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Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study

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Summary

Background—Global rollout of dolutegravir-based antiretroviral therapy (ART) has been hampered in part by insufficient safety data in pregnancy. We compared birth outcomes among women initiating dolutegravir-based ART with those among women initiating efavirenz-based ART in pregnancy in Botswana.

Methods—In this observational study, we captured birth outcome data at eight government hospitals throughout Botswana (~45% of all deliveries in the country) in an ongoing study that started on Aug 15, 2014. In 2016, Botswana changed first-line ART from efavirenz-tenofovir-emtricitabine to dolutegravir-tenofovir-emtricitabine, including for pregnant women. This analysis includes women starting either efavirenz-based ART or dolutegravir-based ART during singleton pregnancy (regimen started and delivery occurring between Aug 15, 2014, and Aug 15, 2016, for efavirenz-based ART and between Nov 1, 2016, and Sept 30, 2017, for dolutegravir-based ART). We excluded births to mothers who had switched regimen or stopped ART. The primary outcomes

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Contributors

RZ and RLS contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. DLJ contributed to the design of the study, analysis and interpretation of data, and drafting of the manuscript. GM and MD contributed to the acquisition of data and to critical revision of the manuscript. MM, ME, TG, CP, JM, and SL contributed to conception and design of the study and critical revision of the manuscript. LBH contributed to the conception and design of the study, interpretation of data, and critical revision of the manuscript.

Declaration of interests

We declare no competing interests.

were the combined endpoints of any adverse outcome (stillbirth, preterm birth [<37 weeks' gestation], small for gestational age [SGA; less than the tenth percentile of birthweight by gestational age], or neonatal death [within 28 days of age]) and severe adverse outcomes (stillbirth, neonatal death, very preterm birth [<32 weeks' gestation], and very SGA [less than the third percentile of birthweight by gestational age]). We fitted log-binomial regression models, controlling for maternal age, gravidity, and education, to estimate adjusted risk ratios (aRRs).

Findings—Our analysis included 1729 pregnant women who initiated dolutegravir-based ART and 4593 who initiated efavirenz-based ART. The risk for any adverse birth outcome among women on dolutegravir versus efavirenz was similar (33·2% *vs* 35·0%; aRR 0·95, 95% CI 0·88–1·03), as was the risk of any severe birth outcome (10·7% *vs* 11·3%; 0·94, 0·81–1·11). We found no significant differences by regimen in the individual outcomes of stillbirth, neonatal death, preterm birth, very preterm birth, SGA, or very SGA.

Interpretation—Adverse birth outcomes were similar among pregnant women who initiated dolutegravir-based and efavirenz-based ART. Dolutegravir-based ART can be safely initiated in pregnancy.

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Introduction

Integrase strand inhibitor-based antiretroviral therapy (ART) with dolutegravir has become a preferred regimen for first-line HIV treatment because of its efficacy, tolerability, limited drug–drug interactions, and a high barrier to resistance.[1,2] Use of dolutegravir in low-income and middle-income countries is likely to be cost-effective,[3,4] particularly once low-cost generic dolutegravir becomes widely available. However, in part because of insufficient data on the safety of dolutegravir in pregnancy, WHO has refrained from recommending dolutegravir-based treatment as the preferred first-line ART regimen for use in national treatment programmes in countries where harmonisation of ART regimens for all adults (including pregnant women) is important.[5]

To our knowledge, no previously published studies have evaluated the safety of dolutegravir in pregnancy. Outcomes from a total of 112 pregnancies exposed to dolutegravir have been reported in the literature,[5] which is an insufficient number to evaluate risks of adverse birth outcomes (the antiretroviral pregnancy registry requires 200 pregnancies before reporting).[6] Additionally, more than half of these pregnancies (67 [60%]) come from post-marketing surveillance in which there is no comparator group.[5] By contrast, there is now sufficient data showing that the WHO first-line recommended regimen efavirenz-tenofovir-emtricitabine is safer in pregnancy than are older ART regimens containing nevirapine, lopinavir-ritonavir, and zidovudine-lamivudine.[7,8] Therefore, to justify a transition to dolutegravir-based ART, dolutegravir needs to be shown to be at least as safe as efavirenz-based ART in pregnancy.

Botswana was the first country to recommend use of dolutegravir in pregnancy, and offers a unique opportunity to study the safety of in-utero exposure to dolutegravir. In June, 2016, there was a swift rollout of new guidelines by the Botswana national HIV treatment programme, recommending initiation of dolutegravir-tenofovir-emtricitabine instead of efavirenz-tenofovir-emtricitabine for all adults with HIV, including pregnant women.[9] We

have been conducting a large birth outcomes surveillance study at eight sites in Botswana since August, 2014, and have been able to take advantage of this unique landscape to compare birth outcomes among women initiating dolutegravir versus efavirenz with the same nucleoside reverse transcriptase inhibitor (NRTI) backbone.

Methods

Study design and participants

Methods from the Tsepamo study have been previously described.[8] In summary, data were abstracted from obstetric records of all women who delivered liveborn or stillborn infants at 24 weeks' gestational age or later at eight government maternity wards in Botswana, representing approximately 45% of all births in the country.[10] Two sites were tertiary referral centres and the remainder were primary and district hospitals.

From January, 2012, up to May, 2016, Botswana national HIV treatment guidelines recommended efavirenz-based ART (efavirenz-tenofovir-emtricitabine) for adults with CD4 cell count of 350 cells per mL or lower, and for all pregnant women regardless of CD4 count.[11] In May, 2016, guidelines were updated and recommended dolutegravir-based ART (dolutegravir-tenofovir-emtricitabine) for all adults with HIV, regardless of CD4 cell count or pregnancy status.[9] All HIV services, including testing, treatment, laboratory monitoring, and clinical care, are provided free of charge to Botswana citizens.

In this analysis, we included singleton births to women who started dolutegravir-based ART at any time during pregnancy and gave birth between Nov 1, 2016, and Sept 30, 2017, and to women who started efavirenz-based ART during pregnancy and gave birth between Aug 15, 2014, and Aug 15, 2016. Although dolutegravir-based ART was rolled out in May, 2016, births to women on this regimen before November, 2016, were not comparable to births on efavirenz-based ART because births shortly after the rollout included a high proportion of women who had started dolutegravir late in pregnancy (often associated with late presentation for antenatal care and worse birth outcomes) and women who had a preterm or very preterm birth. Inclusion of data from this period could have led to an artificially high rate of adverse birth outcomes among the dolutegravir group. Therefore, births to mothers who had switched or stopped ART were excluded from analyses.

Ethical approval for this study was granted by the Human Research and Development Council in Botswana and by the Office of Human Research Administration at Harvard TH Chan School of Public Health.

Data collection

Data were abstracted from the maternity obstetric cards (medical record throughout pregnancy) at the postnatal ward at each site. Information included maternal demographics, maternal medical history, self-reported alcohol and tobacco use, laboratory values measured in pregnancy (haemoglobin and rapid plasma reagin), maternal diagnoses and medications prescribed during pregnancy, and birth information for the infant. HIV blood test results in pregnancy were collected for all women, and for women with HIV, further information was gathered on the timing of HIV diagnosis, most recent CD4 cell count, and history of

antiretroviral use (including start date, regimen, and any switch or discontinuation during pregnancy).

As in our prior analyses,[8] we used the estimated gestational age documented by nurses at the time of delivery for our analysis. This was typically calculated during antenatal care on the basis of the last menstrual period documented at first antenatal care visit, and was confirmed by ultrasound when available. If the last menstrual period was unknown or suspected to be incorrect, and if no ultrasound was available, fundal height measurements were occasionally used by midwives to estimate gestational age.

Outcomes

The primary outcomes were the combined endpoints of any adverse outcome and any severe adverse outcome. The former comprised stillbirth, preterm birth, small for gestational age (SGA), or neonatal death, and the latter comprised stillbirth, very preterm birth, very SGA, or neonatal death. Secondary endpoints were the individual outcomes for stillbirth, preterm birth, very preterm birth, SGA, very SGA, and neonatal death. Stillbirth was defined as fetal death (summed Apgar score of 0). Preterm birth was a birth at less than 37 weeks' gestation and very preterm was a birth at less than 32 weeks' gestation. An infant was considered SGA if less than the tenth percentile and very SGA if less than the third percentile of birthweight by gestational age using Intergrowth-21 norms (defined from 24 to 42 weeks' gestation).[12,13] Neonatal deaths comprised deaths within 28 days of age among infants who had never left the hospital. Congenital abnormalities were a further secondary outcome, and were detected by the nurse midwife during the neonatal surface examination and photographed if maternal consent was obtained. Photographs were then evaluated and classified by a specialist in Boston (LBH) who was blinded to HIV and ART status. Congenital abnormalities were considered major if they had clinical, surgical, or cosmetic significance. Positional and genetic deformities were excluded.

Statistical analysis

Birth outcomes were analysed for women with singleton pregnancy by ART regimen and among HIV-negative women. We used the exact method to estimate 95% CIs around the prevalence of each outcome. To compare the risk of each primary and secondary birth outcome between the two treatment groups, we calculated the unadjusted and adjusted risk difference for each outcome using additive binomial regression and calculated the unadjusted and adjusted risk ratio (aRR) using a log-binomial regression model. We chose covariates for adjusted analyses a priori based on our previous analyses[8,9] and included maternal age (<18 years, 18–35 years, or >35 years), gravidity (1, 2–5, or >5), and low education (none or primary *vs* secondary or higher). The sample size needed for analyses was based on an ability to have 80% power to detect a relative risk of 1·3 for any severe birth outcomes (and therefore more power to detect this risk ratio among the most common outcomes of any adverse birth outcome, namely preterm birth and SGA). In a secondary analysis, we used the same methodology but a separate model to evaluate the risk of the primary outcomes among HIV-negative women compared with women with HIV who had initiated either dolutegravir-based ART or efavirenz-based ART. In a further secondary analysis, to assess for potential temporal changes in birth outcomes, we also included HIV-

negative women who delivered during the two ART exposure periods (August, 2014–August, 2016, and November, 2016–October, 2017). We did two a-priori sensitivity analyses. The first model excluded women who started ART from 0–4 weeks' gestation and the second model included only women who started ART after their first antenatal care visit.

Statistical analyses were done using SAS, version 9.3. All reported p values are based on a two-sided test with a significance level of α=0·05.

Role of the funding source

The funders of this study had no role in the design; collection, analysis, or interpretation of data; writing of the manuscript; or decision to submit the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 15, 2014, and Aug 15, 2016, 11708 women with HIV delivered singletons, of whom 4593 (39%) began efavirenz-based ART after conception. Between Nov 1, 2016, and Sept 30, 2017, 5418 women with HIV delivered singletons, of whom 1729 (32%) began dolutegravir-based ART after conception. 51167 HIV-negative women had singleton delivery during these two time periods.

Age, parity, socioeconomic indicators, timing of initiation of antenatal care, and site of delivery were similar among women on dolutegravir-based ART and efavirenz-based ART (table 1). HIV-negative women were more likely to be younger, primiparous, and have higher educational attainment than women infected with HIV. HIV-positive and HIV-negative women had similar timing of initiation of antenatal care.

The time from first presentation at antenatal care to initiation of ART was shorter among those on dolutegravir compared with efavirenz, resulting in a slightly earlier median gestational age at ART initiation for women starting dolutegravir-based ART compared with women starting efavirenz-based ART (table 2). Median CD4 count was similar among women who started dolutegravir-based ART and efavirenz-based ART, although a greater proportion of women in the efavirenz group had a CD4 count test during pregnancy (2054 [44·7%] *vs* 247 [14·2%]; table 2).

Overall, 2180 (34·5%) of all births to women infected with HIV included in this analysis resulted in any adverse birth outcome and 704 (11·1%) in a serious adverse birth outcome. The occurrence of any adverse birth outcome was similar among women initiating dolutegravir-based ART (574 women [33·2%, 95% CI 31·0–35·5]) and women initiating efavirenz-based ART (1606 women [35·0%, 95% CI 33·6–36·4]; table 3). The occurrence of any severe adverse birth outcome was also similar among women initiating dolutegravir-based ART (185 women [10·7%, 9·3–12·3]) and women initiating efavirenz-based ART (519 women [11·3%, 10·4–12·3]; table 3).

We observed no di3erence in preterm birth, very preterm birth, SGA, very SGA, stillbirth, or neonatal death among women initiating dolutegravir-based ART compared with those

initiating efavirenz-based ART (table 4). In adjusted analyses, we found no increased risk of preterm birth, very preterm birth, SGA, very SGA, stillbirth, or neonatal death (table 3). Sensitivity analyses that excluded participants who had started ART from 0–4 weeks' gestation and that limited the analysis to women who started ART after their first antenatal care visit did not change the results of the analysis (appendix).

Among 675 women with first-trimester exposure to ART (280 to dolutegravir-based ART and 395 to efavirenz-based ART), one major congenital abnormality occurred: skeletal dysplasia in an efavirenz-exposed infant. Additionally, there were six cases of postaxial polydactyly type B (two in infants exposed to dolutegravir and four in infants exposed to efavirenz), which were not considered major abnormalities because all cases were managed by tying off the extra digits after birth.

Among HIV-negative women, 14766 (28·9%) had any adverse birth outcomes, including preterm birth in 7884 (15·6%) of 50683 women, SGA in 7419 (14·8%) of 50172 women, stillbirth in 1061 (2·1%) of 51164 women, and neonatal death in 697 (1·4%) of 50055 women with livebirths (appendix). Severe adverse birth outcomes occurred in 5085 (9·9%) women, including very preterm births in 1807 (3·6%) of 50683 women and very SGA infants in 2708 (5·4%) of 50172 women. Birth outcomes did not differ by time period among HIV-negative women (appendix).

In adjusted analyses, compared with HIV-negative women, women with HIV on either dolutegravir-based or efavirenz-based ART had significantly higher risk of any adverse birth outcomes (aRR 1·23, 95% CI 1·18–1·28) and any severe adverse birth outcomes (1·16, 1·07–1·25). These women also had higher risk of preterm birth (1·18, 1·12–1·25), SGA (1·30, 1·23–1·38), and very SGA (1·28, 1·16–1·42). We found no difference in very preterm birth (1·01, 0·88–1·16), stillbirth (1·08, 0·91–1·29), or neonatal death (0·92, 0·73–1·17; appendix).

Discussion

The 2016 rollout of dolutegravir-tenofovir-emtricitabine in Botswana allowed us to do what, to our knowledge, is the first large study of the safety of dolutegravir-based ART in pregnancy. We found no difference in the risk of adverse birth outcomes among women initiating dolutegravir-based ART compared with women initiating efavirenz-based ART in pregnancy. Compared with HIV-negative women, both groups of women with HIV had a mildly increased risk for adverse birth outcomes and severe adverse birth outcomes.

We have previously shown that women on efavirenz-tenofovir-emtricitabine had fewer adverse birth outcomes than did those on older ART regimens containing nevirapine, lopinivir-ritonavir, or zidovudine plus lamivudine backbone.[7] The finding that dolutegravir-based ART has a similar risk profile to efavirenz-based ART is highly reassuring, and two small studies[14,15] of pregnant women on integrase inhibitors in Europe support these results. The first study[14] found similar rates of preterm and SGA among 81 European women on dolutegravir in pregnancy compared with the general population in the UK. The second study[15] found similar rates of preterm and stillbirth among 479 pregnant women in France on raltegravir compared with the general French population. Although we cannot exclude a

small difference in relative risk between these two regimens—the 95% CIs in our study are 0·88–1·03 for any adverse outcome and 0·81–1·11 for any severe adverse outcome, thus non-significant—these absolute differences would be very small and unlikely to have clinical significance that would outweigh the decision to use the preferred ART regimen for maternal health. We also found no difference in relative risk for all individual birth outcomes, providing reassurance that dolutegravir is likely to be safe when started in pregnancy. Our findings similarly provide further reassurance about the safety of efavirenz in pregnancy, which is widely used throughout the world.

Because we evaluated dolutegravir started in pregnancy, we were unable to adequately evaluate whether the risk of major congenital abnormalities differs by regimen because we only had information about surface abnormalities for a small number of exposures from the first trimester. We report a substantially lower rate of total congenital abnormalities than do the antiretroviral pregnancy registry[6] and IMPAACT P1026s[16] and EPIIC/PANNA data[17]—two pharmacokinetic studies of antiretroviral drugs in pregnancy. One reason for this is that we report only major congenital abnormalities of medical, surgical, or cosmetic importance, excluding minor abnormalities, positional abnormalities, and genetic abnormalities. The other reason is that we ascertain abnormalities that are visible on the neonatal surface examination and therefore do not evaluate for internal defects such cardiac or renal, or defects that are more likely to present after the first few days of life. We do not believe the reason for the low rate of abnormalities is lack of ascertainment, because we did active surveillance on all infants and documented a 1·2% prevalence of postaxial polydactyly type B—a minor abnormality found in first-trimester exposure to dolutegravir or efavirenz—that is consistent with the reported prevalence of this abnormality in African American infants[18] and also similar to the prevalence among HIV-negative women in our birth outcomes study (data not shown). Further research is needed among a larger number of women on dolutegravir from conception, with longitudinal infant follow-up, to fully evaluate congenital abnormalities.

Our results show that women with HIV on either efavirenz-based or dolutegravir-based regimens had a small but significant increase in adverse birth outcomes compared with HIV-negative women. This risk was smaller than in prior studies done when most women with HIV received nevirapine, lopinavir-ritonavir, and zidovudine-lamivudine.[19] However, even small differences can translate into a large number of adverse birth outcomes in a high-prevalence HIV setting, and can adversely affect child health and survival. The reasons for the difference in outcomes by maternal HIV status remain unknown. The difference might be due to chronic HIV infection, comorbidities or coinfections,[20,21] or a direct effect from ART.

Our study has several strengths, including a sample size large enough to evaluate severe birth outcomes, and the same NRTI backbone (tenofovir-emtricitabine) for both regimens, which enabled us to truly compare the effects of dolutegravir and efavirenz. However, our study also had several limitations, including an inability to fully evaluate CD4 cell count because of the low proportion of women on dolutegravir who had a reported CD4 count in pregnancy (14·3%), probably due to the new strategy of test and treat, which does not require a CD4 count for initiation of ART. The data we do have available suggest this is not

a major confounder. The sequential switch from efavirenz to dolutegravir puts our data at risk of historical bias. However, the total interval was short (3 years) and there was no change in birth outcomes among HIV-negative women by calendar year (appendix). Given the observational study design, unmeasured confounding could bias our results. Although we can be reassured because baseline covariates were well balanced between the two groups, we controlled for potential confounders identified in prior similar studies in Botswana and sensitivity analyses with additional baseline covariates did not change our results (appendix). Additionally, we could not compare other outcomes such as early pregnancy loss (<24 weeks' gestation); maternal viral load at the time of delivery; efficacy in prevention of mother-to-child HIV transmission; adherence, tolerability, and toxicity in pregnancy; or paediatric outcomes after birth. Finally, we are unable to assess the quality of data in the medical records or validate gestational age dating, although we feel neither should differ by ART regimen.

In conclusion, adverse birth outcomes were similar for dolutegravir-based ART and efavirenz-based ART when started during pregnancy. Although further studies are needed to determine the safety of dolutegravir exposure from conception and to confirm its efficacy for prevention of mother-to-child HIV transmission, these results should pave the way for wider use of dolutegravir in pregnancy throughout the world.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

Dolutegravir-based antiretroviral treatment (ART) is a preferred first-line ART regimen for adults with HIV because of its efficacy, tolerability, high barrier to resistance, and minimal drug–drug interactions. However, outcomes of only a small number of exposures in pregnancy have been published to date, which precludes evaluation of whether the use of dolutegravir in pregnancy might lead to increases in preterm birth, small for gestational age, stillbirth, neonatal death, or congenital abnormalities. Therefore, dolutegravir is not included as a first-line recommended regimen in pregnancy by WHO or by HIV guideline committees in the USA or Europe. Unavailability of pregnancy safety data has also hampered use of dolutegravir for all adults in low-income and middle-income countries where women of reproductive age make up a large proportion of the HIV-positive population.

Added value of this study

In 2016, Botswana became the first country to change its national ART guidelines to recommend the start of dolutegravir-tenofovir-emtricitabine in pregnancy, rather than the current WHO-recommended regimen of efavirenz-tenofovir-emtricitabine. Our study compared adverse birth outcomes before and after this change in guidelines, among 1729 women who initiated dolutegravir-based ART and 4593 women who initiated efavirenz-based ART. We found no increased risk for adverse birth outcomes, including severe adverse birth outcomes, among women initiating dolutegravir-based ART in pregnancy. These findings support updates to current HIV treatment guidelines to allow initiation of dolutegravir-based ART as a first-line regimen in pregnancy.

Implications of all the available evidence

The results of this study should decrease the barriers to use of dolutegravir in women of reproductive age around the world once further data are gathered regarding the safety of dolutegravir from conception. These findings are particularly important for low-income and middle-income countries where harmonisation of first-line ART for adults and pregnant women is a key factor in the success of HIV treatment strategies.

Table 1

Baseline maternal demographics and pregnancy history among singleton births

		HIV positive (n=6322)	
	HIV negative (n=51167)	**Dolutegravir-based ART (n=1729)**	**Efavirenz-based ART (n=4593)**
Maternal age, years	25 (21–30)	28 (23–33)	28 (23–32)
Data missing	30 (0·1%)	0	0
Married	5684 (11·1%)	114 (6·6%)	325 (7·1%)
Data missing	1336 (2·6%)	33 (1·9%)	109 (2·4%)
Primary or no education	3078 (6·0%)	150 (8·7%)	435 (9·5%)
Data missing	1192 (2·3%)	17 (1·0%)	102 (2·2%)
Occupation			
Housewife or none	27537 (53·8%)	1013 (58·6%)	2508 (54·6%)
Student	4664 (9·1%)	61 (3·5%)	192 (4·2%)
Salaried	16716 (32·7%)	601 (34·8%)	1722 (37·5%)
Missing	2250 (4·4%)	54 (3·1%)	171 (3·7%)
Non-citizen	1690 (3·3%)	5 (0·3%)	77 (1·7%)
Data missing	129 (0·3%)	6 (0·3%)	7 (0·2%)
Primiparous	22125 (43·2%)	446 (25·8%)	1095 (23·8%)
Grand multiparous (≥5 pregnancies)	3570 (7·0%)	188 (10·9%)	551 (12·0%)
Data missing	126 (0·2%)	0	5 (0·1%)
Gestational age at antenatal care presentation, years	17 (13–22)	17 (13–22)	17 (13–22)
Data missing	2535 (5·0%)	39 (2·3%)	163 (3·5%)
Received no prenatal care	1254 (2·5%)	17 (1·0%)	32 (0·7%)
Data missing	393 (0·8%)	0	35 (0·8%)
Alcohol or smoking in pregnancy	4047 (7·9%)	196 (11·3%)	475 (10·3%)
Data missing	3705 (7·2%)	121 (7·0%)	287 (6·2%)
Birth at a tertiary facility	24910 (48·7%)	862 (49·9%)	2315 (50.4%)
Data missing	0	0	0
Birth via cesarean section	11368 (22·2%)	406 (23·5%)	1062 (23·1%)
Data missing	62 (0·1%)	1 (0·1%)	2 (<0·1%)

Data are n (%) or median (IQR). ART=antiretroviral treatment.

Table 2

Baseline HIV-related characteristics among women on dolutegravir-based and efavirenz-based ART

	Dolutegravir-based ART (n=1729)	Efavirenz-based ART (n=4593)
Diagnosed with HIV before pregnancy	452 (26·1%)	1558 (33·9%)
Data missing	0	0
Days from first antenatal care visit to initiation of ART	9 (0–30)	23 (7–45)
Data missing	60 (3·5%)	232 (5·1%)
Gestational week at ART initiation	19 (14–25)	21 (16–27)
Data missing	100 (5·8%)	341 (7·4%)
Number with CD4 result in pregnancy	247 (14·3%)	2054 (44·7%)
CD4 count in pregnancy (cells per mm^3)	411 (282–549)	402 (281–551)
CD4 category in pregnancy		
<200 cells per mm^3	30/247 (12·1%)	257/2054 (12·5%)
200–349 cells per mm^3	66/247 (26·7%)	543/2054 (26·4%)
350–499 cells per mm^3	72/247 (29·1%)	594/2054 (28·9%)
≥500 cells per mm^3	79/247 (32·0%)	660/2054 (32·1%)

Data are n (%), n/N (%), or median (IQR). ART=antiretroviral treatment.

Table 3

Birth outcomes among women initiating dolutegravir-based ART versus efavirenz-based ART in pregnancy

	Dolutegravir-based ART (n=1729)	Efavirenz-based ART (n=4593)
Any adverse birth outcome		
Number of women	574 (33·2%, 31·0 to 35·5)	1606 (35·0%, 33·6 to 36·4)
Unadjusted relative risk	0·95 (0·88 to 1·03)	1 (ref)
Adjusted relative risk	0·95 (0·88 to 1·03)	1 (ref)
Unadjusted risk difference	−1·77% (−4·38 to 0·85)	1 (ref)
Adjusted risk difference	−1·76% (−4·39 to 0·87)	1 (ref)
Any severe birth outcome		
Number of women	185 (10·7%, 9·3 to 12·3)	519 (11·3%, 10·4 to 12·3)
Unadjusted relative risk	0·95 (0·81 to 1·11)	1 (ref)
Adjusted relative risk	0·94 (0·81 to 1·11)	1 (ref)
Unadjusted risk difference	−0·60% (−2·32 to 1·12)	1 (ref)
Adjusted risk difference	−0·51% (−2·24 to 1·23)	1 (ref)

Data in parentheses are 95% CIs or %, 95% CI. ART=antiretroviral therapy.

Table 4

Adverse birth outcomes among singleton births by ART exposure

	Dolutegravir-based ART (n=1729)	Efavirenz-based ART (n=4593)	Unadjusted risk difference (95% CI)	Adjusted risk difference (95% CI)	Unadjusted relative risk (95% CI)	Adjusted relative risk (95% CI)
Preterm birth (<37 weeks)*	309 (18·0%, 16·2 to 19·9)	844 (18·5%, 17·4 to 19·6)	−0·5% (−2·6 to 1·7)	−0·3% (−2·5 to 1·8)	0·97 (0·87 to 1·10)	0·98 (0·87 to 1 to 11)
Very preterm birth (<32 weeks)*	66 (3·8%, 3·0 to 4·9)	160 (3·5%, 3·0 to 4·1)	0·3% (−0·7 to 1·4)	0·4% (−0·7 to 1·4)	1·10 (0·83 to 1·45)	1·09 (0·82 to 1·45)
Small for gestational age (<10th percentile weight-for-gestational-age)*†	297 (17·4%, 15·7, 19·3)	838 (18·5%, 17·4 to 19·7)	−1·1% (−3·2 to 1·0)	−0·9% (−3·1 to 1·2)	0·94 (0·83 to 1·06)	0·94 (0·83 to 1·06)
Very small for gestational age (<3rd percentile weight-for-gestational-age)*†	104 (6·1%, 5·0 to 7·4)	302 (6·7%, 6·0 to 7·5)	−0·6% (−1·9 to 0·8)	0·3% (−1·6 to 1·1)	0·91 (0·74 to 1·13)	0·91 (0·74 to 1·13)
Stillbirth‡	39 (2·3%, 1·6 to 3·1)	105 (2·3%, 1·9 to 2·8)	0·03% (−0·9 to 0·8)	0·1% (−0·9 to 0·8)	0·99 (0·69 to 1·42)	0·99 (0·69 to 1·42)
Neonatal death (<28 days)§	21 (1·2%, 0·8 to 1·9)	60 (1·3%, 1·0 to 1·7)	0·1% (−0·7 to 0·5)	−0·1% (−0·7 to 0·6)	0·93 (0·57 to 1·53)	0·96 (0·58 to 1·57)

Data are n (%, 95% CI), risk difference (95% CI), or relative risk (95% CI). Table includes singleton births only and women with missing data were excluded. All models were adjusted for maternal age, gravidity, and low educational attainment. ART=antiretroviral treatment.

*Missing data for gestational age: 37 participants in the dolutegravir group and 129 participants in the efavirenz group.

†Missing data for birthweight: 14 participants in the dolutegravir group and 45 participants in the efavirenz group.

‡Missing stillbirth status: 25 participants in the dolutegravir group and 102 participants in the efavirenz group.

§Missing neonatal death status: 28 participants in the dolutegravir group and 104 participants in the efavirenz group.