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Perinatal outcomes associated with maternal HIV and antiretroviral therapy in pregnancies with accurate gestational age in South Africa

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Objective: To assess the association of maternal HIV infection and antiretroviral therapy (ART) with perinatal outcomes among women with accurate pregnancy dating and birth weights.

Design: Prospective pregnancy cohort study in Soweto, South Africa.

Methods: Gestational age was estimated by first-trimester ultrasound and birth weight was measured in a standardized manner within 24 h of birth. The primary composite outcome 'adverse perinatal outcome' included preterm birth, low birth weight, small for gestational age, stillbirth and neonatal death (NND). Specific adverse perinatal outcomes were secondary outcomes. Logistic regression models adjusted for multiple confounders.

Results: Of 633 women included in the analysis, 229 (36.2%) were HIV positive and 404 (63.8%) HIV negative. Among 125 HIV-positive women who provided detailed information on HIV and ART, 96.7% had clinical stage 1 of HIV disease and 98.4% were on ART during pregnancy, mostly WHO-recommended efavirenz-based ART. Among 109 HIV-positive women with information on timing of ART initiation, 38 (34.9%) initiated ART preconception and 71 (65.1%) antenatally. No newborns were HIV positive. In univariable analysis, maternal HIV infection was associated with increased risk of the composite 'adverse perinatal outcome' [odds ratio (OR) 1.44; 95% confidence interval (CI) 1.03, 2.03], NND (OR 6.15; 95% CI 1.27, 29.88) and small for gestational age (OR 1.55; 95% CI 1.01, 2.37). After adjusting for confounders, maternal HIV infection remained associated with 'adverse perinatal outcome' (adjusted OR 1.47; 95% CI 1.01, 2.14) and NND (adjusted OR 7.82; 95% CI 1.32, 46.42). No associations with timing of ART initiation were observed.

Conclusion: Despite high ART coverage, good maternal health and very low vertical HIV transmission rate, maternal HIV infection remained associated with increased risk of adverse perinatal outcomes. Larger studies using first trimester ultrasound for pregnancy dating are needed to further assess associations with specific adverse perinatal outcomes.

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Keywords: antiretroviral therapy, HIV, low birth weight, neonatal death, preterm birth, small for gestational age, stillbirth

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Introduction

In 2017, 1.5 million HIV-positive women were pregnant, of whom 91% lived in sub-Saharan Africa [1–3]. South Africa has the highest number of HIV-infected people in the world [1], and one in three pregnant women in South Africa are HIV-positive [4], of whom more than 95% now receive antenatal antiretroviral therapy (ART) [1].

Preliminary data from Botswana recently indicated that preconception dolutegravir (DTG) may be associated with a possible increased risk of neural tube defects (NTD) [5]. These findings highlight the importance of post roll-out birth outcomes surveillance, including for the current WHO-recommended first-line efavirenz (EFV)-based regimen for pregnant and breastfeeding women [6], which is currently used by the vast majority of HIV-positive women in the world, including in South Africa [7].

Untreated maternal HIV infection is associated with increased risk of adverse perinatal outcomes, including preterm birth (PTB), small for gestational age (SGA), low birth weight (LBW) and stillbirth [8]. PTB is the leading cause of neonatal and child mortality worldwide [9], and SGA and LBW are also associated with increased rates of neonatal and child morbidity and mortality [10]. Although ART in pregnancy has clear benefits for maternal health and the prevention of mother-to-child transmission (PMTCT) of HIV, studies assessing the association between ART regimens and timing of initiation of ART and adverse perinatal outcomes have yielded inconsistent results [11–18]. One possible source of this inconsistency is the use of imprecise methods to estimate gestational age and measure birth weight in most studies [11–18]. The most accurate method to estimate gestational age is an ultrasound scan in the first-trimester [19], but studies assessing pregnancy outcomes in the context of maternal HIV infection in sub-Saharan Africa almost always use less accurate methods, such as the date of the last menstrual period [11–14], symphysis-fundal height measurement [12–14], clinical assessment of the newborn [18,20] or a late ultrasound scan [12,21]. Furthermore, birth weight measurements are often poorly performed and/or reported, and often simply captured from routine obstetric records [11,12]. Inaccurate estimation of gestational age and birth weight also inevitably leads to misclassification of SGA newborns. These inaccurate methods may therefore lead to measurement error, misclassification of outcomes and biased estimates that may produce inconsistent findings regarding the effect of ART [11,12,20,22] and timing of ART initiation [12,21,23].

The aim of this study was to investigate the association of maternal HIV infection and ART with adverse perinatal outcomes among pregnant women with accurately determined gestational age and birth weight. To that

end, we conducted a prospective pregnancy cohort study in Soweto, South Africa, in which gestational age was estimated by early ultrasound (<14 weeks' gestation) and birth weight measured in a standardized manner within 24 h of birth.

Methods

Study setting and design

We conducted a prospective pregnancy cohort study at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, South Africa, the only public referral hospital in Soweto (population 1.5 million people). CHBAH implements the South African guidelines for the PMTCT. In 2013, the PMTCT guidelines recommended fixed-dose combination (FDC) of tenofovir disoproxil fumarate (TDF), emtricitabine (FTC)/lamivudine (3TC), EFV for all HIV-positive pregnant women, irrespective of CD4⁺ cell count [24]. In 2015, South Africa implemented option B+ [25], followed in 2016 by the 'treat all' policy, with the same first-line TDF + FTC/3TC + EFV regimen [6].

Study participants

Inclusion criteria: Black South African women, living in Soweto, aged at least 18 years, with a singleton pregnancy and spontaneous conception, and gestational age less than 14 weeks at first visit. Women were excluded if they had a multiple pregnancy, BMI more than 35 kg/m² (as obesity affects the accuracy of ultrasound scans) or intellectual/physical disability.

Data collection

Data were collected from 28 May 2013 to 20 July 2016. All women had a first-trimester dating ultrasound scan and women not known to be HIV-positive were routinely offered an HIV test. At enrolment, detailed information on around 200 items was collected from medical records, antenatal cards and/or interviews, encompassing sociodemographic characteristics; smoking, alcohol and illicit drug use; nutritional supplements; drug history; medical, gynaecological and obstetric history, including history of miscarriage, termination of pregnancy, PTB, LBW, stillbirth, neonatal death (NND) and pregnancy-related complications. Enrolled women were seen every 5 ± 1 weeks to document any changes in health status since the previous visit. Permission was sought from HIV-positive women to collect additional information, including clinical stage of HIV disease, use of ART, ART regimens and timing of ART initiation. Detailed information on maternal HIV and ART was captured from medical records and confirmed by direct interviews. CD4⁺ cell counts during pregnancy were obtained from the National Health Laboratory Service, South Africa, medical records and/or antenatal cards, and the first CD4⁺ cell count measured during pregnancy was

used. Women were followed up until delivery at which time the perinatal outcomes of interest were recorded. 98.7% of women delivered in CHBAH and 1.3% at home. Lastly, information about newborn HIV status, determined before hospital discharge, was taken from the medical records. Few variables had some missing data, but the proportion of missingness was always less than 8%, apart from CD4⁺ cell count, for which it was less than 19%.

Measurements

A trained, dedicated ultrasonographer performed a transabdominal ultrasound scan (Philips HD-9, Philips Ultrasound, Bothell, Washington, USA) to measure the foetal crown-rump length within 3 days of enrolment. Only those women with a confirmed gestational age less than 14 weeks remained in the study. Birth weight of newborns was measured within 24 h of birth using a Seca 376 baby scale and performed independently by two trained anthropometrists. If the two anthropometrists recorded different results and the difference was more than 50 g, the measurement was repeated by each anthropometrist. If the difference was still more than 50 g, a third repetition was carried out; after the third measurement, if the difference was still more than 50 g, the average was used for our analysis. The equipment, which was calibrated twice weekly, was selected for accuracy, precision and robustness, as demonstrated in previous studies [26].

Exposure definitions

The exposures of interest included maternal HIV infection and timing of ART initiation. Among HIV-positive women, if ART was initiated before the estimated date of conception, newborns were classified as exposed to preconception ART. If ART was initiated after the estimated date of conception, newborns were classified as exposed to antenatal ART: first trimester (<15 weeks' gestation), second trimester (15–27 weeks' gestation) and third trimester (>27 weeks' gestation) initiation.

Outcome definitions

The primary outcomes were the composite outcomes 'adverse perinatal outcome' and 'severe adverse perinatal outcome'. 'Adverse perinatal outcome' included PTB (<37 weeks' gestation), LBW (<2500 g), SGA (<10th centile of the INTERGROWTH-21st Newborn Standard birth-weight-for-gestational-age/sex) [27], stillbirth (birth without any signs of life \geq 24 weeks' gestation) and NND (infant death in the first 28 days of life). In addition, the 'severe adverse perinatal outcome' included very PTB (VPTB, <32 weeks' gestation), very LBW (VLBW, <1500 g), very SGA (VSGA, <3rd centile of the INTERGROWTH-21st Newborn Standard) [27], stillbirth and NND. All individual specific adverse perinatal outcomes were analysed as secondary outcomes. Congenital abnormality was defined as any abnormality observed on ultrasound examination and/or at birth.

Statistical analysis

Maternal and newborn characteristics and adverse perinatal outcomes were compared between HIV-positive and HIV-negative women and by timing of ART initiation (preconception vs. antenatal ART) among the HIV-positive group. Continuous variables were compared using two-samples *t* test or Wilcoxon–Mann–Whitney test, as appropriate. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. For PTB, VPTB, LBW, VLBW, SGA, VSGA and NND, analyses were restricted to live newborns. Stillbirth, congenital abnormalities and composite outcomes were calculated as a proportion of all newborns. The associations between maternal HIV infection and timing of ART initiation and adverse perinatal outcomes were examined using unadjusted and adjusted logistic regression, with odds ratios (ORs) and 95% confidence intervals (95% CIs) estimated. Several confounders were defined *a priori* based on the existing literature, including maternal age, smoking, alcohol consumption, prepregnancy BMI, parity and a history of adverse perinatal outcomes. In addition, a number of confounders were identified in our sample, including maternal education, marital status and socioeconomic status. All statistical analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas, USA); *P* values were based on two-sided tests, with a value of *P* less than 0.05 considered to be statistically significant.

Ethical approval

All participants provided written consent upon enrolment. The study was approved by the University of Oxford Tropical Research Ethics Committee and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa.

Results

A total of 680 women with singleton pregnancies and a first-trimester dating scan were recruited, of whom 633 were included in the analyses: 229 (36.2%) HIV positive and 404 (63.8%) HIV negative (Fig. 1, Table 1). The vast majority of women had accurate information on gestational age and birth weight at delivery (Fig. 1). There were 125 HIV-positive women who provided detailed information on HIV/ART. Of these, 117 (96.7%) women had WHO clinical stage 1 and 122 (98.4%) were on ART during pregnancy (Table 2): 120 received HAART, of whom 110 received FDC of TDF + FTC/3TC + EFV, five EFV-based HAART, two nevirapine (NVP)-based HAART, three lopinavir/ritonavir (LPV/r)-based HAART and two received zidovudine monotherapy. Information on timing of ART initiation was available for 109 women: 38 (34.9%)

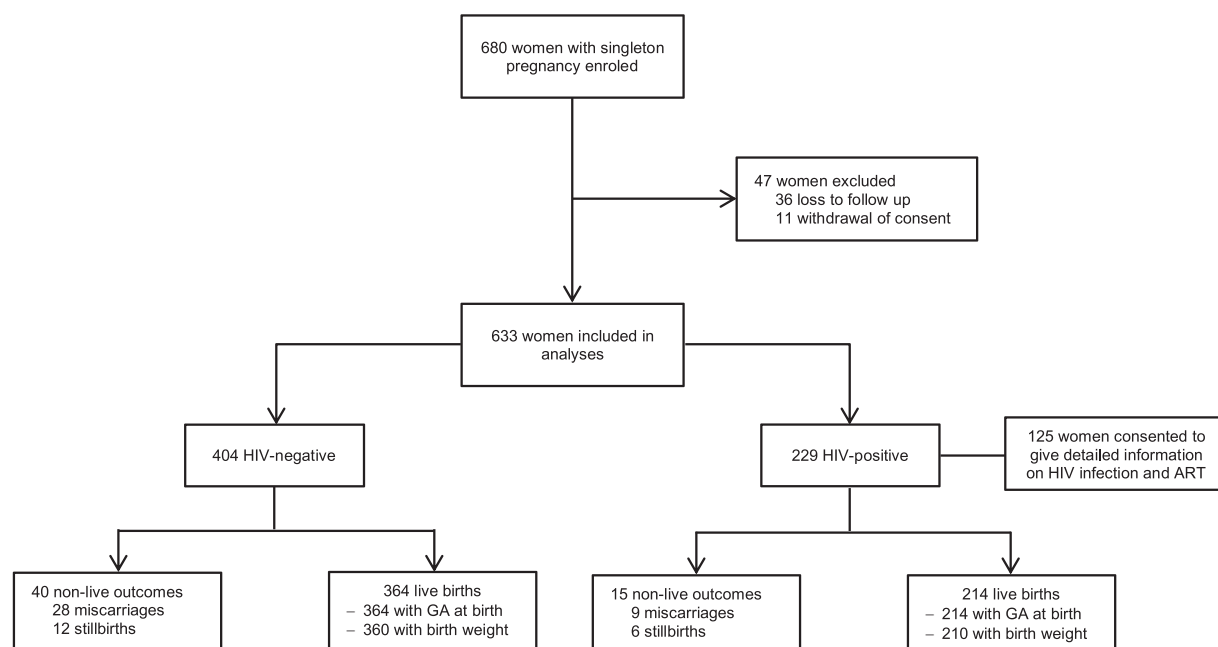


Fig. 1. Flow diagram of study participants. ART, antiretroviral therapy; GA, gestational age.

Table 1. Maternal and newborn characteristics according to maternal HIV status and timing of antiretroviral therapy initiation.

Characteristics	All women, N = 633, n (%)	Women with information on HIV status, N = 633			HIV-positive women with information on timing of ART initiation, N = 109		
		HIV-negative, N = 404, n (%)	HIV-positive, N = 229, n (%)	P value*	Preconception ART, N = 38, n (%)	Antenatal ART, N = 71, n (%)	P value**
Maternal characteristics							
Age (years), median (IQR)	31 (26, 35)	30 (26, 34)	32 (28, 37)	<0.001	33.5 (31, 37)	30 (27, 35)	0.02
Education (years), median (IQR)	12 (11, 12)	12 (12, 12)	12 (11, 12)	0.0001	12 (11, 12)	12 (11, 12)	0.84
Married/cohabiting	245 (38.7)	167 (41.3)	78 (34.1)	0.07	17 (44.7)	29 (40.9)	0.70
Occupation ^a							
Working	227 (35.9)	149 (36.9)	78 (34.1)	0.75	14 (36.8)	23 (32.4)	0.82
Not working	86 (13.6)	55 (13.6)	31 (13.5)		4 (10.5)	10 (14.1)	
Other	320 (50.5)	200 (49.5)	120 (52.4)		20 (52.6)	38 (53.5)	
Smoked during pregnancy	40 (6.3)	24 (5.9)	16 (6.9)	0.60	2 (5.3)	5 (7)	1.00
Alcohol consumption in pregnancy	52 (8.2)	30 (7.4)	22 (9.6)	0.34	3 (7.9)	8 (11.3)	0.74
Socioeconomic status ^b							
Low	121 (19.1)	80 (19.8)	41 (17.9)	0.02	6 (15.8)	12 (16.9)	0.98
Middle	277 (43.8)	160 (39.6)	117 (51.1)		18 (47.4)	34 (47.9)	
High	235 (37.1)	164 (40.6)	71 (31)		14 (36.8)	25 (35.2)	
Prepregnancy BMI							
Underweight (<18.50 kg/m ²)	10 (1.6)	8 (1.9)	2 (0.9)	0.63	0	0	0.12
Normal (18.50–24.99 kg/m ²)	224 (35.4)	138 (34.2)	86 (37.5)		18 (47.4)	20 (28.2)	
Overweight (25.0–29.99 kg/m ²)	234 (36.9)	153 (37.9)	81 (35.4)		13 (34.2)	30 (42.2)	
Obese (≥30 kg/m ²)	165 (26.1)	105 (26)	60 (26.2)		7 (18.4)	21 (29.6)	
Nulliparity	102 (17.2)	75 (20)	27 (12.3)	0.02	2 (5.4)	12 (17.4)	0.08
History of stillbirth	61 (10.3)	44 (11.8)	17 (7.8)	0.13	3 (8.1)	1 (1.5)	0.12
History of termination of pregnancy	39 (6.2)	22 (5.5)	17 (7.4)	0.32	3 (7.9)	7 (9.9)	1.00
History of preterm birth	119 (20)	77 (20.5)	42 (19.2)	0.69	8 (21.6)	12 (17.4)	0.60
History of low birth weight	91 (15.4)	64 (17.2)	27 (12.4)	0.12	4 (10.8)	8 (11.6)	1.00
History of neonatal death	38 (6.4)	23 (6.1)	15 (6.9)	0.73	1 (2.7)	2 (2.9)	1.00
Gestational age at enrolment (weeks), median (IQR)	12 (11, 13)	12 (11, 13)	12 (11, 13)	0.41	11 (10, 13)	12 (10, 13)	0.66
Caesarean section	340 (53.7)	214 (53)	126 (55)	0.62	25 (65.8)	47 (66.2)	0.97
Newborn characteristics							
Female newborn	292 (47.3)	189 (48.5)	103 (45.4)	0.46	23 (60.5)	26 (36.6)	0.02
Gestational age at delivery (weeks), median (IQR)	38.5 (37, 40)	39 (37, 40)	38 (37, 39)	0.24	38 (37, 39)	39 (37, 39)	0.30
Birth weight (g), median (IQR)	2990 (2600, 3260)	2995 (2652.5, 3265)	2962.5 (2540, 3255)	0.25	2940 (2495, 3210)	3070 (2595, 3305)	0.30
Birth-weight-for-gestational-age centile, median (IQR)	33.6 (13.4, 63.1)	34.4 (15.5, 64.2)	31.1 (11.3, 61.2)	0.29	34.9 (8.0, 53.8)	33.9 (11.4, 64.8)	0.69
Congenital abnormalities	11 (1.7)	7 (1.7)	4 (1.8)	1.00	2 (5.3)	2 (2.8)	0.61
HIV positive	0	0	0	–	0	0	–

ART, antiretroviral therapy; IQR, interquartile range.

^aWorking: any paid job; not working: housework and student; other: redundancy or unemployed.

^bSocioeconomic status was determined using asset-based measures at household level categorized as low, middle and high using a wealth index score generated from multiple correspondence analysis.

*P value from chi-square test, Fisher's exact test or Wilcoxon–Mann–Whitney test, as appropriate, for comparisons between HIV-positive and HIV-negative women.

**P value from chi-square test, Fisher's exact test or Wilcoxon–Mann–Whitney test, as appropriate, for comparisons between HIV-positive women with preconception and antenatal ART.

Table 2. Maternal HIV-related characteristics.

Characteristics	HIV-positive women with information on HIV and ART, N = 125, n (%)	HIV-positive women with information on timing of ART initiation, N = 109		P value*
		Preconception ART, N = 38, n (%)	Antenatal ART, N = 71, n (%)	
Clinical HIV stage (WHO)				
Stage 1	117 (96.7)	35 (97.2)	66 (95.7)	0.79
Stage 2	2 (1.7)	0	2 (2.9)	
Stage 3	2 (1.7)	1 (2.8)	1 (1.4)	
Stage 4 (AIDS)	0	0	0	
Received ART during pregnancy	122 (98.4)			
ART regimen				
Zidovudine monotherapy	2 (1.6)	0	2 (2.8)	0.54
HAART	120 (98.4)	38 (100)	69 (97.2)	
CD4 ⁺ cell count during pregnancy				
<200 cells/ μ l	9 (8.3)	1 (3.2)	8 (12.1)	0.03
200–349 cells/ μ l	20 (18.5)	5 (16.1)	13 (19.7)	
350–499 cells/ μ l	43 (39.8)	19 (61.3)	20 (30.3)	
\geq 500 cells/ μ l	36 (33.3)	6 (19.4)	25 (37.9)	

ART, antiretroviral therapy.

*P value from chi-square test or Fisher's exact test, as appropriate, for comparisons between HIV-positive women with preconception and antenatal ART.

initiated ART preconception and 71 (65.1%) initiated during pregnancy (58 during the first trimester, 12 during the second/third trimester and one unknown trimester) (Table 2 and Supplementary Table 1, <http://links.lww.com/QAD/B471>).

The comparison of maternal characteristics by HIV status and timing of ART initiation are presented in Table 1. HIV-positive women were significantly older, less educated, more likely to be parous and had a different distribution of socioeconomic status compared with HIV-negative women. Women receiving preconception ART were significantly older than those on antenatal ART (Table 1), and women on antenatal ART more

commonly had low or high CD4⁺ cell counts (Table 2). Among women who initiated ART during pregnancy, maternal characteristics were comparable between those who initiated ART during the first trimester and second/third trimester (Supplementary Table 1, <http://links.lww.com/QAD/B471>).

Adverse perinatal outcomes among all women

Among all 633 women included in the analysis, 210 (33.2%) had an adverse perinatal outcome, and 75 (11.9%) a severe adverse perinatal outcome. Among the 578 live births there were 99 (17.1%) PTB and 26 (4.5%) VPTB; 114 (20%) LBW and 21 (3.7%) VLBW; and 106 (18.7%) SGA and 30 (5.3%) VSGA (Table 3, Fig. 2).

Table 3. Adverse perinatal outcomes according to maternal HIV status and timing of antiretroviral therapy initiation.

Adverse perinatal outcomes	All women, N = 633, n (%)	Women with information on HIV status, N = 633		P value*	HIV-positive women with information on timing of ART initiation, N = 109		P value**
		HIV-negative, N = 404, n (%)	HIV-positive, N = 229, n (%)		Preconception ART, N = 38, n (%)	Antenatal ART, N = 71, n (%)	
Adverse perinatal outcome ^a	210 (33.2)	122 (30.2)	88 (38.4)	0.04	16 (42.1)	23 (32.4)	0.31
Severe adverse perinatal outcome ^b	75 (11.9)	44 (10.9)	31 (13.5)	0.32	4 (10.5)	7 (9.9)	1.00
PTB (<37 weeks)	99 (17.1)	56 (15.4)	43 (20.1)	0.15	9 (24.3)	10 (14.7)	0.22
VPTB (<32 weeks)	26 (4.5)	15 (4.1)	11 (5.1)	0.57	2 (5.4)	1 (1.5)	0.28
LBW (<2500 g)	114 (20)	67 (18.6)	47 (22.4)	0.28	10 (27)	11 (16.7)	0.21
VLBW (<1500 g)	21 (3.7)	13 (3.6)	8 (3.8)	0.90	2 (5.4)	1 (1.5)	0.29
SGA (<10th centile)	106 (18.7)	58 (16.2)	48 (23)	0.04	10 (27)	13 (19.7)	0.39
VSGA (<3rd centile)	30 (5.3)	17 (4.7)	13 (6.2)	0.45	3 (8.1)	3 (4.6)	0.66
Stillbirth	18 (2.8)	12 (3)	6 (2.6)	0.80	0	1 (1.4)	1.00
NND	9 (1.6)	2 (0.6)	7 (3.3)	0.02	1 (2.7)	2 (2.9)	1.00

ART, antiretroviral therapy; LBW, low birth weight; NND, neonatal death; PTB, preterm birth; SGA, small for gestational age; VLBW, very low birth weight; VPTB, very preterm birth; VSGA, very small for gestational age.

^aAdverse perinatal outcome includes PTB, LBW, SGA, stillbirth and NND.

^bSevere adverse perinatal outcome includes VPTB, VLBW, VSGA, stillbirth and NND.

*P value from chi-square test or Fisher's exact test, as appropriate, for comparisons between HIV-positive and HIV-negative women.

**P value from chi-square test or Fisher's exact test, as appropriate, for comparisons between HIV-positive women with preconception and antenatal ART.

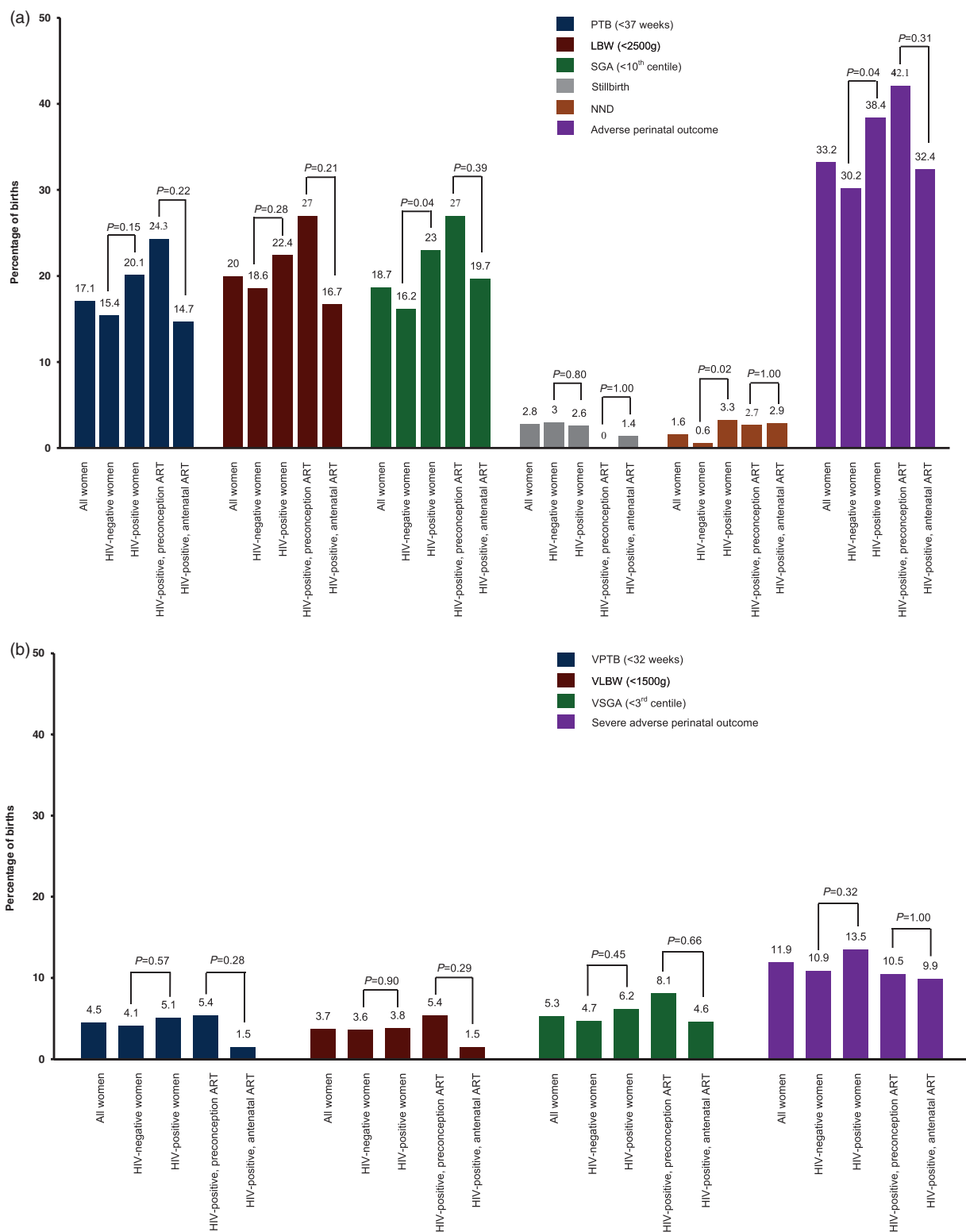


Fig. 2. Incidence of adverse perinatal outcomes according to maternal HIV status and timing of ART initiation. (a) Preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA), stillbirth, neonatal death (NND) and adverse perinatal outcome (composite outcome of preterm birth, low birth weight, small for gestational age, stillbirth and neonatal death). (b) Very preterm birth (VPTB), very low birth weight (VLBW), very small for gestational age (VSQA) and severe adverse perinatal outcome (composite outcome of very preterm birth, very low birth weight, very small for gestational age, stillbirth and neonatal death). P values for comparisons are indicated on top of the bars (Table 3). ART, antiretroviral therapy.

Table 4. Unadjusted and adjusted associations^a between maternal HIV status and timing of antiretroviral therapy initiation and adverse perinatal outcomes.

Adverse perinatal outcomes	Women with information on HIV status, <i>N</i> = 633		HIV-positive women with information on timing of ART initiation, <i>N</i> = 109	
	OR (95% CI) for HIV-positive (Ref: HIV-negative)	<i>P</i> value*	OR (95% CI) for preconception ART (Ref: antenatal ART)	<i>P</i> value**
Adverse perinatal outcome ^b				
Unadjusted	1.44 (1.03, 2.03)	0.04	1.52 (0.67, 3.42)	0.32
Adjusted	1.47 (1.01, 2.14)	0.04	1.17 (0.45, 3.08)	0.75
Severe adverse perinatal outcome ^c				
Unadjusted	1.28 (0.78, 2.09)	0.32	1.08 (0.29, 3.93)	0.91
Adjusted	1.38 (0.81, 2.36)	0.24	1.56 (0.35, 6.84)	0.56
PTB (<37 weeks)				
Unadjusted	1.38 (0.89, 2.15)	0.15	1.86 (0.68, 5.10)	0.22
Adjusted	1.40 (0.86, 2.26)	0.17	2.27 (0.70, 7.32)	0.17
VPTB (<32 weeks)				
Unadjusted	1.26 (0.57, 2.80)	0.57	3.83 (0.34, 43.71)	0.28
Adjusted	1.26 (0.53, 3.02)	0.60	–	–
LBW (<2500 g)				
Unadjusted	1.26 (0.83, 1.92)	0.28	1.85 (0.70, 4.90)	0.21
Adjusted	1.15 (0.73, 1.82)	0.55	1.92 (0.60, 6.15)	0.27
VLBW (<1500 g)				
Unadjusted	1.06 (0.43, 2.59)	0.90	3.71 (0.33, 42.42)	0.29
Adjusted	1.14 (0.43, 3.04)	0.79	–	–
SGA (<10th centile)				
Unadjusted	1.55 (1.01, 2.37)	0.04	1.51 (0.59, 3.89)	0.39
Adjusted	1.45 (0.91, 2.33)	0.12	1.09 (0.32, 3.76)	0.89
VSGA (<3rd centile)				
Unadjusted	1.33 (0.63, 2.81)	0.45	1.85 (0.35, 9.68)	0.47
Adjusted	1.50 (0.66, 3.44)	0.34	3.23 (0.38, 27.88)	0.29
Stillbirth				
Unadjusted	0.88 (0.33, 2.37)	0.80	–	–
Adjusted	0.77 (0.24, 2.41)	0.65	–	–
NND				
Unadjusted	6.15 (1.27, 29.88)	0.02	0.92 (0.08, 10.46)	0.94
Adjusted	7.82 (1.32, 46.42)	0.02	–	–

95% CI, 95% confidence interval; ART, antiretroviral therapy; LBW, low birth weight; NND, neonatal death; OR, odds ratio; PTB, preterm birth; Ref, reference; SGA, small for gestational age; VLBW, very low birth weight; VPTB, very preterm birth; VSGA, very small for gestational age.

^aAdjusted for maternal age, education, marital status, smoking, alcohol consumption, socioeconomic status, prepregnancy BMI, parity, history of stillbirth, history of preterm birth, history of low birth weight and history of neonatal death.

^bAdverse perinatal outcome includes PTB, LBW, SGA, stillbirth and NND.

^cSevere adverse perinatal outcome includes VPTB, VLBW, VSGA, stillbirth and NND.

**P* value from unadjusted and adjusted logistic regression, as appropriate, for the associations between maternal HIV infection and adverse perinatal outcomes.

***P* value from unadjusted and adjusted logistic regression, as appropriate, for the associations between timing of ART initiation and adverse perinatal outcomes.

Adverse perinatal outcomes by maternal HIV status

The incidence of specific adverse perinatal outcomes, with the exception of stillbirth, was higher in HIV-positive than HIV-negative women (Table 3, Fig. 2). Maternal HIV infection was associated with a significant increase in the risk of the composite 'adverse perinatal outcome' (38.4 vs. 30.2%; OR 1.44; 95% CI 1.03, 2.03), NND (3.3 vs. 0.6%; OR 6.15; 95% CI 1.27, 29.88) and SGA (23 vs. 16.2%; OR 1.55; 95% CI 1.01, 2.37). After adjustment for maternal age, education, marital status, smoking, alcohol consumption, socioeconomic status, prepregnancy BMI, parity and a history of adverse perinatal outcomes, maternal HIV infection remained associated with the composite 'adverse perinatal outcome' [adjusted OR (AOR) 1.47; 95% CI 1.01, 2.14] and NND (AOR 7.82; 95% CI 1.32, 46.42), but not SGA

(AOR 1.45; 95% CI 0.91, 2.33) (Table 4). There were no cases of mother-to-child transmission of HIV identified at hospital discharge (Table 1).

Adverse perinatal outcomes by timing of antiretroviral therapy initiation

Among HIV-positive women, the incidences of composite and specific adverse perinatal outcomes were higher among women who initiated ART preconception than those who initiated ART antenatally, except for stillbirth and NND (Table 3, Fig. 2). However, none of the adverse perinatal outcomes were significantly associated with timing of ART initiation in either the unadjusted or adjusted models (Table 4). The inclusion of CD4⁺ cell count during pregnancy in the models did not change these associations (data not shown). Due to the limited number of outcome events, we could not perform

adjusted analyses of the associations between timing of ART initiation and VPTB, VLBW, stillbirth and NND.

Among HIV-positive women who initiated ART antenatally, the incidences of all adverse perinatal outcomes assessed were higher among women who initiated ART in the first trimester compared with second/third trimester (Supplementary Table 2, <http://links.lww.com/QAD/B471>). However, trimester of ART initiation was not significantly associated with the composite 'adverse perinatal outcome', or PTB, LBW and SGA in both univariable and multivariable analyses. Adjusted models could not be fitted for VPTB, VLBW, VSGA, stillbirth and NND due to the limited number of outcome events (Supplementary Table 3, <http://links.lww.com/QAD/B471>).

Congenital abnormalities

Overall, 11 (1.7%) of 633 births had congenital abnormalities (Table 1): hydronephrosis, hypotrophy of cerebrum, dilated ventricles, gastroschisis, narrow chest and disorganized pelvis, spina bifida (born to an HIV-positive woman with first-trimester initiation of ART), malformation of lower limbs, club foot, polydactyly, ventricular septal defect and gross congenital malformation.

Discussion

The benefits of ART during pregnancy in reducing new paediatric HIV infections and improving maternal health are indisputable. In this study, there were no newborns diagnosed with HIV and, among the subgroup of HIV-positive women with ART information, 96.7% were asymptomatic of HIV disease (Tables 1 and 2). However, our findings showed that HIV-positive women still have significantly higher overall rates of adverse perinatal outcomes compared with HIV-negative women (38.4 vs. 30.2%, $P=0.04$) (Table 3, Fig. 2), despite high ART coverage with WHO-recommended first-line TDF + FTC/3TC + EFV. On the other hand, treated maternal HIV infection was not significantly associated with PTB, which is in agreement with an existing study [20], but in contrast to other studies [11,12,17,28]. The lack of association between maternal HIV infection and LBW in our study is similar to another study [12], but not others [11,17]. Our finding of nonsignificant association between maternal HIV infection and SGA is consistent with two studies [11,12], but in contrast to another study [17]. The lack of significant associations between maternal HIV infection and a number of specific perinatal outcomes could be due to limited statistical power to detect modest effects because of the sample size and the number of events for some outcomes. Our study, including over 630 women with an HIV prevalence of 36% and a composite outcome prevalence of 30%, was adequately powered to detect ORs at least 1.5. For analyses including a smaller subset of patients (such as the

HIV-positive women with ART initiation information) or a less common outcome (like some of the rare perinatal outcomes), there was less statistical power, as evidenced by the wider CIs of the ORs for these comparisons. Imprecise and varying methods to determine gestational age and birth weight might also contribute to inconsistent results between studies.

HIV-positive women in our study had a higher incidence of NND (3.3%) compared with women treated with EFV-based ART in Botswana (1.9%) [29]. The rate of NND was also higher than that reported for HIV-positive women on DTG-based ART (1.2%) [14] and NVP-based ART (1.9%) [13], but similar to women treated with LPV/r-based ART (2.8%) [13]. In contrast, we found a low rate of NND (0.6%) in the HIV-negative women, despite the high overall rate of adverse perinatal outcomes, such as PTB, SGA and LBW. A recent study from South Africa reported that the most common causes of early NND are PTB-related complications (49.2%) [30]. Of the nine NNDs that occurred in our study, eight infants were born less than 28 weeks' gestation (six born to HIV-positive and two born to HIV-negative women) and one at 35 weeks' gestation (to an HIV-positive woman), and all nine infants had a birth weight less than 1500 g and were admitted to the ICU. It is likely that maternal HIV infection significantly increased the risk of NND in our study because of the higher incidence of extremely PTB.

As well as the composition of the ART regimen, the timing of initiation of ART has been reported to correlate with adverse perinatal outcomes, with preconception initiation being associated with higher rates of adverse perinatal outcomes than antenatal initiation [13,16]. In our study, the overall rate of adverse perinatal outcomes among the 38 women known to have initiated ART preconception (42.1%) was higher than that reported in women who received EFV-based preconception ART in a study in Botswana (36.7%) [29]; however, the rate of adverse perinatal outcome was lower among the 71 women who initiated ART antenatally (32.4%) in our study compared with EFV-based antenatal ART in Botswana (35.0%) [29]. Despite the 10% difference (42.1 vs. 32.4%) in adverse perinatal outcome rates in the preconception and antenatal initiation groups in our study, the association between timing of ART initiation and adverse perinatal outcome was NS. This could be due to inadequate statistical power, given the limited number of women with available ART information, and the small number of outcome events (as judged by the wide CIs for the ORs for this subgroup). Furthermore, the limited statistical power could be a reason why this study was unable to detect an increased risk of PTB among women who initiated ART preconception than those who initiated antenatally. This finding was in contrast to a meta-analysis by Uthman *et al.* [16] which has shown a 40% increase in the risk of PTB among women with

preconception initiation of ART in low-income and middle-income countries. Regarding the nonsignificant associations between timing of ART initiation and LBW and SGA, our findings were similar to those reported by another South African study [12].

Questions have been raised as to whether reported associations between timing of ART initiation and perinatal outcomes could be due to selection bias, as the women in the antenatal initiation group, who often start ART late in pregnancy in African settings [18], might not have the same opportunity as women on preconception ART to experience adverse events within a study, as these may have occurred prior to possible enrolment, for example PTB [31]. Although in our study all women were recruited prospectively very early in pregnancy, thereby minimizing the aforementioned selection bias, our study had limited ability to draw firm conclusions regarding ART timing of initiation, due to limited power.

The rates of congenital abnormalities in our study were similar between HIV-positive and HIV-negative women (1.8 vs. 1.7%, $P=1.00$), despite most HIV-positive women commencing ART either preconception or in the first trimester (Supplementary Table 1, <http://links.lww.com/QAD/B471>). This finding is similar to the results from a Ugandan study (in which 77% of HIV-positive women received EFV-based HAART) [32] and the Antiretroviral Pregnancy Registry [33].

Our study has several strengths. This is, to our knowledge, the first prospective pregnancy cohort study conducted in sub-Saharan Africa investigating adverse perinatal outcomes in HIV-positive women in which all women had a first-trimester ultrasound scan. Ultrasound in the first trimester is the most accurate method to date a pregnancy [19] which minimizes misclassification of gestational age at birth. All women in our study were recruited at less than 14 weeks' gestation and prospectively followed up which enabled us to capture adverse perinatal outcomes from an early gestational age. Pregnant women commonly present late for antenatal care in sub-Saharan Africa [18], which not only hampers accurate gestational age assessment but also leads to an underestimation of adverse perinatal outcomes in prospective studies, as adverse outcomes may occur prior to enrolment. Furthermore, the measurement of birth weight was directly performed by trained anthropometrists using standardized techniques and instruments, and was conducted within 24 h of birth, which minimized random measurement error and misclassification of birth weight. We used the INTERGROWTH-21st Newborn Standards [27] to determine which newborns were SGA, thereby enabling international comparison with other studies using the same standard [12,13,17,29]. Extrapolating from the subgroup with information on ART, the population studied had high ART coverage and most

HIV-positive women initiated EFV-based ART preconception or in the first trimester. This enabled assessment of adverse perinatal outcomes in HIV-positive women on first-line WHO-recommended ART, as implemented in most affected countries in the world [7]. A large number (>200) of variables relating to socioeconomic, medical and obstetric risk factors were collected through direct measurements, interviews, medical records and antenatal cards. Data quality was very high, with a very small number of missing data; for example, only eight (1.4%) of 578 live newborns had missing birth weight data, which is a great achievement in a very busy hospital in a low resource setting. Logistic regression models were used to adjust for multiple confounders, identified either *a priori* or based on our data, including detailed information on adverse perinatal outcomes in previous pregnancies.

Nevertheless, this study has some limitations. First, we were unable to demonstrate causal inference due to the nature of the observational study (potential unmeasured confounding). Second, the rarity of events found in several adverse perinatal outcomes (including VPTB, VLBW, VSGA, stillbirth and NND) limited our ability to perform adjusted analyses of the association between these outcomes and timing of ART initiation. Third, limited information on timing of ART initiation among HIV-positive women, due to limited consent given, resulted in limited statistical power for the association between timing of ART initiation and adverse perinatal outcomes. Fourth, it may be difficult to generalize our findings to other settings with different populations and risk factors.

It is crucial to optimize ART regimens during pregnancy to further improve perinatal outcomes and associated neonatal and child morbidity and mortality, as well as eliminate HIV transmission and improve maternal health. As of the end of 2017, almost 60 low- and middle-income countries have incorporated or are planning to include DTG in their national guidelines, as a preferred first-line drug. However, clinical evidence of DTG safety in pregnant women is still very limited [34]. A study from Botswana recently reported that DTG-based ART had similar adverse perinatal outcomes to EFV-based ART among women who initiated ART antenatally, although these were still higher than their HIV-negative counterparts [14]. In addition, an interim analysis of the same cohort in Botswana indicated a potential association between DTG-based ART initiated preconception and an increased risk of NTD [5]. Therefore, ongoing surveillance of pregnancy outcomes among HIV-positive women on ART remains crucial.

Despite high coverage with WHO-recommended EFV-based ART, good maternal health and a very low rate of mother-to-child HIV transmission, maternal HIV infection remains associated with an increased risk of adverse perinatal outcomes in South Africa. More, larger studies,

including randomized controlled trials, are needed to determine the optimal ART regimen and timing of ART initiation in pregnant women. To improve the reliability and comparability of future studies, they should recruit women at an early gestational age (<14 weeks); use first-trimester ultrasound to estimate gestational age accurately; measure birth weight in a standardized manner within 24 h of birth; and use the INTERGROWTH-21st Newborn Standard of birth-weight-for-gestational-age/sex to classify SGA.

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Conflicts of interest

There are no conflicts of interest.

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