version 2.1. We defined the pregnancy and postpartum period as the time from the last menstrual period through to 6 weeks after the pregnancy outcome. †Injection site reactions to non-study medications are included, but injection site reactions to the study subcutaneous injection are excluded. ‡Spontaneous abortion (investigator assessed as unrelated to study drug). §Injection site reactions and spontaneous abortions have been excluded.

Table 3: **Adverse events during pregnancy and postpartum***

Discussion

Twice-yearly subcutaneous lenacapavir is well tolerated among pregnant, postpartum, and lactating women. Zero HIV infections occurred among participants who received lenacapavir during pregnancy. Pregnant, postpartum, and non-pregnant participants had similar lenacapavir exposure and infant exposure via breastmilk was minimal.

Pregnancy outcomes—including rates of spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births—were consistent with background rates in South Africa and Uganda.[26,27] The 3% stillbirth rate among participants receiving lenacapavir aligns with the published estimates for the region (2·0–4·0%),[26,27] and the spontaneous abortion rate of 10% falls within the range of global estimates for clinically recognised pregnancies (10–20%),[26–28] although these comparisons should not be interpreted as confirmatory evidence of safety. Livebirth outcomes, including birth anthropometric parameters, were also comparable across randomly allocated groups and consistent with those in other PrEP studies.[10,13] Congenital anomaly rates were slightly higher in the lenacapavir group (5%) than in the emtricitabine–tenofovir alafenamide group (3%); however, they reflect a small absolute number of events and should be interpreted with caution. The heterogeneous anomalies observed are consistent with background incidence and do not demonstrate a consistent pattern suggestive of a drug-related effect.[29]

Maternal safety outcomes during pregnancy and postpartum were similar across groups. The safety of emtricitabine–tenofovir disoproxil fumarate and emtricitabine–tenofovir alafenamide in pregnancy was already established before this study, and it is reassuring that lenacapavir was similarly well tolerated in this first study of its use in pregnant women.[6] Importantly, a high percentage of participants (71%) completed randomised masked phase study drug and the majority of those that chose to discontinue study drug did so due to pregnancy and switched to open-label emtricitabine–tenofovir disoproxil fumarate. There were no discontinuations due to drug-related adverse events and no tolerability concerns. This supports the safety and acceptability of twice-yearly subcutaneous lenacapavir during pregnancy and postpartum. Safety assessment during pregnancy is ongoing in the open-label extension phase of PURPOSE 1. As of publication there have been more than 660 pregnancies on lenacapavir with similar high-level outcome trends among completed pregnancies. The open-label extension allows for continued collection of safety data in pregnancy.

Lenacapavir is metabolised by CYP3A and UGT1A1 enzymes and is a substrate of P-glycoprotein.[7] Although pregnancy can alter the activity of drug-metabolising enzymes and transporters, including increased CYP3A activity,[30] and cause temporal changes in placental P-glycoprotein expression throughout trimesters,[31] no clinically relevant changes in lenacapavir exposure were found during pregnancy or postpartum relative to the non-pregnant period or data from the non-pregnant

	Lenacapavir overall (n=184)	Lenacapavir, abdomen	Lenacapavir, thigh	Placebo overall (n=303)	Placebo, abdomen	Placebo, thigh
Number of participants who received at least one injection during pregnancy or postpartum†	132/184	116	35	185/303	171	34
Injection site reactions‡	44/132 (33%)	40/116 (34%)	7/35 (20%)	23/185 (12%)	23/171 (13%)	1/34 (3%)
Grade 1	38/132 (29%)	34/116 (29%)	7/35 (20%)	18/185 (10%)	18/171 (11%)	1/34 (3%)
Grade 2	6/132 (5%)	6/116 (5%)	0	5/185 (3%)	5/171 (3%)	0
Grade ≥3	0	0	0	0	0	0
Serious injection site reactions	0	0	0	0	0	0
Injection site reactions leading to discontinuation of study drug	0	0	0	0	0	0

Data presented as number (%). The denominator for injection site reactions was number of participants who received at least one injection during pregnancy and postpartum. F–TAF=emtricitabine–tenofovir alafenamide. F–TDF=emtricitabine–tenofovir disoproxil fumarate. *Injection site reactions were coded according to the Medical Dictionary for Regulatory Activities (version 27.1) and graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events version 2.1. We defined the pregnancy and postpartum period as the time from the last menstrual period through to 6 weeks after the pregnancy outcome. †Participants assigned to F–TAF and F–TDF received placebo injections. ‡Injection site reactions associated with injection dates occurring within the pregnancy and postpartum period are included.

Table 4: **Injection site reactions during pregnancy and postpartum***

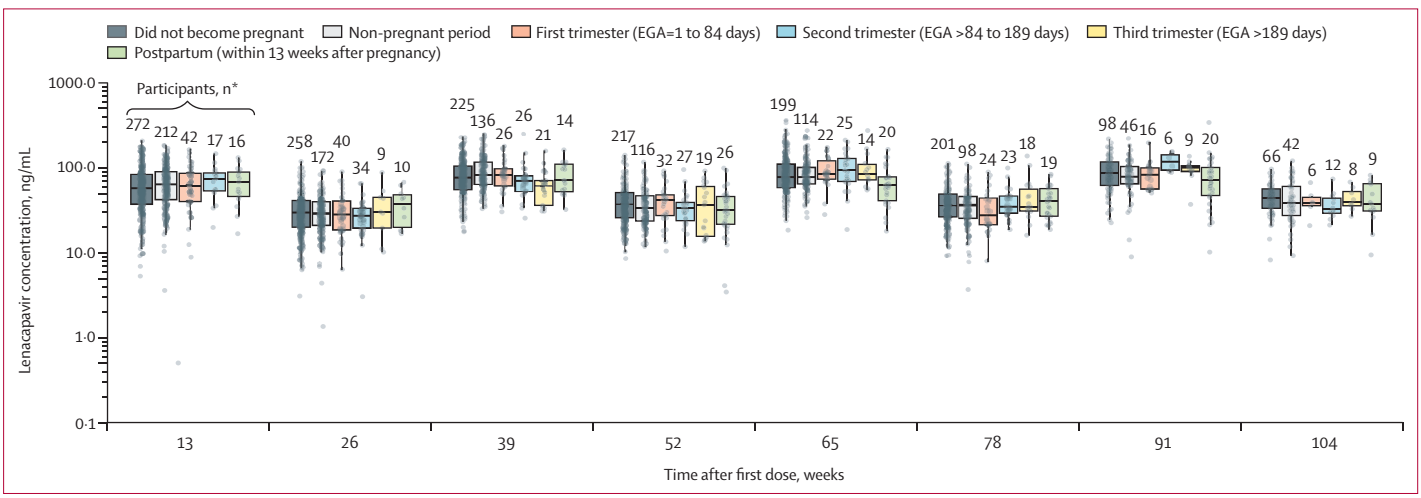

Figure 3: **Box plots of observed lenacapavir concentrations up to week 104, stratified by pregnancy groups, for participants who took lenacapavir on time**

Includes samples collected before, during, and after pregnancy, available as of March 27, 2025, and included in the population pharmacokinetic analysis. On injection days, samples were collected before injection. On-time complete injection was defined as both injections administered in full dose within ±2 weeks of the targeted day relative to the previous injection. If injection was delayed or missed, all samples after 26 weeks of previous injection were excluded. If oral bridging or oral reloading was administered, samples before this period were included only if previous injections were on time; no samples after oral bridging or oral reloading were included. Only data up to week 104 are shown. Data at week 4 and week 8 are excluded. Data below the limit of quantification for lenacapavir (0·5 ng/mL) are excluded. Postpartum refers to the 13 weeks after the end of pregnancy, including childbirth or early pregnancy termination, to align with the study's 13-week visit schedule. The non-pregnant period refers to the time before pregnancy or after the postpartum window. EGA=estimated gestational age. *n values in the plots are the number of participants with quantifiable lenacapavir concentration at that timepoint.

population. These findings support the use of lenacapavir for PrEP during pregnancy and postpartum with no dose adjustment needed.

The presence of lenacapavir in breastmilk was expected due to its lipophilic nature, but plasma concentrations in breastfed infants were very low, consistent with the poor oral bioavailability of lenacapavir.[7] These minimal concentrations detected in breastfed infants might be the result of low-level placental transfer or could reflect very low levels of transfer via breastmilk. No adverse effects of lenacapavir on breastfed infants were observed as a result of this limited systemic exposure.

The evaluation of pregnancy, lactation, and infant pharmacokinetics was nested in a large, well controlled randomised PrEP study. In this large substudy of pregnant women on lenacapavir, we observed no difference from expected pregnancy outcomes. For further reassurance, pregnant people on lenacapavir should continue to be observed in real-world datasets and in the Antiretroviral Pregnancy Registry to characterise outcomes in larger populations of pregnant people.

Although this study provides information on lenacapavir exposure through all stages of pregnancy and postpartum, data on the initiation of lenacapavir in late pregnancy were limited by excluding pregnancy at enrolment. Safety comparison to emtricitabine–tenofovir disoproxil fumarate and emtricitabine–tenofovir alafenamide outcomes within the study should be interpreted with caution given the low adherence to oral PrEP in the PURPOSE 1 study.[5] Pharmacokinetic sampling was systematic, but its

alignment with routine study visits to minimise participant burden might have introduced some variability in the timing of samples because participants became pregnant at various phases during the twice-yearly dosing interval. This restricted standard pharmacokinetic analyses, such as area under the concentration-time curve calculations for each trimester. Potential selection bias might exist, as participants who chose to remain on study drug during pregnancy might differ from those who did not. While we observed breastfed infant drug exposure to be minimal, results were not categorised by breastfeeding exclusivity or intensity, and these data might not capture peak exposures for exclusively breastfed infants during maternal peak plasma concentrations. Gestational age was primarily estimated by last menstrual period, rather than ultrasound, which might affect precision. Finally, infant data, including congenital anomaly diagnoses, were reliant on information available in health records and reported by mothers; long-term follow-up data on infants are not available.

Over half of people who newly acquire HIV each year are women, most of whom are of childbearing age, a testament to the very real need for HIV prevention options that are safe and effective in pregnancy.[1] Pregnant and lactating women have often been excluded from biomedical research, resulting in years-long delays in evidence to inform the use of medications, including new antiretrovirals, during pregnancy.[14,15] Since the first reports of vertical HIV transmission in the early 1980s, followed by the establishment of mother–infant cohorts in New York in 1986, the Antiretroviral Pregnancy Registry in 1989, and the landmark ACTG 076 study of zidovudine for the prevention of vertical HIV transmission, the HIV field has been acutely attuned to the importance of this vulnerable life stage in the epidemic.[9,32] When the first PrEP agent, emtricitabine–tenofovir disoproxil fumarate, entered phase 3 studies, there was not sufficient expectation of efficacy to justify the risk of including pregnant women in the study, but data were collected in participants who became pregnant and, after efficacy and safety were established, studies in pregnancy and lactation quickly followed.[10] Subsequent novel PrEP agents, including the dapivirine ring, did not have sufficient risk-to-benefit data to justify early inclusion of pregnant women in phase 3 studies, nor was the field ready for the ethical shift of pregnancy inclusion, but dedicated pregnancy and lactation studies followed soon after establishing safety and efficacy in non-pregnant people.[12] Simultaneously, scientists, community members, and regulators convened repeatedly to consider the scientific requirements for evaluating new PrEP agents earlier in pregnancy and the ethical considerations needed to support such evaluations.[14,15]

Lenacapavir for PrEP arrived at an opportune moment in this history: groundwork had been laid for earlier study of novel PrEP agents in pregnancy and lactation, preclinical pregnancy safety data for lenacapavir were reassuring, and the science supported the probable benefit of new PrEP agents in general. Moreover, the long-acting nature of lenacapavir precluded drug discontinuation in the event of pregnancy, in essence guaranteeing its study through the course of pregnancy. This fortuitous coalescence of factors allowed PURPOSE 1 to be the first HIV PrEP study to evaluate the safety, efficacy, and pharmacokinetics of a novel agent through the duration of pregnancy and lactation concurrent with primary study results. This resulted in the inclusion of these key data in regulatory approvals and supported WHO guidelines which may help accelerate the use of lenacapavir for PrEP in pregnant and lactating women.[4]

In conclusion, lenacapavir was highly efficacious and well tolerated in pregnant and lactating women, with no clinically significant differences in pharmacokinetics compared with women who did not become pregnant. We demonstrated the feasibility and value of including pregnant and lactating women in phase 3 studies, underscoring the importance of equitable study design in advancing global HIV prevention efforts. Our findings support the use of twice-yearly subcutaneous lenacapavir for PrEP in pregnant and lactating women who want or need PrEP.

Contributors

L-GB, DDD, LM, PA, JMB, CCC, RS, MD, and FMK designed the study. L-GB, DM, IH, GK, NK, CEL, MM, TP-P, RP, NS, SBP, PA, JMB, CCC, RS, MD, and FMK collected study data. PA, MI, JL, and RS completed pharmacokinetic analyses and pharmacokinetic modelling. PW oversaw biostatistical analysis. L-GB, DM, IH, GK, CEL, MM, TP-P, RP, NS, SBP, PA, JMB, AB, CCC, MI, JL, RS, PW, MD, and FMK analysed and interpreted data. L-GB, SBP, PA, JMB, AB, CCC, MI, JL, RS, PW, and MD had full access and verified the underlying study data. All authors contributed to manuscript development and had final responsibility for the decision to submit for publication.

Declaration of interests

L-GB has received medical writing support from Gilead Sciences; honoraria for advisories from Gilead Sciences, Merck, and ViiV Healthcare; grants (to the Desmond Tutu Health Foundation) from Johnson & Johnson and ViiV Healthcare; and has served on the Data Safety Monitoring Board for the PrEPVACC HIV Vaccine Trial. DM has received medical writing support from Gilead Sciences. DDD has received medical writing support from Gilead Sciences; grants from Gilead Sciences, Merck, and ViiV Healthcare; and speaker fees from Gilead Sciences, Merck, and ViiV Healthcare. IH has received medical writing support from Gilead Sciences. GK has received medical writing support and materials and drugs for trial conduct from Gilead Sciences. NK has received medical writing support from Gilead Sciences. CEL has received medical writing support from Gilead Sciences. MM has received medical writing support from Gilead Sciences. LM has received medical writing support from Gilead Sciences. TP-P has received medical writing support from Gilead Sciences; grants or contracts from Abbott, the Gates Foundation, MSD, US National Institutes of Health, US National Institute of Mental Health, USAID (to the Magee-Womens Research Institute), and South African Medical Research Council/Department of Science, Technology, and Innovation; and reports a leadership or fiduciary role for MOSAIC PAAC (paid to their institution) and DPP advisory board (unpaid). RP has received medical writing support from Gilead Sciences, and grants from DAIDS and NIH. NS has received medical writing support from Gilead Sciences. SBP, PA, JMB, AB, CCC, MI, JL, RS, PW, and MD are employees of, and hold stock or grants in, Gilead Sciences. FMK has received medical writing support from Gilead Sciences.

Data sharing

Gilead Sciences (Foster City, CA, USA) shares anonymised individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting no conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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