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Reassuring Birth Outcomes with Tenofovir/Emtricitabine/Efavirenz used for Prevention of Mother to Child Transmission of HIV in Botswana

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Abstract

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Background—Prior to introduction of tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV), 3-drug antiretroviral treatment (ART) was associated with increased adverse birth outcomes when used for prevention of mother-to-child HIV transmission (PMTCT) in Botswana.

Methods—We extracted obstetric records from all women at the 2 largest maternities in Botswana from 2009-11 when Botswana National Guidelines recommended ZDV from 28 weeks gestational age (GA) for CD4 ≥350 and ART for CD4 <350, and again in 2013-14 after implementation of TDF/FTC/EFV for PMTCT regardless of CD4 or GA. We compared use of TDF/FTC/EFV in pregnancy with other 3-drug ART regimens, and with initiation of ZDV, among women with similar CD4 cell counts. Outcomes included small for gestational age (SGA), preterm delivery (PTD) (<37 weeks GA), and stillbirths (SB).

Results—Among 9445 HIV-infected women delivering during the study period, 170 were on TDF/FTC/EFV at conception and 1468 initiated TDF/FTC/EFV during pregnancy. Adverse birth outcomes were high overall (3% SB, 21% PTD, and 18% SGA), and among women receiving TDF/FTC/EFV (3% SB, 22% PTD and 12% SGA). There was no difference in PTD or SB among women initiating TDF/FTC/EFV compared with ZDV or other 3-drug ART, but initiating TDF/FTC/EFV was associated with fewer SGA infants than other 3-drug ART (aOR 0.4, 95% CI 0.2,0.7).

Conclusions—Adverse birth outcomes remain high among HIV–infected women. TDF/FTC/EFV was at least as safe as other ART, and associated with fewer SGA infants when initiated during pregnancy. Larger studies are needed to evaluate birth outcomes and congenital abnormalities among women on TDF/FTC/EFV at conception.

Keywords

HIV; Stillbirth; Preterm Delivery; Small for Gestational Age; PMTCT; Antiretroviral Therapy

Introduction

Expansion of programs to provide antiretroviral (ARV) medication during pregnancy has dramatically reduced mother to child HIV transmission (MTCT) in low- and middle-income countries [1]. Further reductions in MTCT are expected as countries rapidly adopt universal 3-drug ART for all pregnant and breastfeeding women (WHO Option B), including those opting for life-long ART continuation beyond the PMTCT period (WHO Option B+) [1,2]. TDF/FTC/EFV is recommended by WHO as the preferred regimen for prevention of MTCT (PMTCT) because of the simplicity of the regimen, minimization of drug-drug interactions, and harmonization with the adult HIV treatment guidelines [3-12]. However, data for birth outcomes with TDF/FTC/EFV remain insufficient [13-22].

Prior to 2012, National PMTCT guidelines in Botswana recommended 3-drug ART (Zidovudine/Lamivudine/Nevirapine, ZDV/3TC/NVP) for women with CD4 cell count ≤350 cells/mm^3 and ZDV-alone from 28 weeks gestational age (GA) for women with CD4 cell count >350 cells/mm^3. In 2012, Botswana rolled out new national HIV treatment guidelines that recommended TDF/FTC/EFV as the preferred regimen for adults with CD4 ≤ 350 cells/mm^3 and for all HIV-infected pregnant and breastfeeding women [23]. This

study evaluated adverse birth outcomes among women on TDF/FTC/EFV during pregnancy, and the potential impact of TDF/FTC/EFV on implementation of PMTCT.

Methods

Study Population

From May 2009-April 2011 and from April 2013-April 2014, we abstracted data from obstetric records of women who delivered live born or stillborn infants at the two largest public maternity wards in Botswana, Princess Marina Hospital (PMH) in Gaborone and Nyangabgwe Referral Hospital (NRH) in Francistown. These sites delivered almost 25% of all births in the country [24]. We excluded women who delivered prior to arrival to the hospital, women who were transferred from other hospitals after delivery, and women who delivered at gestational age (GA) < 24 weeks. Detailed information was only recorded on the first-born infant in the case of a pregnancy with multiple gestations during the study.

During the study period, HIV-infected women received PMTCT care from Botswana government providers and according to Botswana National HIV guidelines. Botswana Ministry of Health recommended routine HIV testing of all pregnant women and for citizens of Botswana the government provided free antenatal care services, HIV testing, infant formula and ARVs. In 2009-2011, HIV-infected women not already on ART were eligible to start ZDV at 28 weeks gestation if their CD4 cell count was >350 cell/mm^3 and eligible to receive 3-drug ART (generally ZDV/3TC/NVP) if their CD4 cell count was ≤ 350 cell/mL. Some women across all CD4 cell counts also accessed ZDV/3TC/LPV/r as part of a government pilot program for 3-drug universal PMTCT. During this time period, TDF/FTC/EFV was avoided in women of childbearing age due to concerns for neural tube defects in the event of pregnancy. New Botswana National Guidelines were implemented in 2012, and during the 2013-2014 study period TDF/3TC/EFV was recommended for all HIV-infected adults with CD4 cell count ≤ 350 cells/mm^3, and for pregnant women regardless of CD4 cell count. Women on ART at conception continued their ART regimen and were not switched to TDF/FTC/EFV.

Data Extraction

Data was abstracted from maternal obstetric records (covering outpatient antenatal care and inpatient care during labor and delivery) at the time of discharge from the postnatal ward. Abstracted information included maternal demographics, maternal medical history, self-reported alcohol and tobacco use, results of HIV testing, laboratory values measured in pregnancy (hemoglobin, rapid plasma regain [RPR], blood type, RH factor), medications taken at the time of conception, maternal diagnoses during pregnancy, vitamins and antibiotics prescribed during pregnancy, and infant outcomes. Diagnoses were recorded as per documentation of the treating physician or midwife, except for maternal anemia which was defined as hemoglobin ≤10 g/dL and maternal hypertension which was defined as systolic blood pressure ≥140 or diastolic blood pressure ≥90 in pregnancy. The estimated GA included in the obstetric record was used for analyses and if missing, GA was calculated using LMP. Antenatal clinic nurses estimated GA by date of LMP in most cases, but used fundal measurements or ultrasound if LMP was unknown. For HIV-infected women, we

collected the date of HIV diagnosis, most recent CD4 cell count, and antiretroviral history (including ARV start date, regimen and any switch or discontinuation during pregnancy). Infant data were abstracted from the medical record, and included gender, birth weight, delivery complications and admission to the neonatal unit.

Exposure and Outcome Definitions and Statistical Analysis

The primary exposure was use of any antiretroviral medication during pregnancy. Antiretroviral use was categorized as ART initiated prior to pregnancy (ART at conception), ARVs initiated during pregnancy, and no antiretroviral drugs received prior to the onset of labor or induction. Women who switched or terminated their ARV regimen were excluded from analysis except if they initiated ZDV and were switched to ART, in which case regimen at delivery was used. Sensitivity analysis was performed including all women who changed regimens during pregnancy, in which case conception regimen was used for those continuing in pregnancy and delivery regimen was used in women initiating ARVs. ZDV and NVP given during labor and delivery, when it was too late to be a causative factor in the birth outcome, were not considered in the analysis.

The 4 primary outcomes were SB, PTD, very preterm delivery (vPTD) and SGA. SB was defined as fetal death (APGAR 0,0,0) and included both macerated and fresh stillbirth; preterm delivery was a birth at <37 weeks gestational age; very preterm delivery was a birth at <33 weeks of age. An infant was considered SGA if below the 10^{th} percentile of birthweight by gestational age using norms specific to infants born in Botswana [25]. Because norms were only available for gestational ages 30-40 weeks, infants delivered outside of this range were excluded from the SGA analysis. A second analysis was performed defining SGA using World Health Organization norms which had no gestational age restrictions[26].

To limit lead-time bias when comparing outcomes among women initiating ARVs in pregnancy, we restricted the analysis to women who initiated ARVs prior to 30 weeks GA and who delivered at or after 30 weeks GA. To compare PMTCT regimens offered within similar CD4 cell count strata during the different PMTCT eras, we restricted analyses of ZDV vs. TDF/FTC/EFV to women with CD4 >350 cells/mm^3 and other 3-drug ART vs. TDF/FTC/EFV to women with CD4 ≤350 cells/mm^3.

Among women on ART at conception, we considered ‘other ART’ as all 3-drug ARV regimens with exception of the single-pill co-formulation TDF/FTC/EFV or the 2-pill formulation of TDF/FTC (Truvada) plus EFV. For analysis of both conception ART and intitiation of ARVs, ART without a specified regimen was considered to be non-Atripla 3-drug ART in 2009-11 (as TDF/FTC/EFV was not used) but was considered to be unknown ART in 2013-14 as there was no way to discern if it was TDF/FTC/EFV. Sensitivity analysis were performed that included and excluded women on ART without a specified regimen.

Unadjusted and adjusted logistic regression analyses were used to evaluate the association of ART use and the 4 primary outcomes. Given the link between immunodeficiency and adverse outcomes in prior studies [26-28] CD4 cell count was included as a covariate in all

analyses. The remainder of covariates in adjusted analyses were determined through stepwise selection with retention of variables with p<0.2. Statistical analyses were performed using SAS, version 9.3 (SAS institute, Cary, NC). All reported p-values are based on a 2-sided test.

Ethical Approval

Approval was granted by human subjects committees in Botswana and at the Harvard School of Public Health.

Results

There were 32,583 birth outcomes recorded, 20,057 (62%) at PMH and 12,526 (38%) at NH, representing almost 25% of all births in Botswana during surveillance periods [23]. In 2009-2011, 20,716 (64%) records were abstracted, and in 2013-2014, 11,867 (36%) were abstracted. In total, 31,463 (97%) women had a known HIV status, and 9445 (30%) were HIV positive.

Differences in demographics, HIV status, and birth outcomes by time period are shown in Table 1. Improved PMTCT indicators were seen in 2013-2014 compared with 2009-2011. In 2013-14, women were more likely to be tested for HIV (99 vs. 95%, p<0.0001) and more likely to receive ARVs during pregnancy (88% vs. 84%, p<0.0001) (Table 1). The proportion of women receiving fewer than 4 weeks of ARVs prior to delivery decreased from 25% in 2009-2011 to 17% in 2013-2014. Almost 3 times as many women initiated ARVs before 28 weeks GA in 2013-14 compared with 2009-2011 and the difference was even greater among those with low CD4 cell counts (75% vs. 31%, p<0.0001).

During the entire study period, 2602 (28%) HIV-infected women were on ART at conception, 5247 (56%) initiated ARVs during pregnancy, 1390 (15%) received no ARVs during pregnancy and 206 (2%) received ARVs during pregnancy but the timing was unknown. CD4 cell count was known in 4022 (43%). Median CD4 cell count was 395 cells/mm^3 overall, and differed by time period (Table 1) and ARV exposure category (Table 2).

Adverse birth outcomes were high among HIV-infected women (SB 5%, PTD 27%, vPTD 10%, SGA 19%), and lower among HIV-uninfected women (SB 3%, PTD 19%, vPTD 6%, SGA 10%)(p < 0.0001 for all comparisons). Among HIV-uninfected women the prevalence of all adverse birth outcomes was the same in 2009-11 and in 2013-14.

Women Initiating Antiretrovirals in Pregnancy

Data were collected on 5247 women who initiated ARVs in pregnancy: 1468 (28%) initiated TDF/FTC/EFV; 778 (15%) initiated other 3-drug ART; 2923 (56%) initiated ZDV; and 78 (1%) initiated unspecified ARVs. Twenty-eight (1%) women initiating ARVs either switched regimens (N=19) or had unknown regimen switch status (N=9) during pregnancy and were excluded from further analysis. Other 3-drug ART regimens included ZDV/3TC/NVP (36%), unspecified ART in 2009-11 (38%) which was almost exclusively ZDV/3TC/NVP given National ARV guidelines, ZDV/3TC/Lopinavir/ritonavir (19%),

TDF/FTC/NVP(4%), and other ART (3%). Pregnancy CD4 cell count was available in 59%, and 70% started ARVs by 30 weeks GA. Median CD4 cell count by exposure categories are shown in Table 3.

Overall, adverse birth outcomes occurred in 1167 (36%) of women who initiated ARVs before 30 weeks GA and adverse outcomes were less common among women initiating TDF/FTC/EFV than women initiating any other ARV (aOR 0.4 95% CI 0.3,0.6) (Table 2). Among women with CD4 ≤350 cells/mm^3 those who initiated TDF/FTC/EFV had fewer SGA infants (aOR 0.5, 95% CI 0.3,0.8) and no significant differences in PTD (aOR 0.5, 95%CI 0.2,1.2) or SB (aOR 0.1, 95%CI 0.01,1.0) compared with women initiating other 3-drug ART in pregnancy. Among women with CD4 >350 cells/mm^3, women initiating TDF/FTC/EFV had fewer SGA infants (aOR 0.7, 95%CI 0.5,1.0) but this was not statistically significant and there was no difference in PTD (aOR 1.1, 95%CI 0.6,2.1) or SB (aOR 0.9, 95% CI 0.4, 2.1) compared with initiating ZDV. Compared with women initiating any other ARV (ART or ZDV) without CD4 restriction, TDF/FTC/EFV had fewer SGA infants (aOR 0.5, 95% CI 0.4,0.7) and no statistically significant difference in PTD (aOR 0.7, 95%CI 0.5,1,1) or SB (aOR 0.6, 95% CI 0.3,1.3) (Table 3).

Women Continuing Antiretroviral Therapy in Pregnancy

Data were collected on 2602 women on ART at conception; 170 (7%) were on TDF/FTC/EFV, 669 (26%) were on ZDV/3TC/NVP, 287 (11%) were on TDF/FTC/NVP, 61 (2%) were on TDF/FTC/LPV/r, 49 (2%) were on ZDV/3TC/LPV/r, 977 (38%) were on other non-TDF/FTC/EFV regimens, and 389 (15%) were on unknown ART regimens. Thirty-five (1%) of these women switched ART during pregnancy and 7 (0.1%) had unknown ART switch status and were excluded from further analysis. Pregnancy CD4 cell count was available in 613 (24%) and was similar among women on TDF/FTC/EFV compared with women on other 3-drug ART (475 vs. 426 cells/mm^3, p=0.7).

Adverse birth outcomes occurred in 1085 (50%) of all women on ART at conception; 6.3% SB, 31.2% PTD, 11.7% vPTD and 22.6% SGA (Table 4). Compared with women on other 3-drug ART at conception, women on TDF/FTC/EFV at conception had fewer overall adverse outcomes (33% vs. 51%), fewer SB (4.9% vs. 6.4%), and fewer infants SGA (8% vs. 24%) but none of these findings were statistically significant in adjusted analysis (Table 4). Rates of PTD (28% vs 32%) and vPTD (10% vs. 12%) were similar among women on TDF/FTC/EFV at conception compared with women on other ART at conception. Results did not differ if women who changed ART during pregnancy were included in the analysis.

Tolerability of TDF/FTC/EFV in pregnancy

Among women who initiated ARVs during pregnancy, only 1 (0.06%) woman initiating TDF/FTC/EFV changed regimens compared with 18 (2%) of women initiating other 3-drug ARVs (p<0.0001). Five (3%) women on TDF/FTC/EFV at conception changed regimens during pregnancy (only 1 was after guidelines were updated), compared with 30 (1%) women on other 3-drug ART at conception.

Discussion

We performed the first study of birth outcomes within a national program using TDF/FTC/EFV as the recommended regimen for the prevention of mother to child transmission of HIV. We confirmed earlier findings from Botswana that SB, PTD, vPTD and SGA were more common in HIV-infected women than in HIV-uninfected women and also that women on ART from conception had particularly high rates of all adverse outcomes [15]. However, we found no increased risk of any adverse birth outcome with the use of TDF/FTC/EFV when initiated during pregnancy or started prior to conception when compared with other commonly used PMTCT regimens, including ZDV-alone. We also identified that initiation of TDF/FTC/EFV during pregnancy was associated with fewer SGA infants when compared with women initiating other 3-drug ART. TDF/FTC/EFV was well tolerated in pregnancy.

Our finding that there was no increased risk of adverse birth outcomes among women initiating TDF/FTC/EFV in pregnancy compared with women initiating ZDV-monotherapy differs from most recent studies that compare initiation of ART with initiation of ZDV in pregnancy (Table 5) [15,18,30-33]. Unlike our study, prior studies included few women on EFV-based ART, suggesting the possibility that EFV could have fewer adverse effects at the placental level than either NVP or PIs, though additional studies will be needed to confirm this finding. However, our findings are reassuring in light of randomized data from a large RCT (PROMISE) that found more severe adverse birth outcomes among women initiated on TDF/FTC/LPV/r compared with CBV/3TC/LPV/r in pregnancy [30]. Our finding that TDF was not associated with adverse birth outcomes when combined with EFV adds support to the argument that a drug interaction between TDF and LPV/r may have contributed to adverse birth outcomes in PROMISE [34-36].

Our finding that women exposed to TDF/FTC/EFV had fewer SGA infants than women exposed to other ARVs was unexpected given previous concern that TDF may be associated with decreased infant growth[37]. TDF/FTC/EFV exposure primarily occurred in the 2013-14 data collection period, so it is possible that changes in SGA over time could explain this finding. However, this seems unlikely as there was no difference in SGA among HIV-uninfected women between the two time periods, which would be expected if SGA were declining due to other factors in obstetric care or environment in Botswana. There were no differences in gestational age at delivery between these two time periods in any ARV-exposure group, so differences in measurement of GA that could lead to differences in SGA between the time periods were an unlikely source of bias. Also, the effect estimates were almost identical when using 2 different scales to define SGA—WHO birthweight-for-GA norms and birthweightfor-GA norms specific to Botswana.

This study has similar overall rates of all adverse outcomes as previous studies in Botswana[15] and these rates are strikingly high. Among women on ART at conception, half (49.9%) experience an adverse birth outcome, including 10% born before 33 weeks gestation and more than 5% stillborn. Although there have been significant improvements in under-5 mortality globally, neonatal mortality has not decreased at a similar pace and the WHO now considers addressing neonatal mortality a top priority [38, 39]. As preterm

delivery is the most common cause of neonatal mortality, it is critical to understand the underlying mechanism associating HIV, ART and adverse birth outcomes. Further exploration of current hypotheses linking ART to chronic placental insufficiency [22], decreased progesterone [40,41] and immunomodulatory dysfunction, (particularly Th1/Th2 shift [42]) are needed.

Our study has several strengths, including the large sample size and reasonable generalizability to the overall population since > 95% of women deliver in a hospital (including 25% of all births in Botswana at these 2 hospitals). There were few women with unknown HIV status, a high proportion of women received ARVs in pregnancy, and a large number of women were on ART prior to conception. However, there were potential limitations, including the fact that PMH and NRH are referral hospitals, and referral of high-risk pregnancies to these maternities may overestimate adverse birth outcomes in Botswana. A relatively high number of women were missing CD4 cell counts, particularly among women in the second surveillance period (2013-14) (when CD4 cell counts were not needed in order to initiate ART). Many variables were self-reported, including prior medical history, alcohol and tobacco use, and routine laboratory data, particularly RPR testing for syphilis, was inconsistently performed and reported. The gestational age of infants was estimated based primarily on LMP, which is not as reliable as early ultrasound. All information was abstracted from the medical records and we cannot confirm the accuracy of the recorded information. However, the maternity obstetric card is standardized throughout Botswana and prompts midwives to record specific information, and we found that information from the obstetric record was very complete. We do not believe there was any differential data entry error by ART regimen that would systematically bias the results of this large study.

Given the observational nature of our study, causation cannot be established and multiple sources of bias are possible. We tried to minimize lead-time bias by comparing only groups that had the same “at risk” time for an outcome, limiting comparisons of women on TDF/FTC/EFV at conception to women on other ART at conception and restricting the analysis of women initiating ARVs in pregnancy to those who did so prior to 30 weeks and only including outcomes occurring at or after 30 weeks. This was particularly important as it was protocol for ZDV to be initiated at 28 weeks of gestation, while there was no restriction on the initiation of TDF/FTC/EFV which occurred at a median of 21 weeks. Since TDF/FTC/EFV was initiated in women of all CD4 cell counts but 350 CD4 cells/mm^3 was used as a threshold for ZDV vs. other ART regimens, we tried to minimize bias by indication by restricting analysis of women initiating ARVs to appropriate CD4 strata. We also tried to minimize bias by confounding through adjusted analysis including covariates previously found to be associated with poor infant outcomes and using separate logistic regression models for each outcome as they may have different risk factors and different mechanisms. However, our associations could still be biased by unmeasured confounding, particularly as one CD4 cell count in pregnancy was the only measure of immune status available, and it is possible that nadir CD4 cell count, trend in CD4 cell count in pregnancy, or viral load might explain some differences.

In conclusion, this study provides reassuring observational data that implementing PMTCT programs with universal TDF/FTC/EFV is unlikely to worsen rates of SB, PTD and SGA

and may be associated with a decreased risk of SGA. The potential decrease in both overall adverse events and SGA with TDF/FTC/EFV needs to be confirmed by larger studies, and studies powered to evaluate potential associations between neural tube defects and TDF/FTC/EFV are also needed. This study also highlights the very high rates of adverse birth outcomes among HIV-infected pregnant women. Further understanding of the risk factors and mechanisms underlying poor outcomes in order to design appropriate interventions is a crucial step for decreasing neonatal mortality rates worldwide.

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Table 1
Baseline characteristics, HIV status and Birth Outcomes by Data Collection Period

	HIV-Uninfected		HIV-Infected	
	2009-2011	**2013-2014**	**2009-2011**	**2013-2014**
Maternal Characteristics				
Age (years)	25.3yrs	25.7yrs	28.9yrs	30.2yrs
Unmarried	85.5%	82.3%	87.5%	87.4%
None/Primary Education	7.3%	5.4%	15.2%	11.3%
No Salary	49. 5%	59.7%	51.6%	54.1%
Non-Citizen	12.9%	8.2%	9.2%	7.0%
Any Medical History	12.6%	13.7%	17.4%	19.5%
Hypertension in pregnancy	16.8%	16.7%	19.1%	17.5%
Anemia in pregnancy	35.9%	25.8%	59.0%	48.1%
Obstetric Characteristics				
Primiparous	48.1%	45.5%	20.6%	15.9%
Grand Multiparous (Gravida≥ 5)	5.6%	6.4%	13.5%	18.0%
Received NO prenatal care	4.1%	3.1%	5.7%	4.8%
Median gestational age	39 [37,40]	39 [37,40]	38 [36,40]	38 [36.40]
Mean birthweight	2992g	2992g	2775g	2781g
Birth Outcomes				
Stillbirth	2.7%	2.7%	4.9%	4.8%
Preterm Delivery	19.4%	18.5%	27.7%	28.0%
Very Preterm Delivery	6.2%	6.7%	10.3%	10.8%
Small for Gestational Age	12.2%	12.6%	26.8	17.6%
PMTCT Program Characteristics				
Unknown HIV status	n/a	n/a	4.7%	1.2%
No ARVs during Pregnancy			16.1%	12.3%
Initiated ARVs <4wks prior to delivery			24.7%	17.0%
Initiated ARVs <28wks GA			22.0%	59.8%
Initiated ARVs <28wks GA and CD4 <350			31.4%	75.3%
Days between HIV diagnosis and initiation of ARVs (mean)			65	39
Immunologic Profile				
Proportion with CD4 cell count recorded	n/a	n/a	44.8%	38.6%
Median CD4 cell count			388	415
Median CD4 cell count among women initiating ARVs by 30 weeks GA			391	391
Median CD4 cell count among women on ART at conception			388	500
Median CD4 cell count among women on no ARVs during pregnancy			345	365

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Table 2

Baseline Characteristics by PMTCT Regimen

	TDF/FTC/EFV at conception N=165	Other 3-drug ART at conception N=2006	TDF/FTC/EFV initiated in pregnancy N=1461	ZDV initiated in pregnancy N=2920	Other 3-drug ART initiated in pregnancy N= 760
Maternal Age (mean)	32.5yrs	32.3yrs	28.5yrs	27.6yrs	29.0yrs
Unmarried	137 (83%)	1619 (81%)	1290 (90%)	2600 (91%)	654 (89%)
No/Primary Education	25 (15%)	364 (18%)	101 (7%)	343 (12%)	86 (12%)
Unemployed	80 (48%)	868 (43%)	791 (57%)	1401 (52%)	305 (44%)
Non-Citizen	7 (4%)	40 (2%)	42 (3%)	135 (5%)	30 (4%)
Primiparous	9 (5%)	154 (8%)	344 (24%)	768 (26%)	180 (24%)
Grand Multiparous	47 (28%)	487 (24%)	172 (12%)	323(11%)	82 (11%)
Median Week of presentation to antenatal care (IQR)	18 [12,24]	17 [13,22]	17 [13,22]	20 [16,25]	18 [14,22]
Any Medical History	39 (24%)	386 (19%)	218 (15%)	354 (12%)	93 (12%)
Hypertension in Pregnancy	26 (16%)	423 (21%)	240 (16%)	494 (17%)	144 (19%)
Anemia in Pregnancy	42 (25%)	530 (26%)	484 (51%)	977 (55%)	317 (67%)
Antibiotics in pregnancy	60 (36%)	876 (44%)	680 (47%)	1382(48%)	367 (49%)
Low maternal weight (<50kg)	16 (10%)	199 (10%)	164 (11%)	294 (10%)	94 (12%)
Median CD4 cell count (IQR)[+]	475 [295,586]	426 [300,554]	393 [276,533]	429[324,568]	222 [158,349]

Excluding women with unknown time of initiation of ARVs (N=3), women on unknown ART regimens (N=467), women who changed ARVs during pregnancy (N=53) or had unknown change status (N=12)

[+]CD4 cell count was available in 32% of women on TDF/FTC/EFV at conception, 22% of women on other 3-drug ART at conception, 55% of women initiating TDF/FTC/EFV in pregnancy, 60% of women initiating ZDV in pregnancy and 65% of women on other 3-drug ART initiated in pregnancy.

Table 3

Adverse Birth Outcomes among women who initiated TDF/FTC/EFV compared with Other ARV regimens in Pregnancy

	CD4 <350[&]			CD4>350[&]			All CD4 Strata[~]		
	Initiated Atripla in pregnancy N=231	Initiated Other 3-drug ART in pregnancy[+] N=243	aOR (95%CI)	Initiated Atripla in pregnancy N=335	Initiated ZDV in pregnancy N=752	aOR (95% CI)	Initiated Atripla in Pregnancy N=1054	Initiated any other ARV in pregnancy N=2172	aOR (95%CI)
Stillbirth[$]	4(1.7%)	12(4.9%)	0.1 (0.01,1.0)	9 (2.7%)	21 (2.8%)	0.9 (0.4,2.1)	18 (1.7%)	70 (3.2%)	0.6 (0.3,1.3)
Preterm[$$] **<37wks**	45 (19.5%)	48(19.8%)	0.5 (0.2,1.2)	60 (17.9%)	123(16.4%)	1.1 (0.6,2.1)	192 (18.2%)	450 (20.7%)	0.7 (0.5,1.1)
Small for Gestational Age [$$$]									
Botswana Norms	24 (10.4%)	50 (20.6%)	0.5 (0.3,1.1)	53 (15.8%)	157 (20.9%)	0.6 (0.4,1.0)	125(11.9%)	459 (21.1%)	0.4 (0.3,0.6)
WHO Norms	35 (15.2%)	62 (25.5%)	0.5 (0.3,0.8)	83 (24.8%)	216 (28.7%)	0.7 (0.5,1.0)	202 (19.2%)	602 (27.7%)	0.5 (0.4,0.7)
Any Adverse Outcome[*]	61 (26%)	97 (40%)	0.4 (0.2,0.7)	104 (31%)	272 (36%)	0.4 (0.3,0.6)	287 (27%)	880 (41%)	0.4 (0.3,0.6)

Analysis is limited to women who initiated ARVs before 30 weeks of gestation and to events that occurred after 30 weeks of gestation and excludes women with unknown ART regimen (N=78), women who changed ARVs during pregnancy (N=19) or had unknown change of ARVs (N=9)

[&]Women with unknown CD4 cell count excluded from analysis

[~]Analysis Includes women with unknown CD4 cell count

[+]Other 3-drug ART regimens included ZDV/lamivudine (3TC)/nevirapine (NVP) (36%), unspecified ART (38%) which was likely mostly ZDV/3TC/NVP given National ARV guidelines, ZDV/3TC/Lopinavir/ritonavir (19%), TDF/FTC/NVP(4%), and other ART (3%).

[$]Among all women initiating Atripla (unrestricted by GA) total SB = 39/1461 (2.7%). Among all women initiating other ART (unrestricted by GA),total SB = 31/760 (4.1%). Among all women initiating ZDV (unrestricted by GA) total SB = 76/2920 (2.6%)

[$$]Among all women initiating Atripla (unrestricted by GA) total PTD = 318/1461 (21.8%). Among women initiating other ART (unrestricted by GA), total PTD = 172/760 (22.6%). Among women initiating ZDV (unrestricted by GA), total PTD = 598/2920 (20.5%).

[$$$]Among all women initiating Atripla (unrestricted by GA), total SGA = 178/1461 (12.2%). Among all women initiating other ART (unrestricted by GA), total SGA = 153/760 (20.1%). Among women initiating ZDV (unrestricted by GA), total SGA = 587/2920 (20.1%)

[*]Any adverse outcome is defined as any SB, PTD or SGA, but is less than the sum of the 3 outcomes because of overlap between PTD and SGA.

Table 4
Adverse Birth Outcomes among women on ART at Conception

	TDF/FTC/EFV at Conception N=165	Other 3-drug ART at Conception N=2006	OR (95% CI)	aOR (95% CI)
Stillbirth	8 (4.9%)	128 (6.4%)	0.7 (0.4,1.6)	0.4 (0.1,2.9)^
Preterm	47 (28%)	631 (31%)	0.9 (0.6, 1.2)	0.9 (0.3, 2.9)#
Very Preterm	17 (10%)	236 (12%)	0.9 (0.5, 1.5)	0.9 (0.1, 8.0)@
SGA				
Botswana norms	14 (8%)	476 (24%)	0.3 (0.2,0.5)	0.4 (0.1,1.4)~
WHO norms	22 (13%)	636 (32%)	0.3 (0.2,0.5)	0.3 (0.1, 1.0)~
Any Adverse Outcome+	55 (33%)	1030 (51%)	0.5 (0.4, 0.7)	0.5 (0.1, 1.2)*

Analysis excludes women with unknown ART regimen at conception (N=389), women who changed ART during pregnancy (N=34) and women who had unknown change of ART (N=3)

+ Any adverse outcome is defined as any SB, PTD or SGA, but is less than the sum of the 3 outcomes because of overlap between PTD and SGA.

^ adjusted for hypertension and CD4 cell count <250

adjusted for hypertension, anemia, low weight and CD4 cell count <250

@ adjusted for anemia, low weight and CD4 cell count <250

~ adjusted for maternal age, education, employment status, anemia, and CD4 cell count<200

* adjusted for any anemia, maternal age, low maternal weight, CD4 cell count <250

Table 5

Studies Comparing Adverse Birth Outcomes among women on ART vs. Zidovudine-monotherapy

	Fowler et al., CROI 2015 [30]	Sibiude et al, CID 2012 [31]	Chen et al, JID 2012 [15]	Kesho Bora Study Group, Lancet 2011 [32]	Briand et al, AIDS 2009 [33]	Townsend et al, AIDS 2007 [18]
Study Design (name)	RCT (PROMISE)	Observational cohort (ANRS)	Birth Surveillance	RCT (Kesho Bora)	Observational cohort (ANRS)	National Birth Surveillance (NSHPC)
Region	5 African countries and India (14 sites)	France (90 sites)	Botswana (6 sites)	Kenya, Burkina Faso and South Africa (5 sites)	France (90 sites)	UK and Ireland
Years	2011-2014	1990-2009	2009-2011	2005-2008	1990-2006	1990-2005
Total Births on ARVs (N)	3,523	11,377	7,915	824	8,192	4,445
Overall Rate of:						
Stillbirth	NR	NR	4.6%	1.0%	NR	1.0%
Preterm	17.1%	12.9%	19.6%	12.2%	NR	13.3%
LBW	15.4%	NR	18.4% (SGA*)	9.4%	4.1% (SGA^)	NR
Antiretroviral Comparison	ZDV-mono vs. ZDV/3TC/LPV-r vs. TDF/FTC/LPV-r Initiated during pregnancy	ZDV-mono vs. ART (19% PI-based, 81% non-PI based) Initiated during and prior to pregnancy	ZDV-mono vs. ART (87% ZDV/3TC/NVP, 9% ZDV/3TC/LPV-r) Initiated during pregnancy	ZDV-mono vs. ZDV/3TC/LPV-r Initiated during pregnancy	ZDV-mono vs. ART (77% PI-based, 15% NNRTI-based, 5% triple NRTI) Initiated during and prior to pregnancy	Mono/Dual (85% ZDV) vs. ART (54% NNRTI-based, 37% PI-based, 6.7% NNRTI- and PI-based, 2% NRTI-only) Initiated during and prior to pregnancy
CD4 count	Median Overall: 530 cells/uL Eligible only if >350 cells/uL	>500 cells/uL: 45.5% (ZDV), 35.8% (ART) <200 cells/uL: 8.5% (ZDV), 10.1% (ART)	Median ZDV: 428 cells/uL Median ART: 225 cells/uL	Median ZDV: 339 cells/uL Median ART: 336 cells/uL Eligible only if 200-500 cells/uL	>350 cells/uL: 59% <200 cells/uL: 8.2%	>500 cells/uL: 48% (Mono/Dual, 30% (ART) <200 cells/uL: 15% (Mono/Dual), 15%(ART)
Stillbirth	NR	NR	ZDV: 1.7% ART: 4.7% aOR: 2.5 (1.6-3.9)	NR	NR	Mono/Dual: 0.57% ART: 1.27% aOR: 2.27 (0.96, 5.41)
Preterm Delivery (<37wks GA)	1. ZDV: 13.1% 2. ZDV/3TC/LPV-r: 19.7% 3. TDF/FTC/LPV-r: 19.4%	ZDV: 9.6% ART: 14.7% aOR: 1.69 (1.38, 2.07)	ZDV: 14.2% ART*:19.8% aOR:1.4 (1.2-1.8)	ZDV: 11% ART: 13% P=0.39	NR	Mono/Dual: 10.1% ART: 14.1% aOR: 1.51 (1.19,1.93)

	Fowler et al., CROI 2015 [30]	Sibiude et al, CID 2012 [31]	Chen et al, JID 2012 [15]	Kesho Bora Study Group, Lancet 2011 [32]	Briand et al, AIDS 2009 [33]	Townsend et al, AIDS 2007 [18]
LBW (<2500g)	1 vs. 2: p=.04 1 vs. 3: p=.09 1. ZDV: 13.1% 2. ZDV/3TC/LPV-r: 19.7% 3. TDF/FTC/LPV-r: 19.4% 1 vs. 2: p=.04 1 vs. 3: p=.09	NR	SGA (<10th%tile) ZDV:14.2% ART*:21.5% aOR:1.5 (1.2-1.9)	ZDV: 7% ART: 11% P=0.06	SGA (<3rd %tile) ZDV: 4.0% ART: 3.9% aOR: 1.04 (0.77,1.42)	BW standardized to GA Mono/Dual: Z-score 0.06 ART: Z-score -0.06 P=0.002
Other Outcome	Severe Adverse Outcomes# 1. ZDV: 6.7% 2. ZDV/3TC/LPV-r: 4.3% 3. TDF/FTC/LPV-r: 9.2% 1 vs. 3: p=0.06 2 vs. 3: p=0.04					

ARVs= antiretrovirals, LBW= low birthweight, SGA=, NR=Not Reported, RCT= randomized control trial, ZDV= zidovudine, 3TC=lamivudine, LPV-r= lopinavir/ritonavir, TDF= tenofovir, FTC=emtricitabine, NVP= nevirapine, ZDV-mono= ZDV monotherapy, Mono/Dual= ZDV-monotherapy or dual NRTI therapy, BW= birthweight, GA=gestational age.

*SGA defined as <10th %tile for GA.

^SGA defined as <3rd %tile for GA.

#Severe Adverse Outcomes include very PTD <34wks, very LBW <1500g and/or stillbirth.