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Emulating a target trial of antiretroviral therapy regimens started before conception and risk of adverse birth outcomes

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Abstract

Objective—To compare the effect of pre-conception initiation of zidovudine, lamivudine, nevirapine (ZDV/3TC/NVP) versus tenofovir, emtricitabine, efavirenz (TDF/FTC/EFV) on adverse birth outcomes.

Design—Emulation of a hypothetical (target) trial using a birth surveillance study in Botswana during an era of CD4-based antiretroviral therapy (ART) initiation.

Methods—In women who initiated ART <3 years from HIV diagnosis, conceived 0.5–5 years after ART initiation, and delivered ≥24 weeks gestation, we estimated risk ratios for stillbirth, preterm delivery (<37 weeks), very preterm delivery (<32 weeks), small-for-gestational-age (SGA) (<10%tile), very SGA (<3%tile), and any adverse or severe birth outcome for first-line ZDV/3TC/NVP vs. TDF/FTC/EFV. We conducted a historical comparison in women who initiated TDF/FTC/EFV in 2012–2015 and ZDV/3TC/NVP in 2004–2011, and a contemporaneous comparison in an era of overlapping use from 2009–2013.

Results—In the historical comparison, 1108 women initiated TDF/FTC/EFV and 637 initiated ZDV/3TC/NVP. In the contemporaneous comparison, 1052 initiated TDF/FTC/EFV and 298

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initiated ZDV/3TC/NVP. TDF/FTC/EFV initiators were younger and more likely to be nulliparous than ZDV/3TC/NVP initiators in both comparisons. In the historical comparison, the adjusted risk ratios (95% CI) comparing ZDV/3TC/NVP with TDF/FTC/EFV were 2.95 (1.76, 4.96) for stillbirth, 1.40 (1.17, 1.67) for preterm delivery, 2.58 (1.70, 3.91) for very preterm delivery, 1.96 (1.64, 2.34) for SGA, 2.32 (1.73, 3.09) for very SGA, 1.54 (1.38, 1.72) for any adverse birth outcome, and 2.20 (1.76, 2.75) for any severe birth outcome, and were similar in the contemporaneous comparison.

Conclusions—Pre-conception initiation of ZDV/3TC/NVP compared with TDF/FTC/EFV may increase the risk of adverse birth outcomes.

Keywords

Stillbirth; Preterm Delivery; Small for Gestational Age; Antiretroviral Therapy; Observational Study; Pregnancy

Introduction

Maternal antiretroviral treatment (ART) in pregnancy has been shown to increase the risk of adverse birth outcomes, including stillbirth, preterm delivery, and small-for-gestational-age (SGA) infants in randomized clinical trials[1, 2]. Recent findings suggest that the risk varies across drugs or regimens, and that outcomes may be worse among infants exposed to ART from conception[2–6]. Ideally, a randomized trial would assign women to one of several commonly prescribed ART regimens before conception and compare birth outcomes between groups, but such a trial is not feasible. Therefore, observational data need to be used to emulate such a trial[7–9].

Our previous analyses of observational data from Botswana found an increased risk of adverse birth outcomes among infants exposed to ART from conception[4, 10], and suggested that exposure to zidovudine (ZDV), lamivudine (3TC), and nevirapine (NVP) in combination had significantly higher risk for all adverse birth outcomes than exposure to tenofovir (TDF), emtricitabine (FTC), and efavirenz (EFV) in combination[6]. However, we cannot exclude the possibility that these results were influenced by residual confounding: women initiated these regimens at different CD4 cell count thresholds, those on NVP-based ART had received it for a longer duration in contemporaneous comparisons, and the risk for adverse birth outcomes may have changed over time. Also, our previous analyses included only a subset of the surveillance datasets that are currently available from Botswana.

Here we describe two alternative approaches to emulate a (hypothetical) target trial of ZDV/3TC/NVP vs. TDF/FTC/EFV: 1) an historical comparison, and 2) a contemporaneous comparison. Each of these approaches addresses a critical component of confounding in the emulation of the target trial. The historical comparison is less susceptible to bias from differences between groups of women initiating each treatment, but susceptible to time trends in prescription patterns and adverse birth outcomes. The contemporaneous comparison is immune to bias from time trends, but is susceptible to bias from differences between groups of women. Because our analyses combine all surveillance data from Botswana, our estimates are more precise than those previously published.

Methods

Data sources

From 2009–2011, data were collected at 6 government maternity sites (Princess Marina Hospital in Gaborone, Scottish Livingstone Hospital in Molepolole, Deborah Retief Memorial Hospital in Mochudi, Nyangabgwe Hospital in Francistown, Letsholathebe Memorial Hospital in Maun, and Ghanzi Primary Hospital)[10] and in 2014–2016 data were collected at 5 of these same sites plus 3 similar sites (Princess Marina Hospital, Nyangabgwe Hospital, Letsholathebe Memorial Hospital, Scottish Livingstone Hospital, Ghanzi Primary Hospital, Sekgoma Memorial Hospital in Serowe, Selebi-Phikwe Goverment Hospital, and Mahalapye Hospital)[4]. The surveillance hospitals are geographically diverse and capture ~ 45% of births nationwide. In Botswana, approximately 95% of women deliver in a hospital.

Our data are restricted to approximately 80,000 women who delivered at ≥24 weeks gestation at these hospitals, of which approximately 20,000 were HIV-infected. We collected information on HIV status, date of HIV diagnosis, ART start date, ART regimen, medical and obstetric history, and birth outcomes as documented in the obstetric cards. The estimated gestational age was documented by nurses at the time of delivery, generally using the last menstrual period and confirmed by ultrasound (~10%) when available. If the last menstrual period date was unknown or suspected to be incorrect, fundal height measurements were occasionally used by the midwives to estimate gestational age.

In Botswana, the recommended first-line three-drug ART regimen changed from ZDV/3TC/NVP to TDF/FTC/EFV in 2012[11]. At this time, the recommended threshold at which ART initiation was initially offered to non-pregnant women also changed from CD4≤250 cells/mm^3 to CD4≤350 cells/mm^3.

The protocol of the target trial

The protocol of our target trial to compare the effect of initiating ART regimens pre-conception on birth outcomes is as follows:

Eligibility criteria—The target trial includes non-pregnant women living in Botswana in or after 2004 who were diagnosed with HIV within the previous 3 years.

Treatment strategies—Initiation of either TDF/FTC/EFV or ZDV/3TC/NVP. Ideally, the hypothetical study intervention would also include conception between 6 months (to allow sufficient time for CD4 cell count reconstitution) and 5 years after randomization (ART initiation) and a birth outcome at ≥24 weeks at a surveillance hospital site in Botswana.

Treatment assignment—Eligible women are randomly assigned to initiate either TDF/FTC/EFV or ZDV/3TC/NVP.

Outcomes—The primary outcomes of interest include stillbirth, defined as fetal death ≥24 weeks gestation with an Apgar score of 0,0,0; preterm delivery (delivery <37 weeks gestation); very preterm delivery (delivery <32 weeks gestation); SGA (<10th percentile of

birth weight using WHO norms); and very SGA (<3rd percentile of birth weight using WHO norms)[12, 13]. The combined endpoint of any adverse birth outcome includes stillbirth, preterm delivery, or SGA and the combined endpoint of any severe adverse birth outcome includes stillbirth, very preterm delivery, or very SGA.

Follow-up period—Women are followed from ART initiation (randomization) until discharge from the maternity ward.

Causal contrast of interest—To compare the two treatment strategies, we estimate the modified intention-to-treat effect of initiating ZDV/3TC/NVP versus TDF/FTC/EFV on each of the outcomes of interest, i.e., the effect among those who became pregnant 6 months to 5 years after randomization.

Analysis plan—For each birth outcome, we fit a log-binomial regression model to estimate the risk ratio of the birth outcome of interest comparing ZDV/3TC/NVP with TDF/FTC/EFV. When the log-binomial model fails to converge we instead fit a Poisson regression model with robust variance[14].

Sensitivity analyses for selection bias—The target trial is susceptible to selection bias because individuals are excluded from the analysis based on events that occur after baseline (randomization). Women who do not become pregnant, become pregnant but not between 6 months and 5 years of ART initiation, become pregnant but miscarry or deliver <24 weeks gestation, do not have a birth outcome at ≥24 weeks gestation at a hospital site in Botswana, deliver twins or triplets, or have missing data for the outcome of interest are excluded from our analysis. In sensitivity analyses, we vary the time from ART initiation to pregnancy window (e.g., allowing a pregnancy date between 0 days and 12 years after ART initiation in the most extreme case), including the first birth among women who deliver twins or triplets, and using inverse probability of censoring weights to adjust for potential selection bias due to incomplete data on birth outcomes.

Emulation of the target trial using observational data

We emulated the target trial by using the combined dataset of our birth outcomes surveillance studies.

Eligibility criteria, Treatment strategies, Follow-up, Outcome, Causal contrasts —Same as in the target trial

Treatment assignment—We conducted two emulations of the randomization component of the target trial to adjust for confounding at the design stage:

1. Historical comparison: Women who initiated TDF/FTC/EFV in 2012–2015, while it was the recommended treatment regimen, and women who initiated ZDV/3TC/NVP in 2004–2011, while it was the recommended treatment regimen.

2. Contemporaneous comparison: Women who initiated TDF/FTC/EFV or ZDV/3TC/NVP in 2009–2013, during an era when both regimens were prescribed.

The historical comparison is less likely to be affected by confounding by indication since the analysis compares generally similar women, but may be affected by temporal trends in adverse birth outcomes. The contemporaneous comparison is less likely to be biased due to time trends in adverse birth outcomes but may be biased if there is confounding by indication that is not successfully adjusted for in the analysis stage, for example, if a clinician prescribes a non-standard regimen to an individual for reasons not collected in the data. The primary difference between women offered ART in different treatment eras was a change in the CD4 cell count threshold at which ART was initially offered to non-pregnant women: from CD4≤200 cells/mm^3 to CD4≤250 cells/mm^3 in 2008 and from CD4≤250 cells/mm^3 to CD4≤350 cells/mm^3 in 2012[11].

Analysis plan—The analysis was the same as in the target trial except that we included the following prognostic factors in our models, which are also predictors of ART treatment regimen[4, 6, 10]: year of ART initiation (2009–2011, 2012–2013; contemporaneous comparison only), time from HIV diagnosis to ART initiation (1 year or less, more than 1 year), age at ART initiation (<25 years, 25–30 years, ≥30 years, unknown), marital status (married, unmarried or unknown), occupation (salaried, unsalaried or unknown), education (none or primary, more than primary, unknown), and parity (0, 1 or more, unknown).

To determine whether there may have been time trends in adverse birth outcomes in Botswana during the time-period of interest, we used data from the HIV-negative women enrolled in the birth outcomes surveillance study and calculated the risk of each adverse birth outcome by calendar year.

Sensitivity analyses—Like the target trial, our emulation is susceptible to selection bias because individuals are excluded from the analysis based on events that occur after baseline (randomization). We performed the same sensitivity analyses for selection bias as in the target trial.

We performed several additional sensitivity analyses for confounding. To explore whether our results could be explained by variations in CD4 cell count across the two treatment groups, we restricted the analysis to the subset of individuals with reconstituted CD4 cell counts (≥200 cells/mm^3) during pregnancy, and to a limited treatment era with the same CD4 cell count threshold for initiating ART (≥250 cells/mm^3) (2008–2011). Other sensitivity analyses are described in Appendix 1.

Due to concerns about measurement error in the last menstrual period documented at the first antenatal care visit, the date of conception was estimated using the reported gestational age at birth and the recorded delivery date in the primary analysis and using the documented last menstrual period in a sensitivity analysis.

Statistical analyses were performed using SAS, version 9.3 (SAS institute, Cary, NC).

Ethical Approval

Ethical approval for this study was granted by Human Research and Development Council in Botswana and by the Harvard T.H. Chan School of Public Health in Boston.

Results

Historical comparison

Of 21,640 HIV-positive women who delivered at one of the selected hospitals at ≥24 weeks gestation, 4,850 (22%) started ART within 3 years of HIV diagnosis while non-pregnant. There were 1,249 women who started TDF/FTC/EFV in 2012–2015 and 1,594 women who started ZDV/3TC/NVP in 2004–2011. Of these, 1,108 women who started TDF/FTC/EFV and 637 women who started ZDV/3TC/NVP had a pregnancy date between 6 months and 5 years after starting ART, a birth outcome at ≥24 weeks, and delivered a singleton birth (Figure 1, Table 1). Compared with women who initiated ZDV/3TC/NVP, women who initiated TDF/FTC/EFV were more likely to have attained a higher level of education, be younger than 25 years of age and be nulliparous. The median number of days from HIV diagnosis to ART initiation was greater among those who initiated ZDV/3TC/NVP compared with those who initiated TDF/FTC/EFV (Table 2). Among women with data on CD4 cell count in pregnancy (25%), the median (IQR) first CD4 cell count during pregnancy was 487 (374, 618) cells/mm^3 for women who initiated TDF/FTC/EFV and 408 (282, 533) for women who initiated ZDV/3TC/NVP cells/mm^3.

Information on birth outcomes was recorded in almost all women included in the study (100% for stillbirth, 98–100% for preterm delivery depending on how date of conception was defined, and 98% for SGA). Of the women included in the analysis, 67 had a stillbirth (3.8%), 395 delivered preterm (22.6%), 90 delivered very preterm (5.2%), 402 delivered an SGA infant (23.4%), 183 delivered a very SGA infant (10.7%), 742 had an adverse birth outcome (42.9%) and 285 had a severe adverse birth outcome (16.5%) (Table 3). The total counts for very preterm delivery, very SGA, and severe adverse birth outcome are included in the total counts for preterm delivery, SGA, and adverse birth outcome, respectively. Comparing ZDV/3TC/NVP with TDF/FTC/EFV, the adjusted risk ratios were 2.95 (1.76, 4.96) for stillbirth, 1.40 (1.17, 1.67) for preterm delivery, 2.58 (1.70, 3.91) for very preterm delivery, 1.96 (1.64, 2.34) for SGA, 2.32 (1.73, 3.09) for very SGA, 1.54 (1.38, 1.72) for any adverse birth outcome and 2.20 (1.76, 2.75) for any severe birth outcome (Table 3).

None of the sensitivity analyses yielded appreciably different results (Appendix Tables 1–2).

Contemporaneous comparison

There were 1,186 women who started TDF/FTC/EFV and 491 women who started ZDV/3TC/NVP between 2009–2013. Of these, 1,052 women who started TDF/FTC/EFV and 298 women who started ZDV/3TC/NVP had a pregnancy date between 6 months and 5 years after starting ART and delivered a singleton birth at ≥24 weeks (Figure 1, Table 1). The baseline characteristics of women in the contemporaneous comparison were similar to those of women in the historical comparison (Table 2). Compared with women who initiated ZDV/3TC/NVP, women who initiated TDF/FTC/EFV were more likely to have initiated

ART in the later calendar years of this restricted time period. Among women with data on CD4 cell count in pregnancy (23%), the median (IQR) first CD4 cell count during pregnancy was 480 (368, 613) cells/mm^3 for women who initiated TDF/FTC/EFV and 448 (367, 597) cells/mm^3 for women who initiated ZDV/3TC/NVP.

The risks of adverse birth outcomes were similar in the contemporaneous comparison and the historical comparison. The adjusted risk ratios were slightly smaller for very preterm delivery and very SGA in the contemporaneous comparison compared with the historical comparison, but were otherwise very similar (Table 3).

HIV-negative women

To evaluate historical trends in birth outcome, we also evaluated HIV-negative women in each study era. Information on birth outcomes for 57,491 HIV-negative women was included in the BHP birth outcomes surveillance study for the years 2009 to 2016. The risk of adverse birth outcomes decreased over calendar time, from 2.54% in 2009–2011 to 2.13% in 2014–2016 for stillbirth (overall risk: 2.30%), from 20.15% in 2009–2011 to 15.78% in 2014–2016 for preterm delivery (overall risk: 17.54%), and from 17.02% in 2009–2011 to 15.20% in 2014–2016 for SGA (overall risk: 15.92%) (Table 4). These patterns were similar when restricting to the 5 study sites included in all surveillance years.

Discussion

We combined two large observational datasets from Botswana to emulate a randomized trial comparing adverse birth outcomes among women initiating ZDV/3TC/NVP and TDF/FTC/EFV prior to conception. Our findings suggest that pre-conception initiation of ZDV/3TC/NVP compared with TDF/FTC/EFV increases the risk of all adverse and severe adverse birth outcomes. The risk of stillbirth after initiating ZDV/3TC/NVP was approximately 3-times the risk of stillbirth after initiating TDF/FTC/EFV, and the risk of any severe adverse birth outcome after initiating ZDV/3TC/NVP was approximately 2-times the risk of any severe adverse birth outcome after initiating TDF/FTC/EFV. To address competing sources of bias we performed historical and contemporaneous comparisons, and our results were similar across all analyses and with those found in a previous study using data from 2014–2016[6].

In the absence of large randomized trials to study drug safety, observational data can be used to emulate a target trial. Outlining the protocol of the target trial and its emulation using observational data makes key components of the study explicit, avoids common biases in observational data analyses, and facilitates a discussion about the limitations of the data. By evaluating how successfully we can emulate each component of the target trial in our observational data, we can attempt to explain how our results may differ from those that would be observed if the target trial could be performed as outlined in the protocol.

A key challenge in emulating a target trial is adjusting for confounding. In this paper, we described two alternative approaches to emulate the randomization of a target trial when confounding adjustment is questionable. The historical comparison compares individuals who initiated the treatment strategy that was recommended by the guidelines at the time they

initiated treatment and the contemporaneous comparison compares individuals who initiated the two treatments during the same time-period. Each approach isolates a potential source of confounding: differences between individuals initiating one treatment compared with another and time-trends in the outcome of interest.

The validity of the historical comparison relies on the assumption that women who initiated TDF/FTC/EFV while it was the recommended treatment regimen (2012–2015) and women who initiated ZDV/3TC/NVP while it was the recommended treatment regimen (2004–2011) are comparable. This assumption may not hold if characteristics of women starting ART changed over calendar time. This is unlikely since the demographics of women included in these comparisons were generally similar by treatment era (Table 2), and small differences between age, time from HIV diagnosis to ART initiation, education, and parity were adjusted for in the analysis. However, because ART was offered at lower CD4 cell count thresholds earlier in the epidemic, it *is* likely that women initiating ART in 2004–2011 had lower nadir CD4 cell counts compared with women initiating ART in 2012–2015. While information on nadir CD4 cell count was not available in our study, we limited potential confounding by disease severity by restricting the analysis to women who became pregnant at least 6 months after initiating ART (to allow sufficient time for CD4 cell count reconstitution) in our primary analysis; restricting our analysis to the subset of individuals with reconstituted CD4 cell counts (≥200 cells/mm^3) during pregnancy in sensitivity analyses; and performing a sensitivity analysis restricted to the time period when ART was started at the same CD4 cell count threshold. Lastly, the historical comparison may also be affected by improvements in birth outcomes in Botswana over time, which appeared to be the case among HIV-negative women evaluated in our parallel analysis. However, these relative differences in outcomes over time were insufficient to explain the much larger differences observed by ART exposure groups.

The validity of the contemporaneous comparison relies on the assumption that restricting the analysis to 2009–2013 eliminated confounding by calendar year. This may not be the case if prescription patterns changed and there were time-trends in adverse birth outcomes within this period. The contemporaneous comparison was designed explicitly to reduce confounding by calendar time, but the validity of its results also depends on the assumption of no residual confounding in general.

In both comparisons, measurement error for preterm delivery and SGA was possible since gestational age was calculated using the recorded last menstrual period date and maternity nurse assessment, but it is unlikely that this error would be differential with respect to ART regimen (the error may affect absolute risk estimates but likely would not affect relative risk estimates). Finally, selection bias in our study was possible since individuals were excluded from the analysis based on events that occurred after baseline. Our results did not materially change in sensitivity analyses designed to adjust for this potential selection bias, but we were not able to adjust for potential selection bias due to the exclusion of women who did not become pregnant or did not have a birth outcome at ≥24 weeks gestation at one of the 8 hospital sites. To our knowledge there is no biological rationale or evidence in the literature for an association between these two ART regimens and the ability to conceive.

The mechanisms by which ZDV/3TC/NVP may increase the risk of adverse birth outcomes compared with TDF/FTC/EFV have been discussed previously[6]. One potential explanation is that ART could affect fetal growth through differential effects on the health of the placenta[15], which is supported by the larger risk ratio comparing the two regimens for SGA than for preterm birth. Our findings differ somewhat from the PROMISE trial[2], which found an increased risk of severe adverse birth outcomes after initiation of ritonavir-boosted lopinavir paired with TDF/FTC versus ZDV/3TC among women with CD4>350 cells/mm^3 randomized after 14 weeks of pregnancy. However, this discrepancy could be explained by different baseline CD4 cell counts, pre-conception versus post-conception treatment initiation, or a potential interaction between TDF and the boosted lopinavir used in the PROMISE trial.

Our analysis included women in Botswana who initiated antiretroviral therapy according to CD4-based initiation guidelines. Although sensitivity analyses by CD4 count thresholds yielded similar results, the effect estimates we observed may differ from the present era where ART is initiated earlier. In addition, our study design required 6 months on ART before conception, possibly excluding women with the lowest CD4 cell counts.

The proposed alternative approaches to emulate the randomized treatment assignment of a target trial may be useful for other studies of drug safety in pregnancy, and for the field of HIV in general as treatment options change over time in developing world settings where the medical standard of care may be improving. For example, when a new drug therapy becomes available but the comparative safety of the standard drug versus the new drug remains unknown, historical and contemporaneous comparisons may be useful to isolate key sources of confounding.

In summary, we conducted two emulations of a target trial to compare the safety of pre-conception initiation of ZDV/3TC/NVP compared with TDF/FTC/EFV on adverse birth outcomes in Botswana. These emulations confirmed previous findings that pre-conception initiation of ZDV/3TC/NVP compared with TDF/FTC/EFV results in an increased risk of adverse and severe adverse birth outcomes. This methodology addresses the concern that previous results could be partly explained by unadjusted confounding, and adds to the growing body of literature suggesting a harmful effect of *in utero* exposure to ZDV/3TC/NVP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ECC, RZ, DLJ, MAH, and RLS conceived and designed the study. ECC performed the statistical analysis with additional input from RZ, DLJ, MAH, and RLS. ECC drafted the manuscript with additional content contributions from RZ, DLJ, MAH, and RLS. All authors contributed to review of the manuscript and all authors read and approved the final manuscript.

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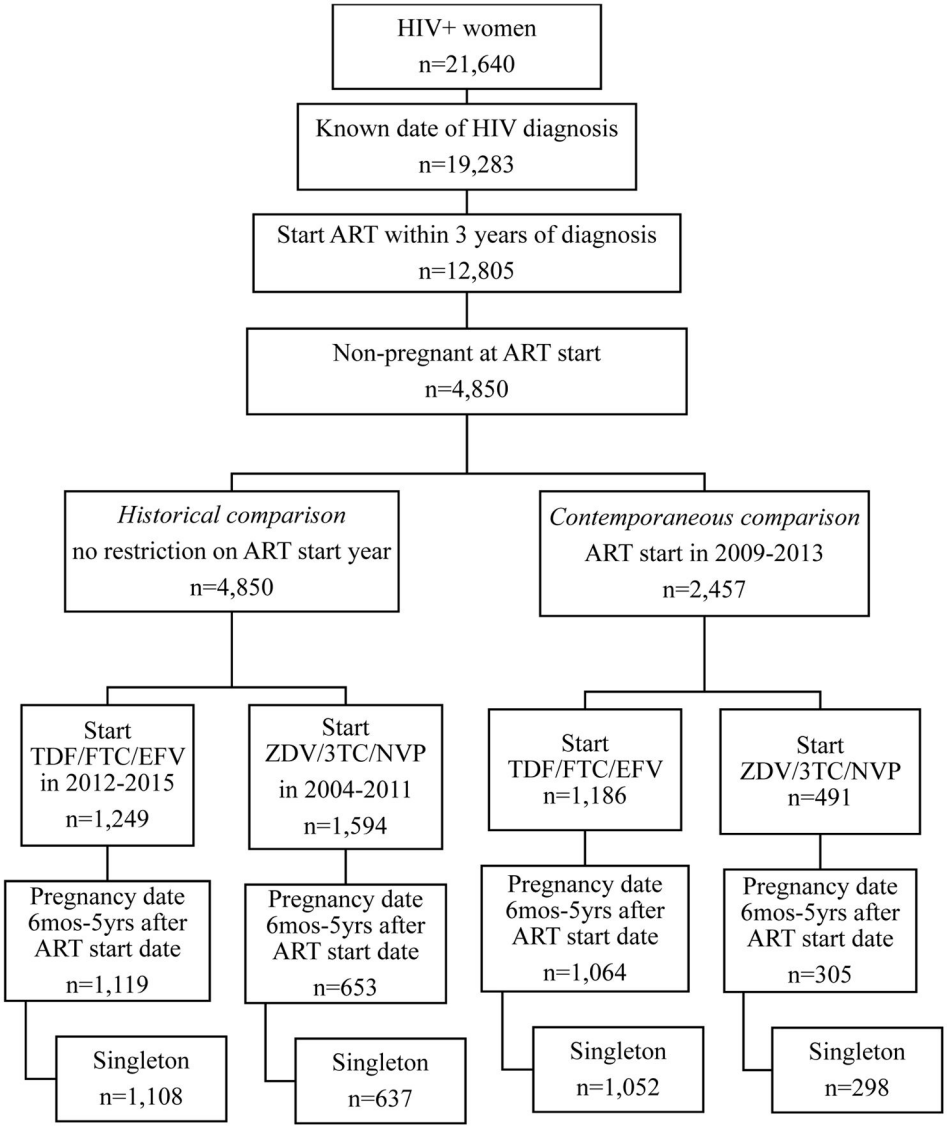

Figure 1.

Eligibility criteria for historical comparison and contemporaneous comparison

*Our study includes HIV positive women who delivered at ≥24 weeks of pregnancy

Table 1

Year of initiation for TDF/FTC/EFV regimens vs. ZDV/3TC/NVP regimens, Botswana birth outcomes surveillance study, 2004–2016.

Year	Recommended CD4 threshold for ART initiation	Number initiated TDF/FTC/EFV	Number initiated ZDV/3TC/NVP
2004	200 cells/mm^3	0	4
2005	200 cells/mm^3	0	65
2006	200 cells/mm^3	0	117
2007	200 cells/mm^3	0	90
2008	250 cells/mm^3	4	117
2009	250 cells/mm^3	9	92
2010	250 cells/mm^3	58	77
2011	250 cells/mm^3	110	75
2012	350 cells/mm^3	419	42
2013	350 cells/mm^3	456	12
2014	350 cells/mm^3	214	0
2015	350 cells/mm^3	19	1

Historical comparison is in grey, Contemporaneous comparison is boxed

Note that the recommended treatment regimen changed from ZDV/3TC/NVP to TDF/FTC/EFV in 2012

Table 2

Characteristics of mother by type of regimen, Botswana birth outcomes surveillance study, 2004–2016

	Historical comparison Number (%)		Contemporaneous comparison Number (%)	
Characteristic	**TDF/FTC/EFV n=1,108**	**ZDV/3TC/NVP n=637**	**TDF/FTC/EFV n=1,052**	**ZDV/3TC/NVP n=298**
Year of ART initiation				
2004–2008	--	393 (61.7)	--	--
2009–2011	--	244 (38.3)	177 (16.8)	244 (81.9)
2012–2013	875 (79.0)	--	875 (83.2)	54 (18.1)
2014–2015	233 (21.0)	--	--	--
Time from HIV diagnosis to ART initiation				
1 year or less	964 (87.0)	507 (79.6)	931 (88.5)	248 (83.2)
More than 1 year	144 (13.0)	130 (20.4)	121 (11.5)	50 (16.8)
Median (IQR) number of days (when month of HIV diagnosis is known)	17 (0, 62) n=178	187 (26, 365) n=483	10 (0, 61) n=138	90 (49, 366) n=94
Age at ART initiation				
Less than 25 years	358 (32.3)	168 (26.4)	328 (31.2)	79 (26.5)
25–30 years	322 (29.1)	222 (34.9)	306 (29.1)	104 (34.9)
30 years or older	395 (35.7)	224 (35.2)	387 (36.8)	99 (33.2)
Unknown	33 (3.0)	23 (3.6)	31 (3.0)	16 (5.4)
Median (IQR) years	28 (23, 32)	28 (25, 32)	28 (24, 32)	28 (25, 32)
Marital status				
Married	95 (8.6)	71 (11.2)	86 (8.2)	29 (9.7)
Single, widowed, divorced, unknown	1,013 (91.4)	566 (88.9)	966 (91.8)	269 (90.3)
Occupation				
Salaried	411 (37.1)	238 (37.4)	383 (36.3)	113 (37.9)
Student, housewife, none, unknown	697 (62.9)	399 (62.6)	669 (63.6)	185 (62.1)
Education				
None or primary	137 (12.4)	139 (21.8)	129 (12.3)	48 (16.1)
Secondary or more	943 (85.1)	465 (73.0)	892 (84.8)	235 (78.9)
Unknown	28 (2.5)	33 (5.2)	31 (3.0)	15 (5.0)

	Historical comparison Number (%)		Contemporaneous comparison Number (%)	
Characteristic	**TDF/FTC/EFV n=1,108**	**ZDV/3TC/NVP n=637**	**TDF/FTC/EFV n=1,052**	**ZDV/3TC/NVP n=298**
Parity				
0	136 (12.3)	9 (1.4)	116 (11.0)	8 (2.7)
1 or more	971 (87.6)	601 (94.4)	935 (88.9)	281 (94.3)
Unknown	1 (0.1)	27 (4.2)	1 (0.1)	9 (3.0)

Table 3

Risk ratio of birth outcomes by regimen, Botswana birth outcomes surveillance study, 2004–2016.

		Historical comparison			Contemporaneous comparison		
Outcome	**Regimen**	**Number of individuals**	**Events, number**	**Adjusted* Risk Ratio (95% CI)**	**Number of individuals**	**Events, number**	**Adjusted* Risk Ratio (95% CI)**
Stillbirth	TDF/FTC/EFV	1,108	25	Ref	1,052	19	Ref
	ZDV/3TC/NVP	637	42	2.95 (1.76, 4.96)	298	18	3.30 (1.75, 6.22) **
Preterm delivery (<37 weeks)	TDF/FTC/EFV	1,108	219	Ref	1,052	210	Ref
	ZDV/3TC/NVP	637	176	1.40 (1.17, 1.67)	298	85	1.43 (1.15, 1.77)
Very preterm (<32 weeks)	TDF/FTC/EFV	1,108	37	Ref	1,052	30	Ref
	ZDV/3TC/NVP	637	53	2.58 (1.70, 3.91)	298	18	2.03 (1.17, 3.51) **
SGA (<10th %tile)	TDF/FTC/EFV	1,096	198	Ref	1,039	188	Ref
	ZDV/3TC/NVP	622	204	1.96 (1.64, 2.34)	295	94	1.82 (1.47, 2.26)
Very SGA (<3rd %tile)	TDF/FTC/EFV	1,096	84	Ref	1,039	80	Ref
	ZDV/3TC/NVP	622	99	2.32 (1.73, 3.09)	295	37	1.77 (1.21, 2.57)
Any adverse birth outcome (Stillbirth, Preterm, SGA)	TDF/FTC/EFV	1,098	398	Ref	1,042	380	Ref
	ZDV/3TC/NVP	630	344	1.54 (1.38, 1.72)	296	163	1.51 (1.33, 1.73)
Any severe adverse birth outcome (Stillbirth, Very preterm, Very SGA)	TDF/FTC/EFV	1,097	130	Ref	1,041	119	Ref
	ZDV/3TC/NVP	630	155	2.20 (1.76, 2.75)	296	59	1.85 (1.38, 2.47)

*Adjusted for years from HIV diagnosis to ART initiation, age, marital status, occupation, education, and parity

**Adjusted for years from HIV diagnosis to ART initiation, age, occupation, education, and parity only

Table 4

Risk of stillbirth, preterm delivery, and delivering small for gestational age infants by year in the HIV-negative population, Botswana birth outcomes surveillance study, 2009–2016.

	Stillbirth			Preterm birth			Small for gestational age		
Year	**# recorded**	**# of deliveries**	**risk (%)**	**# recorded**	**# of deliveries**	**risk (%)**	**# recorded**	**# of deliveries**	**risk (%)**
2009	128	4,094	3.13%	885	4,097	21.60%	716	3,876	18.47%
2010	349	14,174	2.46%	2,810	14,176	19.82%	2,298	13,651	16.83%
2011	105	4,609	2.28%	915	4,609	19.85%	729	4,461	16.34%
2014	139	5,999	2.32%	910	5,921	15.37%	892	5,874	15.19%
2015	364	17,451	2.09%	2,695	17,007	15.85%	2,586	16,805	15.39%
2016	235	11,164	2.10%	1,732	10,889	15.91%	1,612	10,801	14.92%
2009–2011	582	22,877	2.54%	4,610	22,882	20.15%	3,743	21,988	17.02%
2012–2016	738	34,614	2.13%	5,337	33,817	15.78%	5,090	33,480	15.20%
Overall	1,320	57,491	2.30%	9,947	56,699	17.54%	8,833	55,468	15.92%