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Pregnancy outcome among HIV-infected women on different antiretroviral therapies in Ethiopia: a cohort study

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ABSTRACT

Objective The objective of the study was to compare pregnancy outcomes according to maternal antiretroviral treatment (ART) regimens.

Design A retrospective cohort study.

Participants and settings Clinical data was extracted from ART exposed pregnancies of HIV-infected Ethiopian women attending antenatal care follow-up in public health facilities in Addis Ababa between February 2010 and October 2016.

Outcomes The primary outcomes evaluated were preterm birth, low birth weight and small-for-gestational-age.

Results A total 1663 of pregnancies exposed to ART were included in the analyses. Of these pregnancies, 17% resulted in a preterm birth, 19% in low birth weight and 32% in a small-for-gestational-age baby. Compared with highly active antiretroviral therapy (HAART) initiated during pregnancy, zidovudine monotherapy was less likely to result in preterm birth (adjusted OR 0.35, 95% CI 0.19 to 0.64) and low birth weight (adjusted OR 0.48, 95% CI 0.24 to 0.94). We observed no differential risk of preterm birth, low birth weight and small-for-gestational-age, when comparing women who initiated HAART during pregnancy to women who initiated HAART before conception. The risk for preterm birth was higher in pregnancies exposed to nevirapine-based HAART (adjusted OR 1.44, 95% CI 1.06 to 1.96) compared with pregnancies exposed to efavirenz-based HAART. Comparing nevirapine-based HAART with efavirenz-based HAART indicated no strong evidence of increased risk of low birth weight or small-for-gestational-age.

Conclusions We observed a higher risk of preterm birth among women who initiated HAART during pregnancy compared with zidovudine monotherapy. Pregnancies exposed to nevirapine-based HAART also had a greater risk of preterm births compared with efavirenz-based HAART.

Strength and limitation of this study

- This study is the first to evaluate pregnancy outcomes according to different antiretroviral therapies in Ethiopia.
- Prospectively collected information on antiretroviral treatment and effectiveness was extracted from women's medical records.
- The study was conducted in an urban setting and may therefore not be generalisable to women living in rural areas.
- We lacked information on some potential confounders, such as maternal viral load, and we can therefore not exclude residual/unmeasured confounding.
- We cannot exclude the possibility of selection bias due to the proportion of women with missing information.

INTRODUCTION

Antiretroviral therapy (ART) is effective in reducing the risk of mother-to-child transmission of HIV.[1–3] Before 2013, HIV-infected pregnant women not eligible for highly active antiretroviral therapy (HAART) were given zidovudine/single-dose nevirapine (ZDV/SD NVP) or triple antiretroviral drugs as prophylaxis based on the WHO recommendation. However, the WHO revised its recommendations to initiate HAART for all HIV-infected pregnant and breastfeeding women in 2013.[4] This recommendation was further revised to include universal treatment to all HIV-infected individuals in 2015.[5] Studies comparing the safety of HAART versus ZDV monotherapy during pregnancy report inconsistent findings related to preterm birth, where some studies indicate a greater risk of preterm birth associated with HAART,[6–13] and some indicated that the greater risk of preterm birth may be specific to HAART with protease inhibitors (PIs),[14–16] while others reported no strong evidence for an association.[17–19] Some studies have also reported increased risk of low birth weight,[6 11 15] and small-for-gestational-age,[10] among women taking HAART as compared women taking ZDV monotherapy during pregnancy, but majority of studies show no evidence of an association.[14 18 20–24]

Several studies compared safety of PI-based HAARTs with other type of HAART

regimens.[6 25–33] However, non-nucleoside reverse transcriptase inhibitors (NNRTI), specifically NVP or efavirenz (EFV)-based HAARTs, are currently the first-line drugs in resource-limited settings.[5] The comparative safety of these treatment options during pregnancy is not clear, as studies comparing EFV-based HAART with NVP-based HAART reported inconsistent findings.[23 34–36] Moreover, the recommended type of HAART regimens, drug formulations and the frequency of drug intake have been regularly revised,[4] which warrants additional studies comparing pregnancy outcomes according to different types of ART regimens. The role of timing of HAART initiation on risk of adverse pregnancy outcomes is also unclear. A recent systematic review and meta-analysis reported an increased risk of preterm birth and low birth weight associated with initiation of HAART before conception as compared with therapy initiation during pregnancy, but the review was limited by scarcity of studies reporting outcomes of interest.[37]

Ethiopia has a substantial disease burden of HIV/AIDS. It is estimated that 409 037 (1.5%) women in a reproductive age group were living with the virus in 2017.[38] ZDV/SD NVP was historically used as a prophylaxis to prevent mother-to-child transmission of HIV in Ethiopia when women are not eligible for HAART (CD4 count above 350 cells/mm^3 and WHO stages I and II). However, following the change in the WHO recommendation on treatment of HIV-infected pregnant women in 2013, the country recommended lifelong HAART to all HIV-infected pregnant women irrespective of immunological or clinical stage of disease.[39] As a result, 67% of pregnant women with HIV received ART in 2017.[40] There are no previous Ethiopian studies assessing the potential adverse effects of HAART exposure on pregnancy outcome. The objective of our study was therefore to compare pregnancy outcomes according to maternal ART regimens.

METHODS

Population and setting

We conducted a multicentre retrospective medical record review in three public hospitals and nine public healthcare centres in Addis Ababa city, Ethiopia. We extracted information on 2412 ART-exposed pregnancies to HIV-infected women attending prenatal care follow-up between February 2010 and October 2016 by linking information from paper medical records (Antenatal Care Follow-up Form and Antiretroviral Treatment and Follow-up Form) and HIV clinics electronic ART databases. We excluded pregnancies with missing information about type of ART regimen, pregnancies where the ART regimen was changed during pregnancy, pregnancies exposed to ART for less than 2 weeks, pregnancies resulting in abortions (expulsion for fetus before 28 completed weeks) or multiple births and pregnancies with missing information on both gestational age at birth and birth weight (figure 1). This left a total of 1663 pregnancies by 1611 HIV-infected women available for analysis. Our sample size provided us with 80% power to detect an OR ranging from 1.3 to 1.6, given a baseline risk of 12% for preterm birth, 19% low birth weight and 32% small-for-gestational-age taken from previous Ethiopian estimates.[41] This historical medical record review study was regarded as clinical practice and outcome assessment and, therefore, did not require a signed informed consent.

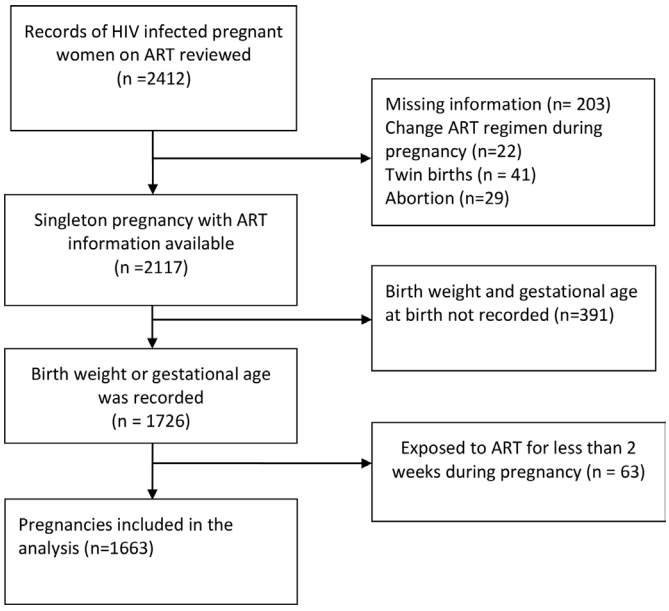

Figure 1 Flow diagram of inclusion and exclusion criteria. ART, antiretroviral therapy.

Patient and public involvement

No patients were involved in setting the research question, nor were they involved in developing plans for recruitment, design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the patient community.

ART exposure

We collected information on ART exposure during pregnancy from the Antiretroviral Treatment and Follow-up Form, which includes information on the type of ART initiated, in addition to clinical and immunological status. The form is completed by healthcare providers as part of the routine care of HIV-infected individuals. ART exposure was categorised as HAART before conception (initiated treatment before conception), HAART during pregnancy (initiated after conception) and ZDV monotherapy. HAART is composed of two nucleoside reverse-transcriptase inhibitors (NRTIs) and one NNRTI or PIs. We subsequently decomposed the group taking HAART to NVP-based HAART, EFV-based HAART and PI-based HAART. We also categorised HAART into tenofovir (TDF)-based HAART, ZDV-based HAART and other HAART regimens according to the NRTI components.

Pregnancy outcomes

The primary pregnancy outcomes evaluated were preterm birth, low birth weight and small-for-gestational-age. Preterm birth was defined as delivery before 37 completed weeks of gestation and severe preterm birth as delivery before 32 completed weeks of gestation. Gestational age at birth was estimated based on ultrasonography (available for more than 75% of the pregnancies), last menstruation period or fundal height. Low birth weight was defined as birth weight below 2500 g, while very low birth weight was defined as a birth weight below 1500 g.[42] Small-for-gestational-age was calculated as weight below 10th percentile according to gestational age and sex-specific distributions using a WHO algorithm,[43] by incorporating sex-specific mean birth weight and SD from a previous national survey conducted in Ethiopia.[44]

Covariates

Additional information was gathered on maternal background characteristics likely to be associated with ART regimen and pregnancy outcomes. This include maternal age in years during the first prenatal care visit, marital status (married and others), education level (no education, primary, secondary and college level education), history of stillbirth/abortion (yes or no), parity (categorised as '0', '1–2' and '3 or more') and maternal weight before conception or during the first trimester pregnancy in kg. Additional information was also gathered on haemoglobin (g/L), CD4 cell count (cells/mm^3) and WHO clinical stages (stages I–IV) during the prenatal care follow-up.

Statistical analysis

We compared the distribution of maternal background characteristics by the type of ART regimens using X^2 test or Fisher's exact test for categorical variables and Kruskal-Wallis for continuous variables. We ran linear regression analysis to compare gestational age at birth and birth weight according to ART regimens, reporting mean difference and 95% CIs. We also ran three logistic regression models to compare adverse pregnancy outcomes according to ART regimens, reporting ORs and 95% CIs. First, we compared the risk of adverse pregnancy outcomes according to HAART during pregnancy, HAART before conception and ZDV monotherapy. Second, we compared adverse pregnancy outcomes according to different HAART regimens, categorising as EFV-based, NVP-based and PI-based HAART. Third, we compared adverse pregnancy outcomes according to HAART regimens categorised as TDF-based, ZDV-based and other HAART regimens. The multivariable analyses were adjusted for maternal age, weight, marital status, education, parity, CD4 cell count during pregnancy and WHO clinical stage during pregnancy. In addition, models comparing different HAART regimens were adjusted for timing of treatment initiation. Variables were categorised as indicated in table 1 and entered using dummy variables. Robust cluster variance estimation was used to account for the inclusion of multiple pregnancies from the same mother. In secondary analysis, the association of year of birth with adverse pregnancy outcomes was evaluated by using Cuzick non-parametric test for trend. We also conducted sensitivity analyses restricting the analysis to pregnancies resulting in a live birth, pregnancies exposed to HAART during pregnancy, pregnancies exposed to ART before 32 weeks of gestation and those with CD4 cell count of above 350 cells/mm^3 at the time of pregnancy. The amount of missing information on individual variables ranged from 2.0% (maternal age) to 30% (education). We therefore imputed a total of 20 data sets, using multiple imputations by chained equations. The model included the exposure variables, all covariates and outcomes. Categorisation of exposures and outcomes was done after imputation. The estimates across the imputed datasets were combined using Rubin's rules.[45] The findings based on imputed data and complete-case analyses were largely similar. We report the findings based on the imputed data as the main results, while the findings from the complete-case analysis are presented in the online Supplementary data. All p values presented are two-sided. The analyses were done using STATA V.13.

RESULTS

We included 1663 singleton pregnancies by 1611 HIV-infected women in the analysis. Half, 826 (50%) of pregnancies were exposed to HAART started before conception, 638 (38%) were exposed to HAART initiated during pregnancy and 199 (12%) were exposed to ZDV monotherapy. Of those exposed to HAART, 852 (58%) were on EFV-based HAART and 580 (40%) were on NVP-based HAART. Based on the NRTI components, 1004 (69%) were TDF-based and 379 (26%) were ZDV-based HAART regimens. Women initiating HAART during pregnancy were younger, less likely to be multiparous and had lower CD4 count as compared with women initiating HAART before conception (table 1). Among women initiating HAART, women on EFV-based HAART were younger and less likely to be multiparous as compared with women on NVP-based HAART (table 1). Women who initiated HAART during pregnancy on average started treatment at 20 gestational weeks (SD=9), while women were placed on ZDV monotherapy at an average of 27 gestational weeks (SD=7). When we compared women who were included in the analysis to women who were excluded due to missing information on ART regimen and/or pregnancy outcomes, we found no significant differences in marital status, education, CD4 count or WHO stage at first visit (see online supplementary table 1).

The median gestational age at birth was 39.5 weeks (IQR 37.7–41.0), while the median birth weight was 3.0 kg (IQR 2.6–3.2). Of the total 1663 pregnancies included in the analysis, 277 (17%) resulted in preterm birth, 322 (19%) of the newborns were low birth weight, 538 (32%) of the newborns were small-for-gestational-age, while 98 (6%) of pregnancies resulted in stillbirth. Rate of preterm birth

Table 1 Characteristics of HIV-infected pregnant women by type of antiretroviral therapy

Characteristics	All pregnancies (n=1663)	Types of ART (n=1663)				HAART regimen category (n=1464)*			
		HAART during pregnancy (n=638)	HAART before conception (n=826)	ZDV mono-therapy (n=199)	P value†	EFV-based HAART (n=852)	NVP- based HAART (n=580)	PI-based HAART (n=32)	P value†
Age, median (IQR), year	29 (26–32)	28 (25–30)	30 (27–33)	28 (25–31)	0.001‡	28 (25–32)	30 (27–32)	30 (27–33)	0.001‡
Missing	29 (1.7)	4 (0.6)	21 (2.5)	2 (1.0)		7 (0.8)	16 (2.7)	4 (12.5)	
Marital status									
Married	1542 (92.7)	593 (93.0)	761 (92.1)	188 (94.3)	0.50	788 (92.5)	538 (92.7)	28 (87.5)	0.75
Others	97 (5.8)	43 (6.7)	44 (5.3)	10 (5.2)		53 (6.2)	32 (5.5)	2 (6.3)	
Missing	24 (1.4)	2 (0.3)	21 (2.5)	1 (0.5)		11 (1.3)	10 (1.7)	2 (6.3)	
Educational status									
No education	149 (9.0)	54 (8.5)	84 (10.2)	11 (5.5)	0.032	78 (9.2)	59 (10.2)	1 (3.1)	0.034
Primary	439 (26.4)	166 (26.0)	230 (27.9)	43 (21.6)		248 (29.1)	140 (24.1)	8 (25.0)	
Secondary	473 (28.4)	168 (26.3)	246 (29.8)	59 (29.7)		221 (25.9)	191 (32.9)	2 (6.3)	
College	94 (5.7)	48 (7.5)	34 (4.1)	12 (6.0)		50 (5.9)	31 (5.3)	1 (3.1)	
Missing	508 (30.6)	202 (31.7)	232 (28.1)	74 (37.2)		255 (29.9)	159 (27.4)	20 (62.5)	
Parity									
Nullipara	461 (27.7)	236 (37.0)	162 (19.6)	63 (31.7)	<0.001	259 (30.4)	130 (22.4)	9 (28.1)	0.001
One to two	955 (57.4)	310 (48.6)	519 (62.8)	126 (63.3)		439 (51.5)	371 (64.0)	19 (59.4)	
Three and above	118 (7.1)	40 (6.3)	69 (8.4)	9 (4.5)		66 (7.8)	41 (7.1)	2 (6.3)	
Missing	129 (7.8)	52 (8.2)	76 (9.2)	1 (0.5)		88 (10.3)	38 (6.6)	2 (6.3)	
History of stillbirth/abortion									
Yes	524 (31.5)	182 (28.5)	284 (34.4)	58 (29.2)	0.023	251 (29.5)	206 (35.5)	9 (28.1)	0.05
No	1123 (67.5)	455 (71.3)	527 (63.8)	141 (70.9)		592 (69.5)	368 (63.5)	22 (68.8)	
Missing	16 (1.0)	1 (0.2)	15 (1.8)	0 (0.0)		9 (1.1)	6 (1.0)	1 (3.1)	
Weight, median (IQR), kg	58 (51–64)	56 (50–63)	57 (51–64)	60 (52–67)	0.003‡	56 (50–63)	57 (51–64)	57 (63–53)	0.23‡
Missing	183 (11.0)	73 (11.4)	85 (10.3)	25 (12.6)		102 (12.0)	52 (8.9)	4 (12.5)	
CD4 count during pregnancy (cells/mm^3), median (IQR)	384 (256–534)	316 (197–500)	421 (290–553)	434 (337–574)	<0.001‡	374 (255–530)	387 (238–529)	363 (194–515)	0.88‡
Missing	179 (10.8)	72 (11.2)	63 (7.6)	44 (22.1)		83 (9.7)	47 (8.1)	5 (15.6)	
Haemoglobin median (IQR), g/L	12 (11–13)	12 (11–13)	13 (11–13)	12 (11–13)	0.45‡	12 (11–13)	12 (11–13)	12 (11–13)	0.36‡
Missing	429 (25.8)	166 (26.0)	217 (26.3)	46 (23.1)		221 (25.9)	154 (26.5)	8 (25.0)	
WHO Clinical Stage									
Stage I	1123 (67.5)	520 (81.5)	432 (52.3)	171 (85.9)	<0.001	647 (75.9)	299 (51.6)	6 (18.8)	<0.001
Stage II	312 (18.8)	69 (10.8)	232 (28.1)	11 (5.5)		130 (15.3)	165 (28.5)	6 (18.8)	
Stage III	121 (7.3)	27 (4.2)	88 (10.7)	6 (3.0)		41 (4.8)	72 (12.4)	2 (6.3)	
Stage IV	40 (2.4)	6 (0.9)	34 (4.1)	0 (0.0)		13 (1.5)	24 (4.1)	3 (9.4)	
Missing	67 (4.0)	16 (2.5)	40 (4.8)	11 (5.5)		21 (2.5)	20 (3.5)	15 (46.9)	
Mode of delivery									

Continued

Table 1 Continued

Characteristics	All pregnancies (n=1663)	Types of ART (n=1663)				HAART regimen category (n=1464)*			
		HAART during pregnancy (n=638)	HAART before conception (n=826)	ZDV mono-therapy (n=199)	P value†	EFV-based HAART (n=852)	NVP- based HAART (n=580)	PI-based HAART (n=32)	P value†
Spontaneous vaginal delivery	1151 (69.2)	461 (72.3)	569 (68.9)	121 (60.8)	<0.001	617 (72.4)	388 (66.9)	25 (78.1)	0.01
Caesarian session	276 (16.6)	86 (13.5)	129 (15.6)	61 (30.7)		103 (12.1)	107 (18.5)	5 (15.6)	
Assisted delivery§	38 (2.3)	16 (2.5)	13 (1.6)	9 (4.5)		14 (1.6)	15 (2.6)	0 (0)	
Missing	198 (11.9)	75 (11.8)	115 (13.9)	8 (4.0)		118 (13.9)	70 (12.1)	2 (6.3)	
Year of delivery									
Before 2013	422 (25.4)	85 (13.3)	182 (22.0)	155 (77.9)	<0.001	46 (5.4)	217 (37.4)	4 (12.5)	<0.001
2013–2014	620 (37.3)	298 (46.7)	283 (34.3)	39 (19.6)		353 (41.4)	212 (36.6)	16 (50.0)	
2015–2016	621 (37.3)	255 (40.0)	361 (43.7)	5 (2.5)		453 (53.2)	151 (26.0)	12 (37.5)	

Data are n (%) or median (IQR).
*The sample excludes zidovudine monotherapy.
†Statistical tests did not consider missing values.
‡Kruskal-Wallis test results, the rest are X^2/Fisher's exact test results.
§Assisted delivery include delivery by forceps or vacuum extraction.
ART, antiretroviral therapy; EFV, efavirenz; HAART, highly active antiretroviral therapy; NVP, nevirapine; PI, protease inhibitor; ZDV, zidovudine.

was 17.9% in women initiating HAART during pregnancy, 18% in women initiating HAART before conception and 7% in women initiating ZDV monotherapy. The proportion of low birth weight was 20.5% in women initiating HAART during pregnancy, 20.7% in women initiating HAART before conception and 10.1% in women initiating ZDV monotherapy. Rate of small-for-gestational-age was 34% in women initiating HAART during pregnancy, 33% in women initiating HAART before conception and 25% in women initiating ZDV mono-therapy. Stillbirth rate was 5% in women initiating HAART during pregnancy, 7% in women initiating HAART before conception and 4% in women initiating ZDV monotherapy. Very preterm births (<32 gestational weeks) occurred in 4% and very low birth weight (<1500 g) in 2% of all pregnancies, but no significant differences in rates related to the different ART regimens.

In adjusted linear regression analysis, compared with infants exposed to HAART initiated during pregnancy, those exposed to ZDV monotherapy had on average 123 g higher birth weight (adjusted mean difference=122.7, 95% CI 28.7 to 216.0). Infants exposed to NVP-based HAART had lower gestational age at birth (adjusted mean difference=−4.2, 95% CI−7.4 to 0.9), and lower birth weight (adjusted mean difference=−78.0, 95% CI −152.3 to −3.8) compared with EFV-based HAART (see online supplementary table 2).

In the adjusted logistic regression analyses, compared with HAART initiated during pregnancy, ZDV monotherapy was less likely to result in preterm birth (adjusted OR 0.35, 95% CI 0.19 to 0.64) and low birth weight (adjusted OR 0.48, 95% CI 0.24 to 0.94), but not small-for-gestational-age (adjusted OR 0.74, 95% CI 0.48 to 1.14) (table 2). Comparing HAART initiated during pregnancy with HAART initiated before conception indicated no differential risk of preterm birth, low birth weight or small-for-gestational-age (table 2). The complete-case analysis showed largely similar results with the imputed analysis (see online supplementary table 3).

Evaluating pregnancies exposed to different categories of HAART indicated that NVP-based HAART was more likely to result in preterm birth (adjusted OR 1.44, 95% CI 1.06 to 1.96), as compared with pregnancies exposed to EFV-based HAART (table 3). However, no differential risk of low birth weight and small-for-gestational-age was demonstrated between EFV-based HAART, NVP-based HAART or PI-based HAART (table 3). Comparing TDF-based HAART with ZDV-based HAART showed no differential risk of preterm birth (adjusted OR 1.16, 95% CI 0.83 to 1.62), low birth weight (adjusted OR 0.99, 95% CI 0.69 to 1.42) or small-for-gestational-age (adjusted OR 0.92, 95% CI 0.66 to 1.28) (table 3). The complete-case analyses showed largely similar results as the main analysis based on the imputed data (see online supplementary table 3).

The distribution of adverse pregnancy outcomes by year of birth was evaluated by Cuzick non-parametric test for trend. But we observed no differences in the proportion of preterm birth (p=0.39), low birth weight (p=0.23)

Table 2 The associations between type of ART regimen with preterm birth, low birth weight and small-for-gestational-age among 1663 pregnancies of HIV-infected women in Ethiopia

	Preterm birth			Low birth weight			Small-for-gestational-age		
Exposure	n/N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	n/N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	n/N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Types of ART									
HAART during pregnancy	114/638 (17.9)	1	1	131/638 (20.5)	1	1	220/638 (34.5)	1	1
HAART before conception	149/826 (18.0)	1.02 (0.77 to 1.35)	0.93 (0.78 to 1.29)	171/826 (20.7)	1.02 (0.75 to 1.38)	0.97 (0.69 to 1.39)	269/826 (32.6)	0.92 (0.72 to 1.19)	1.00 (0.76 to 1.32)
ZDV monotherapy	14/199 (7.0)	0.35 (0.20 to 0.64)	0.35 (0.19 to 0.64)	20/199 (10.1)	0.42 (0.21 to 0.81)	0.48 (0.24 to 0.94)	49/199 (24.6)	0.63 (0.41 to 0.95)	0.74 (0.48 to 1.14)

The result is based on the imputed data.
The models were adjusted for maternal age, weight, marital status, education, parity, CD4 count and WHO clinical stage.
ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; ZDV, zidovudine.

Table 3 The associations between HAART regimen with preterm birth, low birth weight and small-for-gestational-age among 1464 pregnancies of HIV-infected women in Ethiopia

	Preterm birth			Low birth weight			Small-for-gestational-age		
Exposures	n/N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	n/N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	n/N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
HAART category									
EFV-based HAART	136/852 (16.0)	1	1	161/852 (18.9)	1	1	288/852 (33.8)	1	1
NVP-based HAART	119/580 (20.5)	1.36 (1.03 to 1.78)	1.44 (1.06 to 1.96)	137/580 (23.6)	1.32 (0.98 to 1.78)	1.42 (1.00 to 2.00)	193/580 (33.3)	0.97 (0.75 to 1.26)	1.04 (0.78 to 1.38)
PI-based HAART	8/32 (25)	1.75 (0.77 to 3.98)	1.81 (0.78 to 4.18)	4/32 (12.5)	0.64 (0.18 to 2.26)	0.62 (0.17 to 2.28)	8/32 (25.0)	0.65 (0.26 to 1.62)	0.66 (0.25 to 1.75)
HAART category (NRTI)									
TDF-based HAART	172/1004 (17.1)	1	1	209/1004 (20.8)	1	1	344/1004 (34.3)	1	1
ZDV-based HAART	71/379 (18.7)	1.11 (0.82 to 1.52)	1.16 (0.83 to 1.62)	77/379 (20.3)	0.97 (0.69 to 1.35)	0.99 (0.69 to 1.42)	120/379 (31.7)	0.88 (0.64 to 1.21)	0.92 (0.66 to 1.28)
Other HAART regimens*	20/81 (24.7)	1.55 (0.90 to 2.67)	1.56 (0.90 to 2.71)	16/81 (19.8)	0.96 (0.50 to 1.84)	0.95 (0.48 to 1.87)	25/81 (30.9)	0.84 (0.49 to 1.46)	0.86 (0.47 to 1.55)

The result is based on the imputed data.
The models were adjusted for age, weight, marital status, education, parity, CD4 counts, WHO clinical stage and time of HAART initiation.
*Other HAART regimens includes stavudine and abacavir-based HAARTs.
EFV, efavirenz; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitors therapy; NVP, nevirapine; PI, protease inhibitor; TDF, tenofovir; ZDV, zidovudine.

or small-for-gestational-age (p=0.41) across year of birth (see online supplementary figure 1).

A sensitivity analysis excluding pregnancies resulting in a stillbirth (n=98) did not change our findings (see online supplementary table 4). Excluding women with a CD4 count below 351 cells/mm^3 during pregnancy or pregnancies exposed to ART after 32 weeks of gestation did not substantially change the association between HAART during pregnancy and preterm birth as compared with ZDV monotherapy (see online supplementary tables 5 and 6). Comparing NVP-based HAART with EFV-based HAART after excluding women who initiated HAART before conception did not substantially change the main finding (see online supplementary table 7). We also conducted a sensitivity analysis adjusting for year of ART initiation, and the results were similar to what we observed in the main analysis (see online supplementary table 8). A sensitivity analysis adjusting for CD4 count at the time of treatment initiation, instead of adjusting for CD4 count during pregnancy yielded similar results to the main analysis (see online supplementary table 9).

DISCUSSION

This study examining pregnancy outcomes according to ART regimens in resource-limited settings indicated that HIV-infected women who received HAART during pregnancy may have a higher risk of both preterm birth and low birthweight infants compared with those who received ZDV monotherapy. However, since we observed no strong evidence of an association of HAART initiated during pregnancy with small-for-gestational-age, the observed association with low birth weight is likely driven by the increased risk of preterm birth.

Our finding of a higher risk of preterm birth in pregnancies exposed to HAART initiated during pregnancy compared with ZDV monotherapy is in line with previous studies from sub-Saharan Africa[6 10 13] and other low-income and middle-income countries.[8 9] However, a multisite randomised controlled trial in Burkina Faso, Kenya and South Africa reported no increased risk of preterm birth associated with HAART initiated during pregnancy compared with ZDV monotherapy (13% vs 11%, p=0.39).[19] There are studies reporting that an increased risk of preterm birth is limited to PI-based HAART.[14–16] However, in our study, the majority (98%) of pregnancies were exposed to EFV-based or NVP-based HAART, indicating that the risk of preterm birth is not limited to PI-based HAART regimen.

We found that pregnancies exposed to NVP-based HAART had an increased risk of preterm birth compared with EFV-based HAART. Our finding supports the current WHO treatment guideline which recommends EFV-based HAART as a first-line treatment option as opposed to NVP-based HAART for all HIV-infected adults (including pregnant women). Before 2012, EFV-based HAARTs were avoided during early stage of pregnancy due to fear of increased risk of birth defects. After a sufficient amount of evidence indicated that the risk of birth defects was not elevated in pregnancies exposed to EFV-based HAARTs,[46 47] the WHO concluded that it is safe in early pregnancy.[48] No evidence of differential risk of adverse pregnancy outcomes when EFV-based HAART was compared with PI-based HAART. However, the lack of association might be due to the small number of women on PI-based HAART. PI-based HAART was mostly used as second-line treatment in Ethiopia during the study period.

We observed no differential risk of preterm birth, low birth weight or small-for-gestational-age according to whether HAART was initiated before conception or during pregnancy. Our finding differs from a recent systematic review reporting a higher risk of preterm birth if HAART is initiated before conception as opposed to during pregnancy.[37] In contrast to the systematic review, a study from Malawi reported lower incidence of preterm birth associated with initiation of HAART before conception.[49] Previously, advanced disease stage or low level of immunity were criteria used to initiate HAART; therefore, the inconsistent findings regarding the association between timing of HAART initiation with adverse pregnancy outcomes could be confounded by advanced disease stage or low level of immunity at the time of treatment initiation.

There are different plausible biological mechanisms that could explain the positive association between HAART and adverse pregnancy outcomes. For any normal pregnancy to have a successful outcome, there should be a shift from Th1 cytokine production to Th2 cytokines.[50] HAART counteracts this natural shift in the immune system during pregnancy, which could contribute to an increased risk of preterm birth.[50] An earlier study also reported that HAART was associated with placental insufficiency among HIV-infected women with stillbirth.[51] The fact that we observed no strong evidence of an association with small-for-gestational-age might indicate a less pronounced role of placental insufficiency.

HAART has multiple benefits in preventing mother-to-child transmission of HIV,[6] improving maternal clinical outcomes[52] and preventing sexual transmission of HIV.[53] Currently, early initiation HAART for all HIV-infected individuals is gaining acceptance.[5 54] And a growing number of HIV-infected women of reproductive age are on HAART in resource-limited settings,[40] which may in turn increase the proportion of preterm and low birthweight infants. The difference in the rate of preterm birth (17.9 vs 7.0%) and low birth weight (20.5 vs 10.1%) between those exposed to HAART during pregnancy and ZDV monotherapy indicates around a twofold increased risk. Preterm birth is the leading causes of neonatal death globally, and it is a contributing risk factor in over 50% of all neonatal deaths.[55] This highlights the clinical relevance of our findings. The consequences of an increase in preterm births and low birth weight are particularly severe in resource limited settings like Ethiopia, where the health systems lack capacity to manage such complications. It is well known that paediatric and neonatal intensive care units in resource-limited

settings are scarce, and they lack the necessary equipment and skilled health professionals to provide adequate care to premature infants.

In the current study, we were able to account for a large number of potential confounders and performed sensitivity analyses to evaluate the robustness of the findings. However, the study should be understood in light of the following limitations. The study was conducted in an urban area and may not be representative of rural settings. We were not able to account for maternal viral load, as this information was not available for the majority of the women. However, we did adjust for both CD4 count and WHO clinical stage. Notably, previous studies reported that CD4 count was more predictive of birth outcomes than viral load.[7 56] Only 32 (2%) pregnancies were exposed to PI-based HAART and 199 (12%) were exposed to ZDV monotherapy, which limits our conclusion regarding these types of ARTs. Furthermore, PI-based HAART are second-line drugs in Ethiopia. We did not have information on whether the mothers had a history of adverse outcomes in previous pregnancies and could therefore not explore the potential role of confounding linked to adverse pregnancy outcomes in subsequent deliveries. Although sensitivity analyses excluding pregnancies exposed to HAART before conception, did not alter the main findings, confounding due to difference in maternal disease progression, nadir CD4 and immunological ageing in the observed associations cannot be excluded. We cannot exclude the possibility that our findings are influenced by a selection bias due to the exclusion of 30% of the pregnancies as a result of missing information. However, the women excluded were similar to those included with regard to parity, CD4 count and WHO clinical stage. Due to the amount of missing information, we conducted multiple imputations by chained equations. The results of imputed data and complete-case analysis were largely similar. We also relied on the registration of information by healthcare professionals and were unable to differentiate spontaneous and induced preterm term births. As in any observational study, we also cannot exclude the possibility of unmeasured confounding.

CONCLUSIONS

In this study from Ethiopia, we observed a higher risk of adverse pregnancy outcomes in pregnancies exposed to HAART compared with ZDV monotherapy. Furthermore, exposure to NVP-based HAART resulted in an increased risk of preterm birth compared with EFV-based HAART. Currently, the WHO recommends early initiation of HAART for all HIV-infected individuals. The capacity to monitor and manage adverse pregnancy outcomes in resource-limited healthcare settings should be improved to maximise the benefits of HAART and to minimise adverse pregnancy outcome risks. Additional prospective large-scale studies comparing pregnancy outcomes according to different HAART regimens are warranted.

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