Journal of the Pediatric Infectious Diseases Society

BRIEF REPORT

Effect of Gestational Age at Tenofovir-Emtricitabine-Efavirenz Initiation on Adverse Birth Outcomes in Botswana

Rebecca Zash,[1,5,6] Kathryn Rough,[2,3] Denise L. Jacobson,[4] Modiegi Diseko,[5] Gloria Mayondi,[5] Mompati Mmalane,[5] Max Essex,[5,6] Chipo Petlo,[7] Shahin Lockman,[5,6,8] Joseph Makhema,[5] and Roger L. Shapiro[5,6]

[1]Beth Israel Deaconess Medical Center, Division of Infectious Disease, Boston, Massachusetts; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [3]Department of Epidemiology, [4]Center for Biostatistics in AIDS Research, and [5]Division of Immunology and Infectious Diseases, Harvard TH Chan School of Public Health, Boston, Massachusetts; [6]Botswana Harvard AIDS Institute Partnership, Gaborone; [7]Botswana Ministry of Health, Gaborone; and [8]Division of Infectious Diseases, Brigham and Women's Hospital and Harvard TH Chan School of Public Health, Boston, Massachusetts

Among human immunodeficiency virus–positive women in Botswana on the recommended first-line antiretroviral therapy regimen, tenofovir-emtricitabine-efavirenz, initiated within the first or early second trimester, we found no increased risk of stillbirth, neonatal death, preterm/very preterm delivery, or the infant being born small or very small for gestational age. Treatment with tenofovir-emtricitabine-efavirenz <1 year before conception increased the risk of preterm delivery slightly over late-second-trimester treatment initiation (adjusted risk ratio, 1.33 [95% confidence interval, 1.04–1.70]).

Keywords. antiretroviral therapy; human immunodeficiency virus (HIV); prevention of mother-to-child transmission (PMTCT); preterm delivery; small for gestational age; stillbirth.

World Health Organization (WHO) treatment guidelines recommend starting antiretroviral therapy (ART) as soon as possible after human immunodeficiency virus (HIV) diagnosis, even when the diagnosis is made during pregnancy [1, 2]. Safety data for starting ART at different times in early pregnancy can inform these guidelines if differences are identified in the risks for adverse birth outcomes, including preterm delivery, low birth weight, and stillbirth. Such data are particularly important for the WHO first-line recommended regimen, tenofovir-emtricitabine-efavirenz (TDF/FTC/EFV), for which little first-trimester data regarding adverse outcomes are available, because it was avoided previously out of concern for teratogenicity.

We performed a large birth-outcomes surveillance study in Botswana to examine the relationship between the timing of TDF/FTC/EFV initiation in pregnancy and adverse birth outcomes. We restricted our analysis to women who initiated ART at ≤21 weeks' gestational age (GA), because initiating ART after 21 weeks' GA increases the risk of mother-to-child transmission (MTCT) of HIV.

METHODS

This study included birth-outcomes surveillance at 2 government maternity sites from March 2013 to March 2014 (pilot phase) and 6 government maternity sites from August 2014 to August 2016. The study methods we used were described previously [3, 4].

Estimated GA was documented by nurses at delivery, calculated during antenatal care (ANC) on the basis of the last menstrual period (LMP) documented at the first ANC visit, and confirmed by ultrasound, when available. Fundal height measurements were used occasionally if other data were not available or if the date of the LMP was considered incorrect.

Between 2013 and 2016, Botswana guidelines recommended TDF/FTC/EFV as first-line ART for adults with a CD4 cell count of ≤350 cells/mL and for all pregnant women regardless of their CD4 count [5]. Viral load testing was not performed routinely at ART initiation or during pregnancy. HIV-infected women on a TDF/FTC/EFV regimen with a singleton pregnancy were categorized according to their ART regimen initiation date as follows: (1) 1 year to 1 day before the estimated date of conception, (2) 0 days to <8 weeks after conception (early first trimester), (3) 8 to <14 weeks after conception (late first trimester), (4) 14 to <20 weeks after conception (early second trimester), or (5) 20 to <22 weeks after conception (late second trimester, reference group). We excluded women who initiated ART >21 weeks after conception, because starting ART later in pregnancy increased MTCT risk (and therefore would not be recommended) and to ensure sufficient ART exposure. Additionally, we wanted an equal opportunity for an outcome (e.g a woman who started ART at 28 weeks by definitions could not have a 24–28 week preterm). In Botswana, women with fetal loss before 24 weeks' GA are admitted to a general medical ward because it is considered a miscarriage.

Received 4 August 2017; editorial decision 19 December 2017; accepted 17 January 2018; published online April 23, 2018.

Correspondence: R. Zash, MD, Beth Israel Deaconess Medical Center, Division of Infectious Disease, 110 Francis St, Lowry Medical Office Building, Suite GB, Boston, MA 02215 (rzash@bidmc.harvard.edu).

Journal of the Pediatric Infectious Diseases Society 2018;7(3):e148–e51

DOI: 10.1093/jpids/piy006

The primary adverse outcomes were stillbirth, preterm delivery, very preterm delivery, small for gestational age (SGA), very SGA, and neonatal death. Stillbirth was defined as fetal death before delivery (Apgar score 0, 0, 0); preterm delivery was a birth at <37 weeks' GA; very preterm delivery was a birth at <32 weeks' GA; and an infant was considered SGA if he or she was born below the 10th percentile of weight for GA or very SGA if he or she was born below the third percentile of weight for GA according to Intergrowth-21 norms (defined from 24 to 42 weeks' gestation) [6, 7]. Neonatal deaths included deaths that occurred at <28 days of age among live-born infants who had never left the hospital. The combined end point of "any adverse outcome" included stillbirth, preterm birth, SGA, or neonatal death, and the combined end point of "any severe outcome" included stillbirth, very preterm delivery, very SGA, or neonatal death. Low birth weight (<2500 g) and very low birth weight (<1500 g) were secondary end points.

Statistical Analysis

We fit log-binomial regression models to obtain the unadjusted and adjusted risk ratios and 95% confidence intervals of each category of ART timing relative to ART initiation between 20 and 21 weeks' GA. Covariates for adjusted analyses were preselected on the basis of data from similar large birth outcomes studies and included maternal age, educational attainment, and parity. Statistical analyses were performed using SAS 9.3 (SAS institute, Cary, North Carolina).

Ethical Approval

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

RESULTS

Between March 2013 and August 2016, 3384 HIV-infected women with a singleton pregnancy initiated TDF/FTC/EFV between 1 year before conception and 21 weeks' GA (502 at <1 year from conception, 97 between 0 and 7 weeks' GA, 613 between 8 and 13 weeks' GA, 1622 between 14 and 19 weeks' GA, and 550 between 20 and 21 weeks' GA).

In our study population, 3058 (90%) of the women reported an LMP, and the reported LMP date corresponded to gestational age at delivery in 2286 (75%) of them. The proportion of women with an LMP and the proportion with an LMP that corresponded to gestational age did not differ according to timing of ART initiation.

Demographic characteristics of the study population according to the timing of ART initiation are shown in Supplemental Table 1. Women who initiated ART before conception were slightly older, more likely to be a housewife/unsalaried, and less likely to be primiparous than those who initiated ART after conception. Compared with women who started their TDF/FTC/EFV regimen at 20 to 21 weeks' GA, women who initiated this regimen in the early first trimester (0–7 weeks' GA) were more likely to have been diagnosed with HIV before pregnancy and more likely to initiate ART before their first ANC visit. Among 1617 (48%) women with a known CD4 count during pregnancy, the median CD4 count was 401 cells/mL, and only 206 (13%) had a CD4 count of <200 cells/mL. There was no statistically significant difference in CD4 counts according to the timing of ART initiation.

Overall, the risk of adverse birth outcomes was high; 1200 (35%) pregnancies ended in an adverse outcome, and 414 (12%) pregnancies ended in a severe adverse outcome. There was a total of 61 neonatal deaths; 49 (80%) were born preterm, and 38 (62%) were born very preterm.

The risks of stillbirth, neonatal death, very preterm delivery, SGA, very SGA, and the combined end points of any adverse and any severe adverse birth outcome according to the initiation of ART with TDF/FTC/EFV are shown in Table 1. Total adverse birth outcomes, severe adverse birth outcomes, stillbirth, low birth weight, and very low birth weight were most common among births to women who started their TDF/FTC/EFV regimen between 0 and 7 weeks' gestation, but this result was not statistically significant. In an adjusted analysis, women who began TDF/FTC/EFV therapy before conception had a significantly higher risk for preterm delivery (adjusted risk ratio, 1.33 [95% confidence interval, 1.04–1.70]) than women who began TDF/FTC/EFV therapy between 20 and 21 weeks' GA. No other significant associations between the timing of ART initiation and any of the birth outcomes were found (Table 1).

Adding variables into the model that were strongly associated with adverse outcomes, including birth at a tertiary care facility, low weight in pregnancy, history of preterm delivery, and history of stillbirth, did not change the magnitude or direction of any association between ART timing and any adverse birth outcome.

DISCUSSION

We evaluated the safety of starting TDF/FTC/EFV before and during the first half of pregnancy in Botswana. We found that women who initiated TDF/FTC/EFV any time between 1 year before conception and 21 weeks' GA generally had similar birth outcomes. However, women who initiated TDF/FTC/EFV before pregnancy had a small increase in the risk of preterm delivery over that of women who initiated their ART regimen at 20 to 21 weeks' GA.

We know of no previous studies in which the relationship between gestational age at TDF/FTC/EFV initiation and adverse birth outcomes were examined. Studies have found higher risk for adverse birth outcomes with ART when started before conception than when started

Table 1. Adverse Birth Outcomes[a] According to Gestational Age at TDF/FTC/EFV Initiation

	Gestational Age at TDF/FTC/EFV initiation									
	Within 1 year prior to conception N=502		0–7 weeks N=97		8–13 weeks N=613		14–19 weeks N=1622		20–21 weeks N=550	
	N (%)		N (%)		N (%)		N (%)		N (%)	
	RR (95% CI)	aRR (95% CI)	RR (95% CI)	aRR (95% CI)	RR (95% CI)	aRR (95% CI)	RR (95% CI)	aRR (95% CI)	RR (95% CI)	aRR (95% CI)
Any Adverse Outcome	184 (37%)		41 (42%)		213 (35%)		575 (35%)		177 (32%)	
	1.14 (0.96,1.34)	1.16 (0.98,1.38)	1.31 (1.01,1.71)	1.26 (0.95,1.66)	1.08 (0.92,1.27)	1.09 (0.92.1.28)	1.10 (0.96,1.26)	1.12 (0.97,1.28)	ref	ref
Severe Adverse Outcome	55 (11.0%)		13 (13.4%)		72 (11.8%)		204 (12.6%)		70 (12.7%)	
	0.86 (0.62,1.20)	0.86 (0.61,1.22)	1.05 (0.61,1.83)	1.13 (0.65,1.9)	0.92 (0.68,1.26)	0.92 (0.67,1.26)	0.99 (0.77,1.27	1.00 (0.78,1.30)	ref	ref
Stillbirth	17 (3.4%)		4 (4.1%)		14 (2.3%)		47 (2.9%)		14 (2.6%)	
	1.33 (0.66, 2.67)	1.33 (0.66,2.67)	1.62 (0.54,4.82)	1.63 (0.55,4.86)	0.89 (0.43,1.87)	0.86 (0.41,1.79)	1.14 (0.63,2.05)	1.11 (0.61,2.00)	ref	ref
Neonatal Death	7 (1.5%)		1 (1.1%)		17 (2.8%)		27 (1.7%)		9 (1.7%)	
	0.86 (0.32,2.30)	0.81 (0.28,2.33	0.64 (0.08,5.00)	0.71 (0.09,5.61)	1.69 (0.76,3.77)	1.73 (0.75,4.01)	1.02 (0.48,2.16)	1.10 (0.50,2.42)	ref	ref
Preterm Birth	116 (23%)		22 (23%)		120 (20%)		310 (19%)		96 (17%)	
	1.32 (1.04,1.69)	1.33 (1.04,1.70)	1.30 (0.86,1.96)	1.28 (0.84,1.95)	1.12 (0.88,1.43)	1.10 (0.86,1.41)	1.10 (0.88,1.35)	1.08 (0.88,1.34)	ref	ref
Very Preterm Birth	25 (5.0%)		5 (5.2%)		29 (4.7%)		81 (5.0%)		21 (3.8%)	
	1.30 (0.73,2.30)	1.33 (0.75,2.39)	1.35 (0.52,3.49)	1.44 (0.55,3.75)	1.24 (0.71,2.15)	1.23 (0.70,2.17)	1.31 (0.82,2.09)	1.38 (0.85,2.22)	ref	ref
SGA	78 (16%)		19 (20%)		109 (18%)		285 (18%)		98 (18%)	
	0.88 (0.67,1.16)	0.90 (0.68,1.19)	1.10(0.71,1.71)	0.99 (0.62,1.61(	0.99 (0.77,1.27)	1.02 (0.79,1.30)	0.98 (0.80,1.21)	1.00 (0.81,1.24)	ref	ref
Very SGA	27 (5.5%)		7 (7.3%)		34 (5.6%)		100 (6.2%)		42 (7.7%)	
	0.71 (0.44,1.14)	0.70 (0.43,1.15)	0.95 (0.43,2.04)	1.02 (0.47,2.21)	0.72 (0.47,1.12)	0.73 (0.47,1.13)	0.81 (0.57,1.14)	0.82 (0.58,1.16)	ref	ref
Low Birthweight (<2500g)	85 (17%)		21(22%)		101 (17%)		287 (18%)		87 (16%)	
	1.07 (0.81,1.40)	1.08 (0.82,1.42)	1.36 (0.89,2.08)	1.42 (0.93,2.17)	1.03 (0.80,1.35)	1.02 (0.78,1.33)	1.11 (0.89,1.39)	1.12 (0.90,1.40)	ref	ref
Very Low Birthweight (<1500g)	18 (3.6%)		5 (5.2%)		26 (4.3%)		71 (4.4%)		23 (4.2%)	
	0.86 (0.46,1.57)	0.83 (0.45,1.55)	1.23 (0.48,3.15)	1.27 (0.49,3.27)	1.01 (0.58,1.75	0.98 (0.56,1.71)	1.04 (0.66,1.65)	1.07 (0.69,1.71)	ref	ref

Abbreviations: ANC, antenatal care; ART, antiretroviral therapy; GA, gestational age; HIV, human immunodeficiency virus; IQR, interquartile range; TDF/FTC/EFV, tenofovir-emtricitabine-efavirenz.

[a]Adverse outcomes were stillbirth, neonatal death, preterm birth, or small for gestational age; severe adverse outcomes were stillbirth, neonatal death, very preterm birth, or very small for gestational age.

during pregnancy [8, 9], and a previous meta-analysis found increased risk of preterm delivery, very preterm delivery, low birth weight, and stillbirth (borderline) when women started ART before conception or during their first trimester than those who started in their second or third trimester [10]. These findings are consistent with the slightly higher preterm delivery risk we identified in the women who started TDF/FTC/EFV within 1 year before conception.

Our study has several strengths, including the completeness of data collection and a large sample size with the power to compare both common and rare outcomes of a single ART regimen. Limitations of this study include the potential for unmeasured confounding resulting from the observational design and unknown generalizability to other ART regimens and to other settings with different resources and obstetric practices. We did not collect information on spontaneous abortions (defined in Botswana as pregnancy loss at <24 weeks' GA); therefore, selection bias might exist because our conclusions are limited to the birth outcomes we evaluated. Last, it is possible also that there was differential misclassification of GA if women who initiated ART early in pregnancy were more accurate in their recollection of their LMP or more likely to undergo an early ultrasound (which would be more accurate for dating). However, we believe that such misclassification was unlikely for two reasons; among HIV-uninfected women, we found no difference in risks of preterm delivery between those who presented early versus those who presented late to ANC (data not shown), and no linear trend was observed between the timing of ART initiation and preterm delivery.

In conclusion, no differences in adverse birth outcomes were identified among women who initiated a TDF/FTC/EFV regimen between 1 year before conception and 21 weeks of gestation, with the exception of a small increase in preterm deliveries when ART was started before conception. These data provide support for WHO guidelines and other international guidelines that recommend initiating TDF/FTC/EFV at early ANC contacts to maximize opportunities for viral suppression and prevention of MTCT. Our data also support the overall WHO "test and treat" strategy for ART initiation immediately after diagnosis of HIV infection.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

Acknowledgments. We acknowledge the incredibly hard work of our research assistants, Judith Mabuta, Cynthia Dube, Daphne Segobye, Gadifele Koogane, Gosego Legase, Kasegofetse Agisanang, Keemenao France, Mmapula Ofhentse, Naledi Kamanga, Onkabetse Mokgosi, Rosemary Moremi, Shally Morgan, Tsaone Gaonakala, Tshepang Motlotlegi, and Edith Moseki. We also sincerely thank the superintendents, matrons, midwives, doctors, and maternity staff at the participating hospitals (Princess Marina Hospital, Gaborone; Scottish Livingstone Hospital, Molepolole; Sekgoma Memorial Hospital, Serowe; Letsholathebe II Memorial Hospital, Maun; Nyangabwe Hospital, Francistown; Selebi-Phikwe Hospital, Selebi-Phikwe; Mahalapye Hospital, Mahalapye; and Ghanzi Primary Hospital, Ghanzi). In addition, we thank members of the Botswana Ministry of Health. This study would not have been possible without the support of the Botswana–Harvard AIDS Institute Partnership leadership and staff.

Financial support. This work was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at the National Institutes of Health (grant R01 HD080471-01 to R. Z., D. L. J., G. M., M. D., J. M., S. L., and R. S. and grant K23 HD088230-01A1 to R. Z.) and the NIH National Institute of Allergy and Infectious Disease (grant T32 AI007433 to K. R. and R.Z.).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization Programme. Available at: http://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed February 12, 2018.
2. UNICEF. For every child, end AIDS. Seventh stocktaking report, 2016. Available at: https://www.unicef.org/publications/index_93427.html. Accessed February 12, 2018.
3. Zash R, Souda S, Chen JY, et al. Reassuring birth outcomes with tenofovir/emtricitabine/efavirenz used for prevention of mother-to-child transmission of HIV in Botswana. J Acquir Immune Defic Syndr **2016**; 71:428–36.
4. Zash R, Jacobson D, Mayondi G, et al. The comparative safety of antiretroviral therapy regimens in pregnancy. JAMA Pediatr **2017**; 171:e172222.
5. Botswana Ministry of Health. Botswana National HIV & AIDS treatment guidelines, 2012 Version. Available at: https://aidsfree.usaid.gov/sites/default/files/tx_botswana_2012.pdf. Accessed February 12, 2018.
6. Villar J, Cheikh Ismail L, Victora CG, et al; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet **2014**; 384:857–68.
7. Villar J, Giuliani F, Fenton TR, et al; INTERGROWTH-21st Consortium. INTERGROWTH-21st very preterm size at birth reference charts. Lancet **2016**; 387:844–5.
8. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis **2012**; 206:1695–705.
9. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? Clin Infect Dis **2012**; 54:1348–60.
10. Uthman OA, Nachega JB, Anderson J, et al. Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis. Lancet HIV **2017**; 4:e21–30.