

Adverse Pregnancy Outcomes Among HIV-positive Women in the Era of Universal Antiretroviral Therapy Remain Elevated Compared With HIV-negative Women

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Background: Without treatment, HIV infection in pregnant women is associated with adverse pregnancy outcomes. We compared adverse pregnancy outcomes among HIV-positive women on antiretroviral therapy (ART) and HIV-negative women who enrolled for antenatal care in selected health facilities in Maseru district, Lesotho.

Methods: We enrolled a cohort of HIV-positive and HIV-negative women at their first antenatal visit and followed them through delivery. Study data on miscarriage, stillbirth, preterm birth, low birth weight and birth defects were collected through participant interviews and medical record abstraction. We used the Rao-Scott χ^2 test and the *t* test to assess differences in characteristics and outcomes between HIV-positive and HIV-negative women and generalized estimating equations for multivariable analysis.

Results: A total of 614 HIV-positive and 390 HIV-negative pregnant women were enrolled in the study with delivery information on 571 (93.1%) and 352 (90.3%) respectively. In the delivery cohort, the median age at enrolment was 28 years for HIV-positive women and 23 years for HIV-negative women with median gestational ages of 20 and 21 weeks, respectively. A total of 149 singleton pregnancies had documented adverse pregnancy outcomes; 33 (9.6%) HIV-negative pregnancies and 116 (20.6%) HIV-positive pregnancies. Compared to their HIV-negative counterparts, HIV-positive women were more likely to experience an adverse pregnancy outcome, adjusted odds ratio (AOR) 2.6 [95% confidence interval (CI): 1.71–3.97]; an intrauterine death (miscarriage or stillbirth), AOR 2.64 [95% CI: 1.25–5.49]; or a low birth weight delivery, AOR 1.89 [95% CI: 1.16–3.09].

Conclusion: Adverse pregnancy outcomes remained 2–3 times higher among HIV-positive women compared with HIV-negative women despite universal ART.

Key Words: HIV, pregnancy, birth outcomes, Lesotho, ART

(*Pediatr Infect Dis J* 2021;XX:00–00)

HIV infection during pregnancy is associated with an increased risk of adverse pregnancy outcomes.^{1,2} Several studies have shown that untreated maternal HIV infection increases the risk of stillbirth, preterm delivery, low birth weight and small-for-gestational-age infants.^{3–5} In 2013, the World Health Organization (WHO) recommended the use of antiretroviral therapy (ART) for all pregnant and breastfeeding women for the prevention of mother-to-child HIV transmission (PMTCT)⁶; and in 2016, adopted the “treat all” approach for HIV treatment and prevention.⁷

As the “treat all” approach expands across sub-Saharan Africa, increasing numbers of women are conceiving while on ART and additional women are newly diagnosed and initiated on ART when they attend antenatal care (ANC). In settings like Lesotho where HIV prevalence among women of reproductive age is 29.7% and ANC attendance is over 97%, this approach has led to ART coverage of up to 98.5% among pregnant women.⁸

The benefits of ART for PMTCT are well known; however, the effect of antiretroviral drugs on pregnancy outcomes is not fully known. There is inconclusive evidence on the occurrence of adverse pregnancy outcomes such as stillbirth, preterm delivery, low birth weight or small-for-gestational-age deliveries among women on ART. With increased ART use, some studies have shown declining trends for preterm birth, low birth weight and stillbirths.^{9–11} However, other studies show no reduction in adverse pregnancy outcomes among HIV-positive women on ART compared with HIV-negative women,^{12,13} and additional studies suggest differences between antiretroviral drugs in risk for adverse pregnancy outcomes.^{14,15} There is a need to clearly understand the relationship between HIV and adverse pregnancy outcomes in the setting of current WHO guidelines for PMTCT and as new antiretroviral drugs enter widespread use.

The “Integrated Management Team to Improve Maternal-Child Outcomes” (IMPROVE) study was a cluster-randomized prospective cohort study at 12 health facilities to determine the effect of facility-based interventions on PMTCT and maternal child health service delivery and uptake in Lesotho. The IMPROVE intervention included the use of multi-disciplinary team support for pregnant/postpartum women, integrated training on client-centered care and enhanced home visiting early in pregnancy. The IMPROVE study provided the opportunity to compare adverse pregnancy outcomes between HIV-positive women on ART and HIV-negative women receiving ANC in selected health facilities in Maseru District in Lesotho. Maseru is Lesotho’s most populous district with one of the highest HIV prevalence.

Accepted for publication March 27, 2021

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The authors have no conflicts of interest to disclose.

This study was funded by the United States Agency for International Development (USAID) through the Project SOAR (Supporting Operational AIDS Research); award no. AID-OAA-A-14-00060. The contents included here are; however, the responsibility of the authors and do not necessarily represent the official views of USAID.

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ISSN: 0891-3668/21/XXX-0000

DOI: 10.1097/INF.00000000000003174

MATERIALS AND METHODS

Study Design and Setting

Between July 2016 and February 2017, HIV-positive and HIV-negative pregnant women attending their first ANC visit at 12 health facilities in the Maseru district were enrolled into the study and followed every 3 months until 12–24 months postpartum. Two main hospitals and 10 affiliated health centers serving between 150 and 900 pregnant women annually were randomized (each hospital with its 5 affiliated referral health centers forming a cluster) to receive the IMPROVE intervention or the standard of care. Because there were no significant differences in pregnancy outcome by study arms; for this analysis, we combined data from the entire cohort of women who enrolled in the IMPROVE study and compared adverse pregnancy outcomes experienced by HIV-positive women on ART and their HIV-negative counterparts.

Study Population

Pregnant women attending their first ANC visit with known HIV status (including women tested on the day of screening) who lived within the facility catchment area and were willing to provide informed consent were eligible for enrolment. All HIV-positive women and a randomly selected subset of HIV-negative women (~1 woman/week/facility) were screened for study eligibility and enrolment.

Study Procedures

Trained study nurses screened women for study eligibility and obtained written informed consent before study enrolment. Nurses interviewed participants using structured data collection forms and reviewed medical charts and facility registers to obtain information on demographic, clinical and laboratory data. Data were collected on electronic tablets and uploaded into a web-based data management system for data cleaning and analysis. Women who missed study appointments were followed up by phone and if unavailable, home visits were carried out. Information on delivery outcomes, including birth weights, was obtained by review of patient charts, health facility registers and obstetric records. Information on pregnancy loss or deliveries that took place at home or in nonstudy sites was obtained through phone interviews with the mothers and subsequent review of any discharge notes obtained from the nonstudy site.

In accordance with national HIV treatment guidelines, women attending their first ANC were tested for HIV followed by immediate ART initiation if positive. The ART combination of choice was tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV).¹⁶ Tuberculosis (TB) symptom screening was carried out at each visit and daily trimethoprim-sulfamethoxazole was given to women with CD4 \leq 350 cells/mm³ or WHO clinical stage 3 or 4.

Study Outcomes

Gestational age was computed based on dates of the last menstrual period and through obstetric examination of the fundal height. Ultrasound is not routinely available in ANC at primary care health facilities in Lesotho. Preconception ART was defined as ART initiated at least 42 weeks before the date of delivery or at least 30 weeks before the date of a miscarriage. Miscarriage was defined as noninduced pregnancy loss before 28 weeks of gestation; stillbirth was defined as delivery of a baby with no signs of life at or after 28 weeks' gestation¹⁷; and preterm birth was defined as live birth before completion of 37 weeks of gestation.¹⁸ We defined low birth weight as an infant weight at birth less than 2500 g¹⁹; and birth defects were defined as any structural anomalies detected on neonatal examination at birth.

The primary outcome of interest was a composite outcome defined as any adverse pregnancy event and included any of the following: miscarriage (spontaneous abortion), stillbirth, preterm birth, low birth weight and birth defects. In addition, we evaluated the occurrence of the individual pregnancy outcomes.

Statistical Analysis

We summarized baseline data including participant age, marital status, gestational age, level of education, gravidity and syphilis infection during pregnancy in frequency tables. Analysis of pregnancy outcomes was limited to singleton pregnancies. We used the Rao-Scott χ^2 test and the *t* test to assess differences in characteristics and outcomes between HIV-positive and HIV-negative women, accounting for clustering by study site. Generalized estimating equations were used for multivariable analysis, also accounting for correlation between participants within a site. We present odds ratios adjusted for baseline characteristics identified a priori: maternal age, marital status and education (gravidity was also considered but was highly associated with age and therefore not included in final models). Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

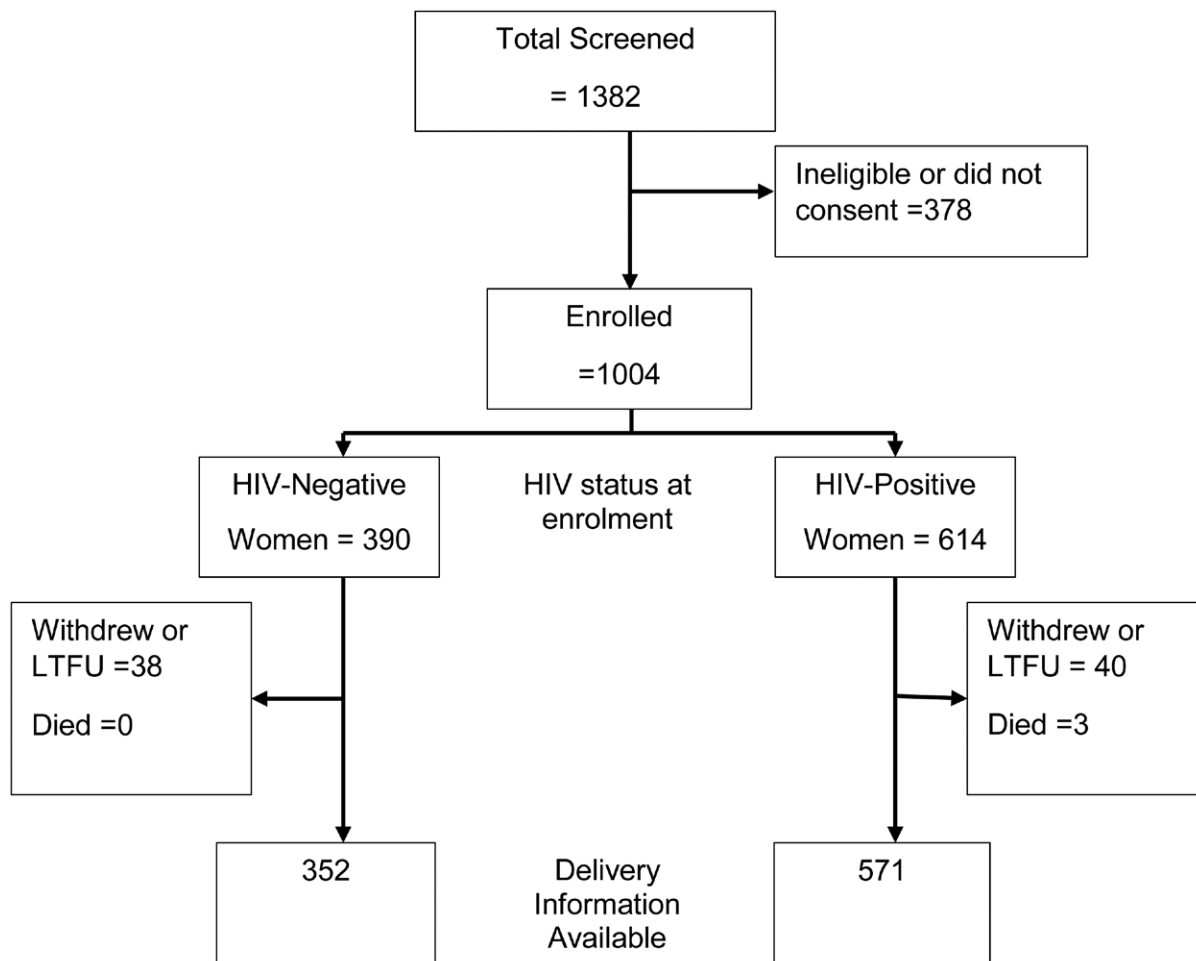
Ethics

The study protocol was reviewed and approved by the Lesotho National Health Research Ethics Committee (FWA00023574), the George Washington University Institutional Review Board (IRB) (FWA00005945) and the Population Council IRB (FWA00000279). All participants provided written informed consent.

RESULTS

Overall, 1,004 pregnant women were enrolled in the study; 614 were HIV positive and 390 were HIV negative (Fig. 1). Pregnancy outcomes were available for 571 (93.0%) HIV-positive women and 352 (90.3%) HIV-negative women, who constitute the delivery cohort with results presented in this paper. In this cohort, the median estimated gestational age at enrolment was 20 weeks for HIV-positive women and 21 weeks for HIV-negative women. Of the HIV-positive women, 150 (26.3%) tested positive for HIV on their first ANC visit, while the remainder knew their HIV status before attending ANC. Among 558 HIV-positive women screened for TB symptoms, 555 (99.5%) had no symptoms. Of these, 120 (21.6%) initiated TB preventive therapy (TPT) and an additional 145 women had recently completed TPT. Two women received TB treatment. All HIV-positive women received ART with approximately 90% on TDF/3TC/EFV. Other ART regimens mainly included TDF/3TC/nevirapine (NVP), zidovudine (AZT)/3TC/EFV or AZT/3TC/NVP. Of 315 women with a viral load test carried out within the 12-month period preceding delivery, 292 (92.7%) had viral loads <1000 copies/ml, of which 280 (88.9%) had <50 copies/ml. HIV-negative women were younger, had a higher level of education and were more likely to be in their first pregnancy compared with their HIV-positive counterparts (Table 1).

There were 17 twin deliveries, 8 from HIV-negative women and 9 from HIV-positive women. Twin deliveries were excluded from the analysis. Overall, the median birth weight was 2.9 kg, (range 0.7–5.2); 2.9 kg (range 0.7–4.4) in HIV-exposed infants and 3.0 kg (range 1.2–5.2) in HIV-unexposed infants. A total of 149 singleton pregnancies were classified as having at least one adverse pregnancy outcome, including 33 (9.6%) HIV-negative pregnancies and 116 (20.6%) HIV-positive pregnancies (Table 2). Forty-eight pregnancies ended in intrauterine death; this included 8 (2.3%) HIV-negative pregnancies (2 miscarriages and 6 stillbirths) and 40 (7.1%) HIV-positive pregnancies (20 miscarriages and 20 stillbirths). Additional adverse outcomes included 53 preterm



LTFU = Loss to follow-up

FIGURE 1. Participant screening and enrolment information.

deliveries among live-born infants; 89 low birth weight infants; and 11 infants with birth defects. Birth defects documented in infants of HIV-negative mothers included 2 infants with cleft lip, 1 infant with congenital heart disease and 1 infant with microcephaly. HIV-positive women delivered 3 infants with club foot, 2 infants with extra digits, 1 infant with hydrocephalus and 1 infant with spina bifida and hydrocephalus.

Compared to their HIV-negative counterparts, a higher proportion of HIV-positive women experienced an intrauterine death (miscarriage or stillbirth), 7.1% versus 2.3% ($P = 0.002$), low birth weight delivery, 13.2% versus 7.9% ($P = 0.010$) and preterm delivery, 7.4% versus 3.8% ($P = 0.046$) in the bivariate analysis (Table 2). No significant difference was seen in the occurrence of birth defects. In a multivariable model that adjusted for maternal age, marital status, level of education and study site, the odds of having any adverse pregnancy outcome remained significantly higher in HIV-positive women compared with HIV-negative women [adjusted odds ratio (AOR) = 2.60, 95% CI: 1.71–3.97] (Table 3). The odds of intrauterine death and low birth weight delivery, including term low birth weight, also remained significantly higher in HIV-positive compared with HIV-negative women.

In the subset of women with at least one syphilis test result during pregnancy, the adjusted odds of adverse pregnancy outcomes

remained significantly higher in HIV-positive women even after the addition of syphilis infection to the model. With syphilis in the model, the AOR was 2.58 (95% CI: 1.63–4.07) for any adverse pregnancy outcome; 2.69 (95% CI: 1.54–4.70) for intrauterine death; 1.34 (95% CI: 0.43–4.15) for preterm and 1.78 (95% CI: 1.07–2.98) for low birth weight. Syphilis infection itself was also significantly associated with any adverse pregnancy outcome ($P = 0.040$) and preterm ($P = 0.001$), but not with intrauterine death or low birth weight.

Initiation of ART was pre-conception in 285 women, during pregnancy in 267 women and 10 women had an unknown time for ART initiation. No significant differences in adverse pregnancy outcomes were observed by the timing of ART initiation (Table 4).

DISCUSSION

In this study, we observed that adverse pregnancy outcomes remained 2–3 times higher among HIV-positive women compared with HIV-negative women despite universal ART. The odds of having any adverse pregnancy outcome were more than 2 times higher among HIV-positive women compared with HIV-negative women. Specifically, intrauterine death (miscarriage and stillbirth) and low birth weight were significantly higher, while preterm deliveries and infants with birth defects were not. Background adverse

TABLE 1. Baseline Characteristics of HIV-negative and HIV-positive Pregnant Women with a Known Delivery Outcome

Baseline Characteristics	Total (n = 923)	HIV-negative women (n = 352)	HIV-positive women (n = 571)	P
Age (years) at first ANC visit (median, range)	26 (14–48)	23 (14–42)	28 (16–48)	<0.0001
Age categories (%)				
<19 years	64 (6.9)	44 (12.5)	20 (3.5)	<0.0001
19–24 years	316 (34.2)	177 (50.3)	139 (24.3)	
>24 years	543 (58.8)	131 (37.2)	412 (72.2)	
Marital status (%)				
Married or living with partner	712 (77.1)	262 (74.4)	450 (78.8)	0.063
Not married/living with partner	211 (22.9)	90 (25.6)	121 (21.2)	
Education (%)				
Primary education or less	293 (31.8)	84 (23.9)	209 (36.7)	<0.0001
Any secondary education	557 (60.4)	236 (67.0)	321 (56.3)	
Beyond secondary school	72 (7.8)	32 (9.1)	40 (7.0)	
Missing	1	0	1	
Gravidity				
First pregnancy	284 (31.1)	166 (47.6)	118 (20.9)	<0.0001
Second pregnancies	329 (36.0)	115 (33.0)	214 (37.9)	
Third pregnancies	173 (18.9)	47 (13.5)	126 (22.3)	
≥ 4 pregnancies	127 (13.9)	21 (6.0)	106 (18.8)	
Missing	10	3	7	
Positive syphilis test during pregnancy (%)				
Yes	23 (2.8)	4 (1.3)	19 (3.6)	0.131
No	807 (97.2)	300 (98.7)	507 (96.4)	
No test results available	93	48	45	

TABLE 2. Adverse Pregnancy Outcomes Among HIV-negative and HIV-positive Women, With and Without Syphilis (Excluding Twin Pregnancies)

Adverse Pregnancy Outcome	All Cohort Women				Excluding Women with Syphilis		
	Total	HIV-negative Women	HIV-positive Women	P	HIV-negative Women	HIV-positive Women	P
Pregnancy outcomes	N = 906	N = 334	N = 562		N = 340	N = 543	
Composite: any adverse outcome (intrauterine death, preterm, low birth weight, birth defect)	149/906	33/344 (9.6%)	116/562 (20.6%)	<0.0001	33/340 (9.7%)	110/543 (20.3%)	<0.0001
Intrauterine death	48/905	8/344 (2.3%)	40/561 (7.1%)	0.002	8/340 (2.4%)	38/543 (7.0%)	0.002
Delivery outcomes (excluding miscarriage)	N = 884	N = 342	N = 542		N = 338	N = 523	
Any birth defect	11/882	4/342 (1.2%)	7/540 (1.3%)	0.871	4/338 (1.2%)	7/523 (1.3%)	0.842
Preterm delivery (<37 week)	53/879	13/342 (3.8%)	40/537 (7.4%)	0.046	13/338 (3.9%)	37/519 (7.1%)	0.108
Low birth weight (<2500 g)	89/803	25/317 (7.9%)	64/486 (13.2%)	0.010	25/313 (8.0%)	61/469 (13.0%)	0.016
Term low birth weight (≥37 weeks and <2500 g)	61/764	16/305 (5.3%)	45/459 (9.8%)	0.031	16/301 (5.3%)	44/445 (9.9%)	0.028

pregnancy rates in Lesotho stratified by HIV status have not been previously described; UNICEF data indicates the rate of stillbirth in the overall population as 20/1,000 total births (2%), which is similar to that observed in the HIV-negative cohort in this study.²⁰

Our findings add to the growing body of evidence that HIV-positive women continue to experience more adverse pregnancy

outcomes than their HIV-negative counterparts despite receipt of ART. Recent findings from studies carried out in South Africa, Botswana and the United Kingdom similarly demonstrated higher adverse pregnancy outcomes in HIV-positive women than HIV-negative women, even when ART was initiated at preconception.^{21–23} In contrast, a study in Malawi did not observe significant differences in preterm delivery, low birth weight and small for gestational age between HIV-positive on ART and HIV-negative women; however, they did not assess the intrauterine fetal loss.¹¹ The Malawi authors noted that rates of adverse pregnancy outcomes were high regardless of HIV status. Our study, which similarly did not find differences by HIV status in preterm delivery, had much lower rates of preterm delivery (7.4% in HIV-positive and 3.8% in HIV-negative women) than observed in the Malawi study (10.6% in HIV-positive and 9.5% HIV-negative women). In contrast, the rate of low birth weight among term neonates in the Malawi study (3.8% in HIV-positive and 2.0% in HIV-negative women) was 2–3 times lower than observed in our study (9.8% in HIV-positive and 5.3% in HIV-negative women), which may have limited the power of the Malawi study to detect the significant difference observed in our study.

TABLE 3. Adjusted Odds of Adverse Pregnancy Outcome for HIV-positive Versus HIV-negative Pregnant Women (Excluding Twin Pregnancies)

Adverse Pregnancy Outcome	N	Adjusted Odds Ratio (95% CI)
Composite: any adverse pregnancy outcome	905	2.60 (1.71–3.97)
Intrauterine death (miscarriage or stillbirth)	904	2.62 (1.25–5.49)
Preterm*	854	1.41 (0.64–3.09)
Low birth weight	802	1.89 (1.16–3.09)
Term low birth weight	763	2.31 (1.15–4.63)

*Live born, excluding stillbirths
CI indicates confidence interval.

TABLE 4. Adverse Pregnancy Outcomes Among Women who Started ART Preconception Versus During Pregnancy

Adverse Pregnancy Outcomes	Pre-conception	During Pregnancy	Adjusted Odds Ratio (95% CI)
Composite: any adverse pregnancy outcome	58/285 (20.4%)	53/267 (19.9%)	1.08 (0.69–1.69)
Intrauterine death (miscarriage or stillbirth)	20/285 (7.0%)	15/266 (5.6%)	1.17 (0.64–2.14)
Preterm*	20/274 (7.3%)	20/258 (7.8%)	1.41 (0.95–2.09)
Low birth weight	35/241 (14.5%)	29/241 (12.0%)	1.49 (0.77–2.89)
Term low birth weight	24/228 (10.5%)	21/227 (9.3%)	1.48 (0.68–3.21)

*Live born, excluding stillbirth.
CI indicates confidence interval.

Comparison of stillbirths in our study with other published studies is complicated by the different definitions used for stillbirth. We defined stillbirth as any baby born with no signs of life at or after 28 weeks gestation as recommended by WHO.¹⁷ Some researchers have used a lower gestational threshold of 20 weeks,⁵ while others have used 24 weeks.²¹ Despite these differences in definition, our findings on intrauterine death are in agreement with other studies from both resource-limited and resource-rich countries.^{5,24} Similar to our study, researchers from the United Kingdom/Ireland found that the stillbirth rate in HIV-positive women remained higher than the general population, despite nearly half of their HIV-positive women being on ART before conception.²³ A study in Botswana demonstrated high rates of adverse outcomes, particularly stillbirth, in HIV-positive women co-infected with syphilis compared with HIV-positive and HIV-negative women without syphilis.²² In our study, after controlling for syphilis coinfection, intrauterine fetal death remained higher compared with a similar cohort of HIV-negative women.

Low birth weight is known to increase neonatal morbidity and mortality, and hence it is of concern that we observed higher rates of low birth weight among HIV-positive compared with HIV-negative women, even among the subset of term low birth weight infants. There are mixed findings related to the association between treated maternal HIV infection and low birth weight.^{13,21,24} In one of the largest observational studies of birth outcomes in HIV-positive and HIV-negative women in the Botswana Tsepamo birth surveillance study, there were no differences in pregnancy outcomes between HIV-positive women receiving EFV and dolutegravir (DTG)-based ART regimens. However, similar to our study, the rate of adverse pregnancy outcomes, including small for gestational age, were higher among HIV-positive women receiving EFV or DTG compared with HIV-negative women.²⁵

The proportions of women who experienced preterm birth were not significantly different between the HIV-positive and HIV-negative groups. Data on the association of ART with preterm birth are conflicting, and some studies suggest that ART regimens may differ in their association with preterm birth.^{11,26–31} Most of the HIV-positive women in our cohort were on a combination of TDF, 3TC and EFV, which has appeared to have a lower rate of adverse pregnancy outcomes than other ART regimens in a study in Botswana.²⁵

The lack of association of maternal ART with birth defects seen in our study is consistent with findings from other studies, as well as the Antiretroviral Pregnancy Registry, that confirm the safety of EFV-based ART regimens as used in our cohort of women.^{21,32–34} The lack of association between this regimen and birth defects is reassuring; however, as countries move away from EFV to DTG-based regimens, there is a need for continued pharmacovigilance of pregnant women receiving the newer ART regimens for adverse outcomes.³⁵

The underlying etiology for the discrepancy in birth outcomes between HIV-positive and HIV-negative women is unclear.

One study evaluated the prevalence of placental growth disorders in HIV-positive pregnant women on ART, reporting a higher prevalence of such disorders compared with international reference values, noting that restriction of placental growth was most common.³⁶ Another study has suggested that altered angiogenesis may be a mechanism underlying adverse outcomes in women with HIV receiving ART.³⁷

We noted that the timing of ART initiation did not have any influence on the occurrence of adverse events. While a meta-analysis in 2017 suggested preconception ART was associated with higher rates of adverse outcomes, this report included older studies using less optimal ART regimens.³⁸ Other studies using ART regimens recommended over the past 5 years such as the EFV-based ART regimen used in Lesotho have, similar to our study, not found timing of ART to be associated with adverse outcome.^{39–41}

Our study had several strengths. We prospectively followed up women and collected primary data in a public healthcare setting that implemented the WHO guidelines for HIV treatment and PMTCT. The data presented here may, therefore, be relevant to the many settings where the same WHO guidelines have been adopted. In addition, the quality of data collected was high, with only a few missing values for some of the variables. Nevertheless, interpretation of our findings should take into consideration the following limitations. Gestational age was determined using the date of the last menstrual period and fundal height measurements. Although these are established ways of determining gestational age, they are not as precise as ultrasound measurement. In addition, there may have been some underreporting of adverse pregnancy outcomes since women were enrolled at different time points when they came to facilities for their first ANC. Some women may have experienced adverse events at home and never visited the clinics for their ANC, or those lost to follow-up before delivery may have experienced an intrauterine death. Lastly, a priori computation of power to assess differences in pregnancy outcomes among women who started ART preconception versus during pregnancy was not carried out.

CONCLUSIONS

Our findings indicate that despite optimization of maternal health through ART, pregnancy outcomes among HIV-positive women remain worse than those among HIV-negative women residing in the same area. Whether this is due to the effects of the underlying HIV infection, the antiretroviral drugs or both is not clear. Further research is needed to examine the reasons for this persistent discrepancy to enable interventions to improve outcomes among HIV-positive women and their children.

ACKNOWLEDGMENTS

We acknowledge the study participants for their cooperation, time and effort, and the support obtained from the study health facilities, the Maseru District Management Team (DHMT) and the

Lesotho Ministry of Health. We thank the USAID for funding this study, specifically Dr. Justine Mirembe and Mr. Ian Membe from USAID/Lesotho and Anouk Amzel from USAID/Washington who were instrumental in the development and funding of this study. We also are indebted to the SOAR leadership team at the Population Council for their continued input and support.

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