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The safety of a dolutegravir (DTG)-based antiretroviral treatment (ART) regimen for pregnancy and birth outcomes in Ethiopia: evidence from multicenter cohort study

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Abstract

Background A dolutegravir (DTG)-based antiretroviral regimen has been rolled out for pregnant women in low- and middle-income countries since 2020. However, available safety data are limited to a few clinical trials and observational studies. Hence, we present real-world pregnancy and birth outcome safety data from a large sample multicenter cohort study in Ethiopia.

Methods A retrospective cohort study was conducted in fourteen hospitals across Ethiopia from 2017 to 2022. HIV-infected pregnant women were followed from the date of prevention of mother-to-child transmission (PMTCT) care enrolment until the infant was 6–8 weeks old. The primary safety outcome was a composite of adverse pregnancy events comprising spontaneous abortion, intrauterine fetal death (IUFD) before onset of labor, preterm birth, and maternal death. Additionally, a composite adverse birth outcome was assessed, comprising intrapartum fetal demise, low birth weight, and neonatal death. Finally, a composite of adverse pregnancy or birth outcome was also investigated. The exposure of interest was the antiretroviral treatment (ART) regimen used during pregnancy for PMTCT of HIV.

Results During the study period, 2643 women were enrolled in routine PMTCT care. However, 2490 (92.2%) participants were eligible for the study. A total of 136/1724 (7.9%, 95% CI: 6.7–9.3%) women experienced adverse pregnancy outcomes. Fewer women in the DTG-based group (5.4%, 95% CI: 3.7–7.5%) had adverse pregnancy outcomes than in the Efavirenz (EFV)-based group (8.3%, 95% CI: 6.6–10.3%), $P=0.004$. After controlling for baseline differences, the DTG group had a 43% lower risk of adverse pregnancy outcomes (adjusted odd ratio (AOR), 0.57; 95% CI, 0.32–0.96%) and a 53% lower risk of preterm birth (AOR, 0.47; 95% CI, 0.22–0.98%) compared to the EFV group. A total of 103/1616 (6.4%, 95% CI: 5.2–7.7%) women had adverse birth outcomes. Although the difference was not statistically significant, fewer women in the DTG group (30/548; 5.5%, 95% CI: 3.7–7.7%) than in the EFV group (57/830; 6.9%, 95% CI: 5.2–8.8%) had adverse birth outcomes.

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Conclusions In this study, we observed that DTG-based regimens were associated with better pregnancy and birth outcome safety profiles, reaffirming the WHO recommendation. However, a prospective study is recommended to assess uncaptured maternal and perinatal adverse outcomes, such as congenital abnormalities, and infant growth and neurocognitive development.

Keywords Pregnancy, Birth, Safety, ART, DTG

Background

Human immunodeficiency virus (HIV) remains a major global public health problem [1]. In 2022 alone, 630,000 [480,000–880,000] people died from HIV-related causes, and 1.3 million [1.0–1.7 million] people acquired new HIV [2]. Moreover, an estimated 1.3 million women and girls living with HIV become pregnant each year [2]. In the absence of antiretroviral therapy (ART), HIV-exposed infants are likely to acquire the infection during pregnancy, labour, delivery, or breastfeeding [3]. In addition to acquiring the virus, babies of HIV-infected women have a greater risk of stillbirth, preterm birth, low birth weight, and neonatal mortality and morbidity than babies of non-HIV-infected women [4]. ART for pregnant women is the most effective intervention for reducing mother–to–child transmission (MTCT) of HIV and decreasing maternal and child morbidity mortality.

Since 2016, dolutegravir (DTG)-based ART, (tenofovir disoproxil fumarate (TDF)+lamivudine (3TC)+DTG), has become a preferred first-line regimen [5] over the efavirenz (EFV)-based regimen (TDF+3TC+EFV) because of its efficacy [6], tolerability [7], limited drug-drug interactions, and high barrier to resistance [8]. However, the use of DTG-based regimens for pregnant women in low- and middle-income countries was delayed compared to the non-pregnant adult population due to the lack of pregnancy safety data [9]. This is mainly due to the exclusion of pregnant women from the DTG-based regimen safety and efficacy clinical trials due to perceived vulnerability [10, 11]. The available clinical trials were conducted long after drug registration [12–15].

The safety of any new ART regimen for pregnant women needs to be given great attention in addition to its efficacy in preventing transmission. It is crucial to investigate safety outcomes such as preterm birth, low birth weight, and neonatal mortality, particularly in low-income countries where infant mortality is high. The available evidence on the safety of DTG-based regimens for pregnant women is limited to clinical trials [12, 13, 15]. Furthermore, the clinical trial data have limitations in assessing safety; (1) participants were recruited after conception when the timing of in-utero exposure to ART and adverse outcomes vary [16]; and (2) large numbers of participants are needed to detect differences in rare safety outcomes or small treatment effects [17, 18]. The only available large safety study was the Botswana cohort study [19]. However, further studies are recommended to assess the safety of DTG among women who use ART preconception. Another large cohort study from Brazil was reported. However, the outcomes were limited to congenital anomalies, abortion, and stillbirth [20]. The WHO guidelines also recommend continuous surveillance of safety data [21]. Therefore, we investigated the risk of adverse pregnancy and birth outcomes associated with DTG-based ART regimens in a large multicenter cohort of women seeking routine antenatal care in Ethiopia.

Methods

Study design, settings and period

A multicenter retrospective cohort study was conducted in fourteen [14] public hospitals located in Central and Southern Ethiopia. Ethiopia is located in the north-eastern part of Africa and has an estimated population of 126.5 million in 2023 [22]. An estimated 722,248 people were living with HIV in Ethiopia in 2017 [23], with a decreasing national HIV incidence trend [23]. According to reports from the 2023 Joint United Nations AIDS Program (UNAIDS), 14,200 (82%) HIV-infected pregnant women received lifelong ART in 2022. Moreover, antenatal care HIV testing coverage was more than 95% [2]. Administratively, the hospitals were located in the Oromia, Addis Ababa, Southern Nation, Nationalities and People (SNNP), and Sidama regional states (Fig. 1 and Table 1). Two were primary, three were secondary or general, and the remaining were tertiary hospitals. We could not use northern Ethiopian hospitals due to security concerns when collecting the data. The hospitals were selected based on the availability of the PMTCT service and the high number of HIV-infected pregnant women receiving the service. HIV-infected pregnant women visiting the selected hospitals for routine PMTCT care from the 1st of July 2017 to 30 June 2022 were included. The required data were transferred into a validated Excel checklist form over a 2-month period, from the 1st of January to the end of February 2023.

Study population

The study population included all HIV-infected pregnant women and their HIV-exposed infants who received routine PMTCT care at the selected hospitals. The eligible participants were women with singleton pregnancies, who started ART before the onset of labour, and had documented outcomes. Pregnant women were excluded if (1)

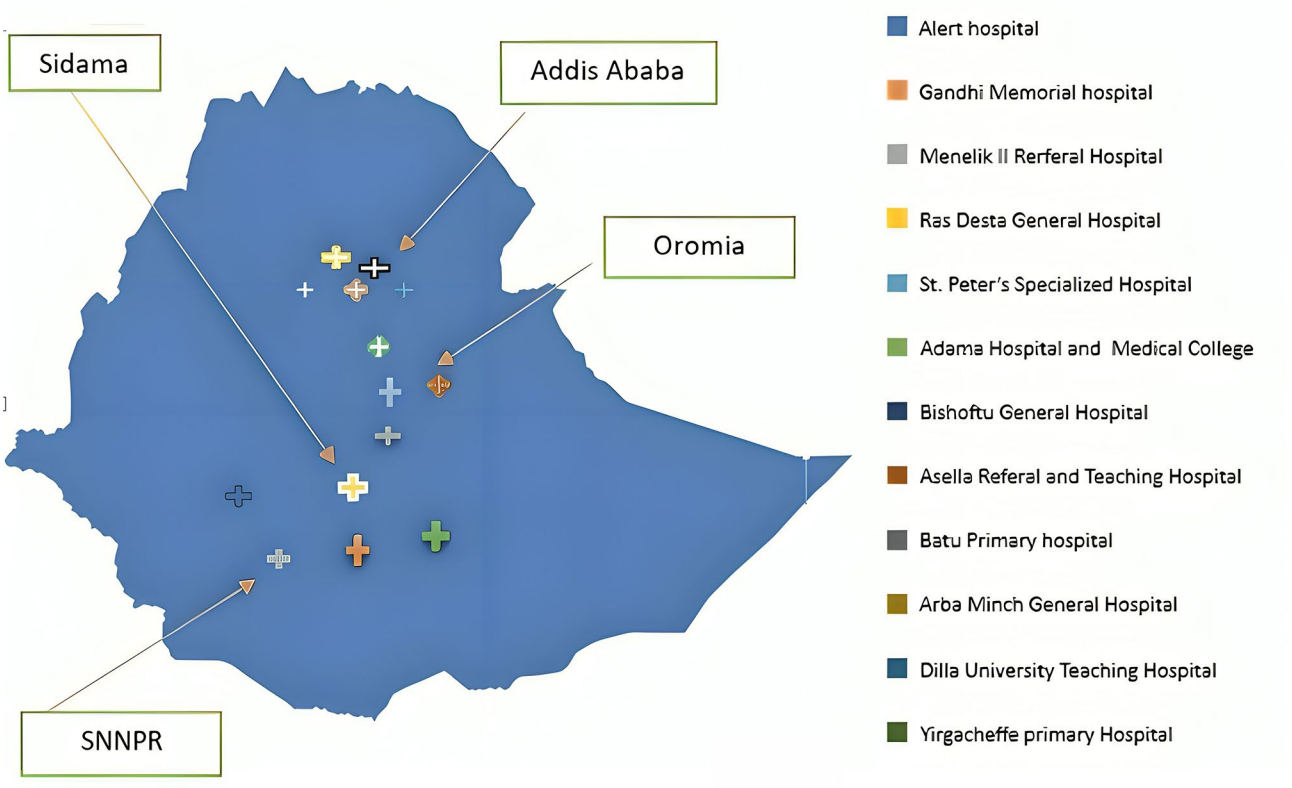

Fig. 1 Geographic distribution of the study hospitals included in the cohort study. SNNPR means Southern Nation, Nationality and People Region

Table 1 The study hospitals characteristics included in the cohort study in Ethiopia from the 2017–2022 cohort years. *N* = 14

Study hospitals	Administrative region	Hospitals level	Catchment population coverage based on national standard (in million)	Total PMTCT care enrolled *N* (%)
Alert hospital	Addis Ababa	Tertiary	3–5	421(15.9)
Gandhi Memorial hospital	Addis Ababa	Tertiary	3–5	166(6.3)
Menelik II Referral Hospital	Addis Ababa	Tertiary	3–5	91(3.4)
Ras Desta General Hospital	Addis Ababa	General	1-1.5	69(2.6)
St. Peter's Specialized Hospital	Addis Ababa	Tertiary	3–5	153(5.8)
Adama Hospital and Medical College	Oromia	Tertiary	3–5	499(18.9)
Bishoftu General Hospital	Oromia	General	1-1.5	167(6.3)
Asella Referal and Teaching Hospital	Oromia	Tertiary	3–5	144(5.5)
Batu Primary hospital	Oromia	Primary	0.1-1	47(1.8)
Arba Minch General Hospital	SNNPR*	General	1-1.5	170(6.4)
Dilla University Teaching Hospital	SNNPR	Tertiary	3–5	235(8.9)
Yirgacheffe primary Hospital	SNNPR	Primary	0.1-1	162(6.1)
Wolaita Sodo University Teaching Referral Hospital	SNNPR	Tertiary	3–5	146(5.5)
Hawassa University Comprehensive Specialized Hospital	Sidama[#]	Tertiary	3–5	173(6.5)
Total			30.2–46.5	2643 (100)

*SNNPR: Southern Nation, Nationality and People Region. # Sidama region was part of SNNPR before 2020

ART was initiated during the labour and delivery period considering the lower likelihood of ART being associated with adverse safety outcomes, (2) HIV-infected women who switched ART regimens during the DTG rollout program or for other reasons to avoid regimens mixed effect, or (3) the woman was lost to follow-up without a documented outcome status.

Outcomes of the study

We investigated two primary safety outcome measures. The first was a composite adverse pregnancy outcome,

defined as the occurrence of at least one of the following: spontaneous abortion (spontaneous termination of pregnancy before 28 weeks of gestation or fetal weight less than 1000gm), intrauterine fetal death (IUFD) (fetal death after 28 weeks of gestation and before onset of labour), preterm birth (delivery of fetus before 37 weeks of gestation and after 28 weeks of gestation among live-born babies), and maternal death during pregnancy or within 42 days of delivery. The second primary safety outcome was a composite adverse birth outcome, defined as the occurrence of at least one of the following: intrapartum fetal demise (defined as intrapartum fetal death assessed by fetal heart monitoring after 28 weeks of gestation or fetal weight of at least 1000 gm), low birth weight (birth weight greater than 1000 gm and less than 2500 gm for a live birth), or neonatal death (death of the newborn before 28 days of age among live births). Secondary outcomes were individual adverse pregnancy or birth outcomes, and a composite of adverse pregnancy and birth outcomes. In this study, abortion is defined as termination of pregnancy before 28 weeks of gestation or fetal weight of less than 1000gm according to the Technical and Procedural Guidelines for Safe Abortion Services in Ethiopia [24, 25]. Preterm birth is defined as birth before 37 completed weeks of gestation [26]. However, extremely preterm births of less than 28 weeks of gestation are categorized as abortion according to the national guidelines [24, 25]. Low birth weight is defined as a birth weight of less than 2500 g [27, 28]. However, extremely low birth weights of less than 1000 gm were recorded as abortions according to national guidelines [24, 25].

Exposure of the study

The exposure of the study was the different ART regimens used for PMTCT of HIV. The DTG-based ART regimen refers to a fixed-dose combination of tenofovir disoproxil fumarate (TDF)+lamivudine (3TC)+dolutegravir (DTG), while the EFV-based regimen includes TDF+3TC+efavirenz (EFV). These two ART regimens were first-line treatment options for pregnant and lactating women before and after the DTG rollout program in Ethiopia. More than ten different ART regimens were also used before the DTG-based regimen rollout and all categorized as "Other" regimens. These regimens were used due to treatment failure or side effects of the first-line regimen. We combined all into one category since our primary safety concern is the recent DTG-based ART regimen compared to the previous first-line regimen.

Covariates

Data on the following covariates were collected: (1) demographic and reproductive variables (study site region, age, gravidity, parity, hospital level, gestational age at the first antenatal care visit), (2) labour and delivery (mode of delivery, place of delivery), and HIV-related characteristics (WHO staging during PMTCT care enrolment, partner HIV status, ART initiation period). We did not include study period as a covariate because of the recent DTG-based ART regimen rollout program in Ethiopia. Gestational age was assessed based on completed weeks using the best available measure: (1) early ultrasound was performed before 22 weeks of gestation, (2) gestational age was calculated from the last normal menstrual period (LNMP) if known, and (3) fetal growth was assessed using symphysis fundal height (SFH) if available in early gestation before 20 weeks. Gestational age during PMTCT care enrolment or ART initiation was assessed based on the abovementioned criteria. Preconception means initiating the ART before the current pregnancy conception. The first, second, and third trimesters included conception to 11 weeks and 6 days, 12 to 27 weeks and 6 days, and after 28 weeks of gestation and before onset of labour respectively.

Study procedures

HIV-infected pregnant women were followed through routine PMTCT care visits from the date of enrolment until 6–8 weeks postpartum according to the national guidelines. HIV testing of HIV-exposed infants using a dry blood sample (DBS) was performed at 6–8 weeks of age. PMTCT services were available to all women attending antenatal, delivery, and postpartum services free of charge. Before the COVID-19 outbreak in Ethiopia in March 2020, women were followed every month until delivery. However, after the COVID-19 pandemic, women were followed every three months during the national lockdown period until September 2021. After PMTCT ART optimization in April 2020, the first-line regimen was changed to a DTG-based regimen, and women with "EFV-based" or "other" ART regimens were switched to DTG-based regimens with different optimization periods among the study hospitals. Routine antenatal and postnatal care and safe delivery practices were provided. Women with a viral load greater than 1,000 copies/ml underwent elective cesarean delivery at 38 weeks of gestation to decrease the transmission rate [29].

Data on safety outcomes were collected from both the routine PMTCT registration logbooks and participants' medical chart records by trained clinicians. All the registrations were paper based during the data collection period. Preterm birth was assessed for women with reliable gestational ages calculated based on the above-stated criteria. Women who were enrolled in PMTCT care late in pregnancy and for whom the gestational age at delivery could not be calculated were excluded from this specific analysis. Similarly, low birth weight was assessed based on the registered birth weight of the newborn. Women who delivered at home or at other health care facilities

were excluded from the birth weight analysis due to a lack of reliable registered birth weights. However, data on other outcomes, such as abortion, IUFD, intrapartum fetal demise, congenital anomalies, neonatal death, and maternal death, were collected from either the registered routine logbooks or participant interviews. These outcome data were registered while the women received the service in the same study hospital or by phone call interviewing the women if they were lost to follow-up in the routine process of adherence management.

Statistical analysis

Data were collected using a pre-tested excel spreadsheet, cleaned and exported to the Statistical Package for the Social Sciences (SPSS) version 26 for analysis. Data cleaning was performed by running simple frequency distributions, summary statistics and cross-tabulations to identify and correct, out-of-range, missing and inconsistent values. Descriptive and summary statistics were used to describe the baseline characteristics categorized by ART regimen. The Pearson $\chi 2$ test was used to determine the differences in the baseline characteristics of participants between the ART regimens. We used the exact method to estimate the cumulative incidence of adverse outcomes and Clopper-Pearson confidence interval for 95% estimation. Multivariate logistic regression was conducted to control for the effects of differences in baseline characteristics on the outcome. Only variables with significant baseline differences at P values less than 0.05 were considered for multivariate logistic regression. Adjusted odds ratios (AORs) with 95% CIs were computed to determine the presence and strength of associations between ART regimens and adverse outcomes. $P<0.05$ was considered to indicate statistical significance. To determine the impact of ART use duration on adverse outcomes, a subgroup analysis was conducted for participants who used ART preconception.

Ethical consideration

The study was reviewed and approved by the Institutional Review Board (IRB) of the College of Medicine and Health Sciences, Hawassa University, with reference number (IRB/076/2022, dated December 10/2022). The need to obtain informed consent from individual participants was waived due to the use of anonymized data from routine healthcare records.

Results

Study cohort participant flowchart

During the study period, 2643 women were enrolled in routine PMTCT care. However, 2490 (92.2%) patients were eligible for the study. A total of 2465 (98.9%) participants were followed up until 28 weeks of gestation, while 2406 (96.6%) women were followed up to 6–8 weeks postpartum). Among the participants who completed the study follow-up period, 53% (1275) of the women used EFV-based ART regimen, 32.2% (775) used DTG-based ART regimen, and 14.8% (356) used Other ART regimens (Fig. 2).

Baseline demographic, reproductive and HIV-related characteristics of the participants

The mean and median ages of the participants were similar, at 29 years. The participants in the DTG group were younger than those in the other groups. Almost all (97%) of the participants were WHO stage one [1] during PMTCT care enrolment. However, a relatively advanced WHO stage was reported in the EFV group. One-tenth (10.6%) of the participants had HIV-negative partners. The majority (85%) of the participants gave birth vaginally and initiated ART preconception. Among the studied baseline characteristics, age, WHO stage, hospital level, administrative region, and ART initiation period were significantly different among the ART regimens, with p values <0.005 (Table 2).

Safety of DTG-based ART regimen for adverse pregnancy outcomes

Among the eligible participants, 1724/2490 (69.2%) women had complete outcome data and were assessed for composite adverse pregnancy outcomes. A total of 136/1724 (7.9%, 95% CI: 6.7–9.3%) women experienced adverse pregnancy outcomes. Compared with those in the EFV-based 75/899 (8.3%, 95% CI: 6.6–10.3%) and "Other ART" 30/248 (12.1%, 95% CI: 8.3–16.8%) regimens, significantly fewer women in the DTG-based 31/577 (5.4%, 95% CI: 3.7–7.5%) regimens had an adverse pregnancy outcome ($P=0.004$) (Fig. 3a & supplementary Table 1). We found that participants in the DTG-based group had a 43% lower risk of the composite adverse pregnancy outcome than did those in the EFV-based group (adjusted OR 95% CI, 0.57 (0.32–0.97), adjusted for age, WHO staging, hospital level, ART initiation and administration region) (Table 3).

The cumulative incidence of preterm birth was 5.1% (86/1674), 95% CI: 4.1–6.3%). However, preterm birth was significantly less frequent in the DTG-based 19/565 regimens (3.4%, 95% CI: 2-5.2%) than in the EFV-based 45/869 (5.2%, 95% CI: 3.8–6.9%) or "other ART" regimens 22/240 (9.2%, 95% CI: 5.8–13.5%), $p=0.003$ (Fig. 3a & supplementary Table 1). Compared to the EFV-based group, the DTG-based group had a 53% lower risk of preterm birth after controlling for baseline differences, with an adjusted OR of 0.47 (95% CI 0.22-1.00) (Table 3). Two out of 2454 (0.1%) women died during the follow-up period—one before delivery and the other after delivery—due to bleeding-related causes. The women were in the EFV- and DTG-based regimens.

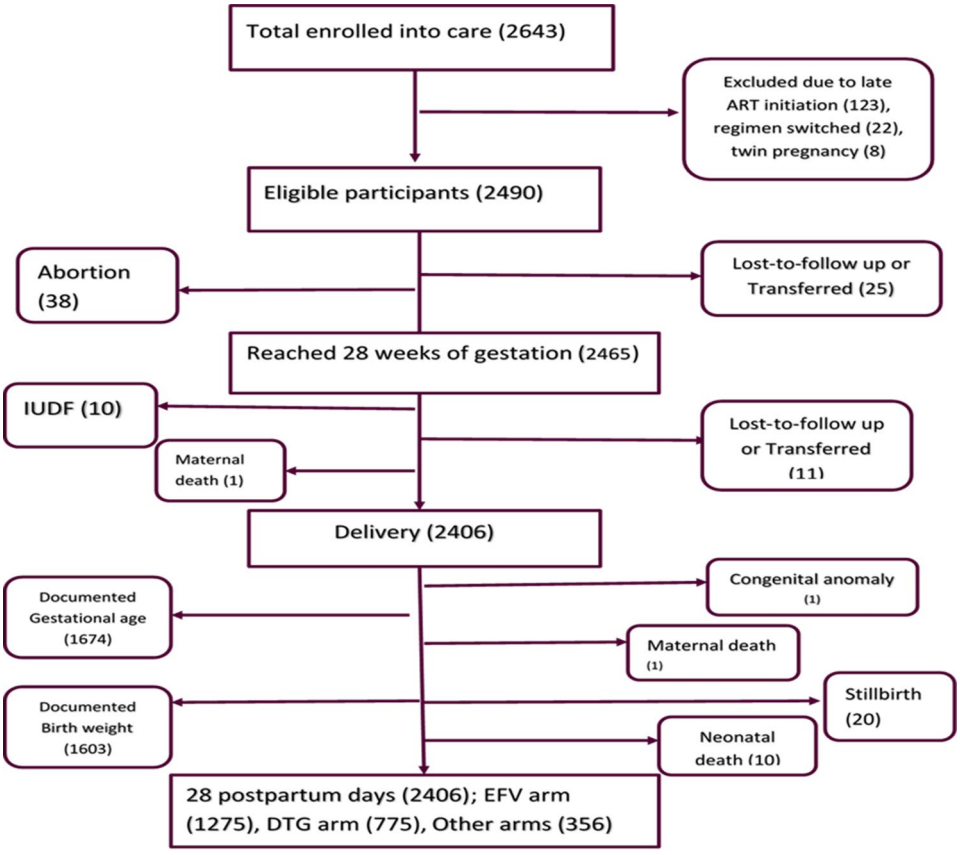

Fig. 2 Study cohort participant flowchart

Safety of DTG-based ART regimens for adverse birth outcomes and any pregnancy and birth outcomes

Among the study cohort, a total of 103/1616 (6.4%, 95% CI: 5.2–7.7%) women had composite adverse birth outcomes. Although not significantly different, fewer women in the DTG–based group (30/548; 5.5%, 95% CI: 3.7–7.7%) had an adverse birth outcome than did those in the EFV-based group (57/830; 6.9%, 95% CI: 5.2–8.8%) or in the "Other ART" group (16/238; 6.7%, 95% CI: 3.9–10.7%), P-value 0.584 (Fig. 4a & supplementary Table 1). Fewer low-birth-weight babies were observed in the DTG-based group (23/543 [4.2%, 95% CI: 2.7–6.3]) than in the EFV-based group (41/819 [5.0%, 95% CI: 3.6–6.7]) or the "Other ART" group (14/236 [5.9%, 95% CI: 3.3–9.8], P-value 0.595). However, we observed a greater risk of neonatal death in the DTG-based group (6/775 [0.8%]) than in the EFV-based group (4/1275 [0.3%]) or in the "other ART" group (0/350 [0%]), P-value 0.083(Fig. 4a & supplementary Table 1). No significant association between ART regimens and adverse birth outcomes was observed after adjusting for differences in baseline characteristics (Table 3). Considering composite adverse pregnancy and birth outcomes, we found that the DTG group had a lower risk than the EFV group, although this difference was not statistically significant; 8.3% (95% CI: 6.1–10.9) vs. 11.5%(95% CI: 9.4–13.9), P-value 0.056 (Fig. 4a & supplementary Table 1).

Safety of DTG-based ART regimens for adverse pregnancy and birth outcomes among preconception ART users only

In the sub-group analysis of preconception ART users only, we observed similar results to all the study participants groups (Figs. 3b and 4b, supplementary Table 1). Preterm birth (P-value 0.001), composite adverse pregnancy outcome (P-value 0.006), and composite pregnancy and birth adverse outcome (P-value 0.056) were lower in the DTG group compared to EFV and other regimes.

Discussion

Ensuring the safety of recently introduced DTG-based ART regimens for pregnant women and HIV-exposed infants is a global concern. Strong safety data from diverse populations are crucial for establishing the regimen's safety profile in both short- and long-term scenarios. To comprehensively investigate adverse pregnancy and perinatal outcomes, including congenital anomalies and miscarriage in early pregnancy, women should start ART preconception. In this study, where 85% of the participants used ART preconception, we observed

Table 2 Baseline demographic, reproductive, and HIV-related characteristics of the study participants categorized by ART regimens. *N* = 2490

Baseline characteristics	Category	TDF + 3TC+ EFV, *N*(%)	TDF + 3TC+ DTG, *N*(%)	Other ART *N*(%)	Total *N*(%)	*P*-value
Administrative region	**Addis Ababa**	503(37.9)	239(30.0)	139(38.1)	881(35.4)	**0.000**
	Oromia	412(31)	273(34.3)	127(34.8)	812(32.6)	
	SNNPR	332(25)	251(31.5)	61(16.7)	644(25.9)	
	Hawassa City	81(6.1)	34(4.3)	38(10.4)	153(6.1)	
Age(years)	**< 25**	156(17.6)	116(20.5)	48(17.8)	320(18.6)	**0.000**
	25–34	593(67)	312(55.1)	162(60.2)	1067(62)	
	≥ 35	593(67)	312(55.1)	162(60.2)	1067(62)	
Gravidity	**1**	189(19.6)	126(20.2)	35(13.3)	350(18.9)	0.111
	2–4	679(70.4)	438(70.3)	196(74.2)	1313(70.9)	
	≥ 5	96(10)	59(9.5)	33(12.5)	188(10.2)	
Parity	**0**	219(22.7)	148(23.8)	42(15.9)	409(22.1)	0.123
	1	299(31)	213(34.2)	94(35.6)	606(32.7)	
	2–4	427(44.3)	250(40.1)	121(45.8)	798(43.1)	
	≥ 5	19(2)	12(1.9)	7(2.7)	38(2.1)	
Hospitals level	**Primary**	102(7.7)	83(10.4)	15(4.1)	200(8)	**0.000**
	Secondary	151(11.4)	187(23.5)	52(14.2)	390(15.7)	
	Tertiary	1075(80.9)	527(66.1)	298(81.6)	1900(76.3)	
WHO clinical staging	**1**	1297(97.7)	767(96.2)	351(96.2)	2415(97)	**0.020**
	2	18(1.4)	26(3.3)	9(2.5)	53(2.1)	
	3	9(0.7)	4(0.5)	5(1.4)	18(0.7)	
	4	4(0.3)	0(0)	0(0)	4(0.2)	
Partner HIV status	**Positive**	1034(77.9)	628(78.8)	280(76.7)	1942(78)	0.893
	Negative	138(10.4)	83(10.4)	43(11.8)	264(10.6)	
	Unknown	156(11.7)	86(10.8)	42(11.5)	284(11.4)	
Mode of delivery	**Vaginal**	1103(85.9)	649(84.2)	298(83.5)	2050(85.0)	0.473
	Emergency CS*	136(10.6)	96(12.5)	42(11.8)	274(11.4)	
	Elective CS#	44(3.4)	24(3.1)	17(4.8)	85(3.5)	
	Instrumental	1(0.1)	2(0.3)	0(0)	3(0.1)	
Place of delivery	**Same hospital**	1139(88.4)	704(90.8)	321(89.9)	2164(89.4)	0.256
	Other facility	134(10.4)	66(8.5)	30(8.4)	230(9.5)	
	Home	15(1.2)	5(0.6)	6(1.7)	26(1.1)	
PMTCT Care enrolment gestation	**1st trimester**	170(12.9)	91(11.5)	48(13.2)	309(12.5)	0.219
	2nd trimester	783(59.5)	450(56.9)	222(61)	1455(58.9)	
	3rd trimester	265(20.1)	183(23.1)	72(19.7)	520(21.1)	
	Labor	31(2.4)	22(2.8)	8(2.2)	61(2.5)	
	Postpartum	67(5.1)	45(5.7)	14(3.8)	126(5.1)	
ART initiation period	**Preconception**	1099(82.8)	657(82.4)	347(95.1)	2103(84.5)	**0.000**
	1st trimester	65(4.9)	29(3.6)	6(1.6)	100(4)	
	2nd trimester	122(9.2)	72(9)	10(2.7)	204(8.2)	
	3rd trimester	42(3.2)	39(4.9)	2(0.5)	83(3.3)	

*CS means caesarean section, # is elective caesarean section at 38 weeks of gestation

a significantly lower risk of preterm birth and composite adverse pregnancy outcomes, as well as a lower risk of composite adverse birth outcomes among the recent roll-out DTG-based regimen users compared to those using the previously used EFV-base regimens or other ART regimens. A similar observation was also documented among preconception ART users only.

Overall, we observed a lower incidence of abortion compared to a study conducted in Brazil [20], and a lower incidence of intrapartum fetal demise, neonatal death and preterm birth [12, 13, 19] than previously reported. Consistent with our findings, no differences in the risk of intrapartum fetal demise, neonatal death, maternal death or congenital anomalies were reported in the Botswana cohort study [19], the IMPAACT 2010 (VESTED)

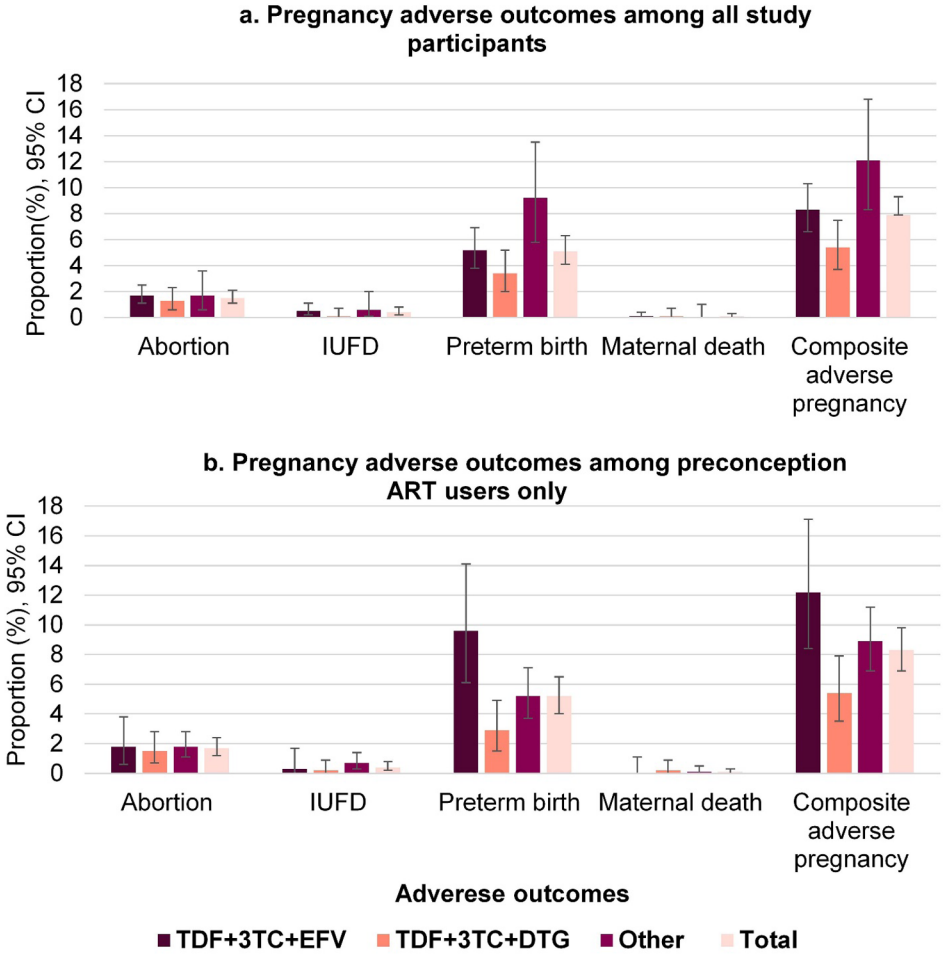

Fig. 3 **a** & **b**. Cumulative incidence of adverse pregnancy outcomes categorized by ART regimens among all HIV-infected women participants (Fig. 3a) and among preconception ART users only (Fig. 3b), enrolled in the selected hospitals in Ethiopia from 2017–2022

randomized clinical trial [12], the DolPHIN-2 randomized clinical trial [13] or a cohort study with a small sample size in the USA [30]. However, a lower risk of preterm birth for the DTG-based regimen was observed in our study.

The inconsistency in preterm birth risk could be due to differences in the study population. Both the clinical trial and cohort study involved participants who started DTG during pregnancy, which could limit the effect on preterm birth. Most (85%) of our study participants initiated ART before conception. The initiation of ART in early gestation or preconception helps decrease mother-to-child transmission and improve pregnancy outcomes [31, 32]. This was supported by our observation of a lower rate of overall adverse pregnancy and birth outcomes. In addition, among the DTG-based regimen users, we observed that preconception ART users had a lower risk of preterm birth (2.9%) compared to all study participants (5.1%). This suggests the importance of early ART initiation, not only for reducing the risk of vertical transmission but also for mitigating the risk of preterm birth. A recent systematic review on the prevalence of preterm birth in the general population in Ethiopia documented a rate of 10.8% (95% CI: 8.71–13.13), with regional variations. The highest prevalence was recorded in the northern Ethiopian regions of Amhara and Tigray, and the lowest in central and southern Ethiopia, where this study was conducted. The lowest prevalence was found in the Oromia region, at 2.8% (95% CI: 2.28–3.31) [33]. Although our study's preterm birth prevalence of 5.1% (95% CI: 4.1–6.3) was lower than the national average, it was higher than the findings from the Oromia region. The majority of the study participants started ART preconception and had frequent antenatal care, indicating frequent contact with healthcare providers. This may have helped them optimize their nutrition, health, and behavioral status, which contributed to reducing the risk of preterm birth before and during pregnancy.

In this study, it was difficult to assess the risk of congenital anomalies, especially neural tube defects (NTDs),

Table 3 Binary and multivariate logistic regression analyses of adverse outcomes and ART regimens adjusted for age, WHO stage, ART initiation period, study site region, and hospital level of care. COR: crude odds ratio, AOR: adjusted odds ratio, CI: confidence interval and * P value less than 0.05

Adverse outcome	ART regimens	COR(95%CI	AOR(95%CI)
Abortion	Others	0.99(0.40–2.47)	0.70(0.26–1.89)
	TDF + 3TC + DTG	0.75(0.35–1.59)	0.83(0.36–1.92)
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
IUFD	Others	1.05(0.22–5.05)	0.00
	TDF + 3TC + DTG	0.24(0.03–1.92)	0.00
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
Preterm birth	Others	**1.85(1.09–3.14)**	1.28(0.63–2.60)
	TDF + 3TC + DTG	0.64(0.37–1.10)	**.47(0.22–0.98)**
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
Maternal death	Others	.000	.000
	TDF + 3TC + DTG	1.66(0.10–26.64)	1.24(0.07–20.79)
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
Composite adverse pregnancy	Others	1.51(0.97–2.37)	0.86(0.47–1.56)
	TDF + 3TC + DTG	**0.62(0.41–0.96)**	**0.57(0.32–0.96)**
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
Intrapartum fetal demise	Others	0.73(0.21–2.53)	.00
	TDF + 3TC + DTG	0.22(0.05–0.96)	.00
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
Neonatal death	Others	0.00(0.00-)	0.00(0.00-)
	TDF + 3TC + DTG	2.48(0.70–8.81)	2.31(0.61–8.80)
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
Low birth weight	Others	1.20(0.64–2.24)	0.67(0.26–1.72)
	TDF + 3TC + DTG	0.84(0.50–1.42)	0.67(0.31–1.44)
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
Composite adverse birth outcome	Others	0.98(0.55–1.74)	0.43(0.17–1.07)
	TDF + 3TC + DTG	0.79(0.50–1.24)	0.69(0.37–1.32)
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**
Composite adverse pregnancy and birth	Others	1.12(0.77–1.82)	0.70(0.39–1.25)
	TDF + 3TC + DTG	**0.69(0.48-1.00)**	**0.61(0.37–1.01)**
	TDF + 3TC + EFV	**1(ref)**	**1(ref)**

Footnote: COR: crude odd ratio, AOR: adjusted odd ratio

despite the low-risk safety signal suggested by WHO. This is due to a lack of active sentinel surveillance programs nationally. We could not confirm whether the cause of abortion, IUFD, or intrapartum fetal demise was related to a congenital anomaly. The other concerning issue was the registration of only surface anomalies and uncommon documentation of minor anomalies. We found only one major congenital anomaly in DTG-based ART, with an incidence of 0.1% (95% CI: 0-0.7). Even for this anomaly, we could not identify the type of anomaly due to a lack of clear documentation on the specific type of anomaly. Even if we assumed that the anomaly was NTD, the incidence was lower than the previously documented prevalence of nearly 1% [34, 35]. In Ethiopia, a higher prevalence of NTDs is reported [36–38]. Apart from the lack of a national folic acid fortification program [39], we do not yet know the causes of this high prevalence. Although it is important to monitor the risk of NTDs among HIV-infected women receiving DTG-based ART regimens, it is unlikely that DTG is a risk factor for NTDs with the unexplained high levels of NTDs in the Ethiopian population.

Compared to the DTG or EFV-based ART regimens, the older "Other ART" regimen group had a greater risk of adverse pregnancy and birth outcomes. This was also shown in a large cohort study from Botswana, where the EFV-based regimen had a better safety profile than the older regimen [40]. This shows the rapid development of newer ART regimens with better safety profiles.

This study provides additional data on the safety of DTG-based ART regimens not only for late pregnancy perinatal outcomes but also for early pregnancy outcomes such as abortion and IUFD compared to EFV-based regimens. It contributes to the growing body of evidence supporting the WHO recommendation for DTG-based regimens as first-line treatments for HIV during pregnancy. Disaggregated data among DTG-based regimen transition by sex and age showed lower rates of DTG uptake among women of childbearing age compared with men [41]. Our findings of a better safety profile will enhance the transition to a DTG-based regimen for women of childbearing age. However, the uncaptured adverse pregnancy and birth outcomes, such as maternal metabolic disorders associated with weight gain, congenital abnormality, the long-term effects on HIV-exposed infants' growth and neurocognitive development need to be assessed in a prospective study. There is an ongoing clinical trial, the PREGART clinical trial (https://www.pregart.eu), implemented by the authors, that aims to evaluate the effects on growth and neurocognitive development. The results will be available as soon as the recruitment is completed.

This study had limitations. First, the retrospective nature of the cohort might not include all determinant factors of adverse pregnancy or birth outcomes. For example, we could not assess the differences in the baseline risk of abortion, intrapartum fetal demise, preterm birth, low birth weight, or comorbidity history due to a lack of documentation of these variables. The study was conducted in public hospitals only. Excluding patients from lower-level healthcare facilities like health centers may affect the findings' generalizability, requiring caution in interpretation. However, primary hospitals, which served as referral centers for health centers were included, suggesting similarities between patients from health centers and primary hospitals. Although very few women are likely to be on lower doses of EFV (EFV 400 mg) because of its alternative first-line treatment option, we did not analyse the standard doses of EFV

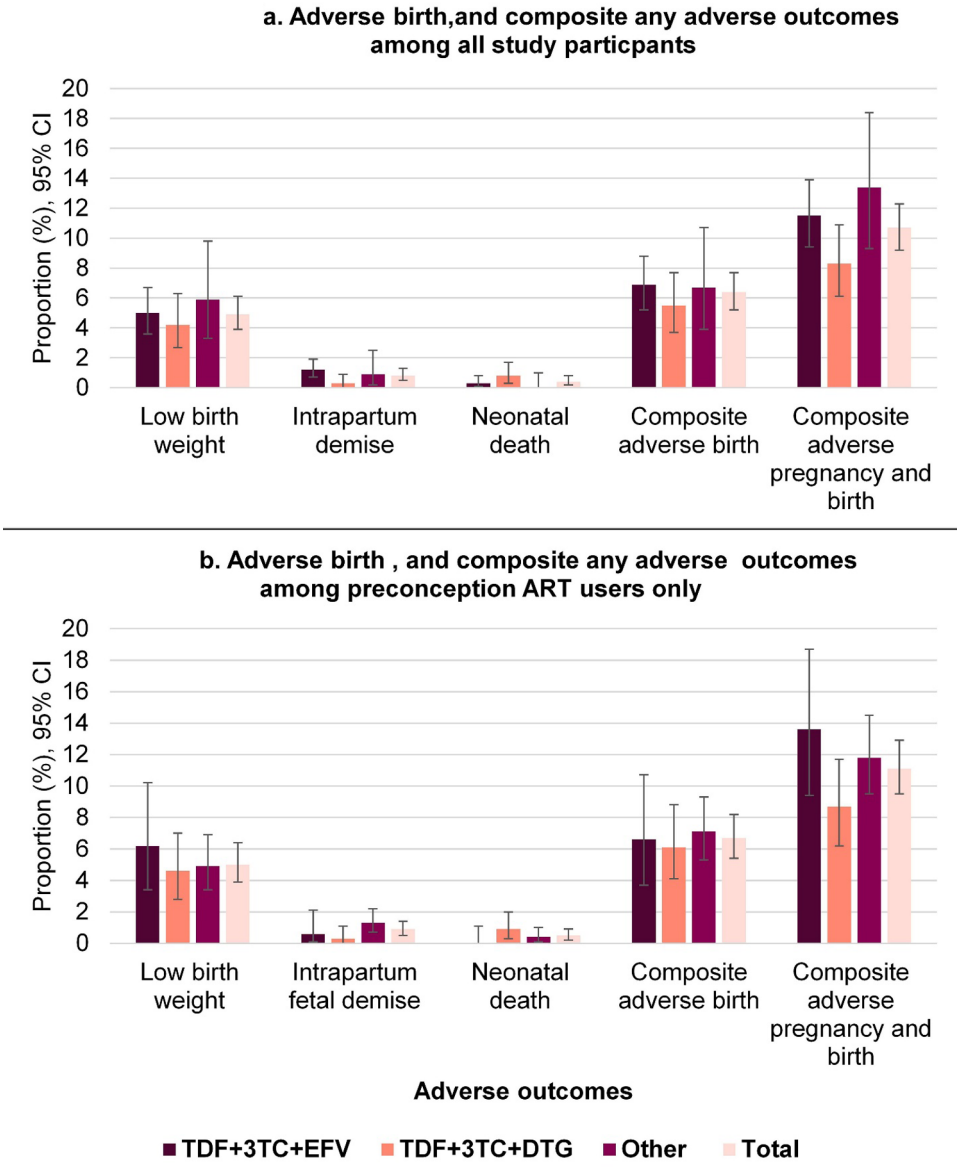

Fig. 4 **a** & **b**. Cumulative incidence of adverse birth outcomes categorized by ART regimens among all HIV-infected women participants (Fig. 4a) and among preconception ART users only (Fig. 4b), enrolled in the selected hospitals in Ethiopia from 2017–2022

(EFV 600 mg) and lower doses separately. Although EFV drug toxicity depends on the dose, it was not reported for birth or pregnancy safety outcomes. We did not control for the effects of elective cesarean section (CS) performed at 38 weeks of gestation on low birth weight and other adverse outcomes during the analysis. However, it is important to note that only 3.5% of the study participants underwent elective CS and were less likely to influence the study outcomes.

Our study has several strengths. First, the large sample size enables us to detect even small differences in adverse outcomes. Second, the cohort was collected in multicenter hospitals with different administrative regions. This enabled us to include participants with different demographic, behavioural, and obstetric care differences, which supported the generalizability of the study. Finally, the study assessed seven adverse outcomes, encompassing both early and late pregnancy, thereby presenting a comprehensive safety profile.

Conclusion

In this study, we observed that the DTG-based regimen had better pregnancy and birth outcome safety profiles than the EFV-based regimen and other regimens, reaffirming the WHO recommendation of DTG as a first-line treatment for HIV during pregnancy. However, a

prospective study is recommended to assess uncaptured maternal and perinatal adverse outcomes, such as maternal metabolic disorders, congenital abnormality, and infant growth and neurocognitive development so that we will have a comprehensive understanding of the both short and long term safety profile of the regimen.

Abbreviations

3TC	Lamivudine
ART	Antiretroviral treatment
CI	Confidence Interval
DTG	Dolutegravir
EFV	Efavirenz
HIV	Human immunodeficiency virus
IUFD	Intrauterine fetal death
LNMP	Last Normal Menstrual Period
MOH	Ministry of Health
MTCT	Mother-to-child transmission
NTDs	Neural tube defects
PMTCT	Prevention of mother-to-child transmission
SPSS	Statistical Package for the Social Sciences
TDF	Tenofovir disoproxil fumarate
UNAIDS	Joint United Nations program on HIV/AIDS
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

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Author contributions

A conceptualized the overall manuscript, analyzed the data, and wrote the first draft of the manuscript with the overall supervision of E. A and B designed the study and conducted the preliminary analysis. S, E, YB, and SV reviewed the draft manuscript. All the authors have read and provided feedback and approved the final draft.

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Data availability

All data relevant to the study are included in this manuscript.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the ethical review boards of the Hawassa University College of Medicine and Health Sciences institutional review board (IRB), with reference number (IRB/076/2022, dated December 10/2022). The members of the ethics committee include Dr. Embiale Mengiste, Dr. Muhammed Ayalew and Dr. Freshet Assefa. Informed consent was waived based on the use of anonymized data from routine healthcare records.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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