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Adverse Pregnancy Outcomes Among Women Who Conceive on Antiretroviral Therapy

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(See the Editorial Commentary by Lockman and De Gruttola on pages 280–1.)

Background. Adverse pregnancy outcomes for women who conceive on antiretroviral therapy (ART) may be increased, but data are conflicting.

Methods. Human immunodeficiency virus–infected, nonbreastfeeding women with pre-ART CD4 counts ≥400 cells/μL who started ART during pregnancy were randomized after delivery to continue ART (CTART) or discontinue ART (DCART). Women randomized to DCART were recommended to restart if a subsequent pregnancy occurred or for clinical indications. Using both intent-to-treat and as-treated approaches, we performed Fisher exact tests to compare subsequent pregnancy outcomes by randomized arm.

Results. Subsequent pregnancies occurred in 277 of 1652 (17%) women (CTART: 144/827; DCART: 133/825). A pregnancy outcome was recorded for 266 (96%) women with a median age of 27 years (interquartile range [IQR], 24–31 years) and median $CD4^+$ T-cell count 638 cells/μL (IQR, 492–833 cells/μL). When spontaneous abortions and stillbirths were combined, there was a significant difference in events, with 33 of 140 (23.6%) in the CTART arm and 15 of 126 (11.9%) in the DCART arm (relative risk [RR], 2.0 [95% confidence interval {CI}, 1.1–3.5]; $P = .02$). In the as-treated analysis, the RR was reduced and no longer statistically significant (RR, 1.4 [95% CI, .8–2.4]).

Conclusions. Women randomized to continue ART who subsequently conceived were more likely to have spontaneous abortion or stillbirth, compared with women randomized to stop ART; however, the findings did not remain significant in the as-treated analysis. More data are needed on pregnancy outcomes among women conceiving on ART, particularly with newer regimens.

Keywords. HIV/AIDS; antiretroviral therapy; pregnancy; conception; pregnancy outcomes.

The benefits of combination antiretroviral therapy (ART) for the prevention of mother-to-child transmission of human immunodeficiency virus (HIV) and for maternal health have been shown in randomized studies [1, 2], and an increasing number of women are conceiving on ART as countries around the world adopt universal treatment ("test and start"). Previous studies have reported an increased risk for adverse pregnancy outcomes in the setting of ART in pregnancy, and some regimens may be safer than others with regard to adverse pregnancy events [3–8]. Several studies have attempted to tease apart contributions of conceiving on ART compared to starting ART later in pregnancy, but published data have largely reported on preterm delivery (PTD), low birth weight (LBW), and small for gestational age (SGA), and have been limited by inability to control for confounding factors such as HIV disease stage, lifestyle (substance use, alcohol, tobacco), and comorbidities [8–11]. Several recent randomized ART studies have provided data on pregnancy outcomes and ART exposures; however, all focus on either PTD, LBW, and/or SGA, and none have specifically reported on rates of stillbirth or spontaneous abortion [1, 12, 13]. Understanding how different ART regimens influence rates of stillbirth and spontaneous abortion is a critical part of the maternal–child health agenda.

The "HAART [highly active antiretroviral therapy] Standard" component of the Promoting Maternal and Infant Safety Everywhere (PROMISE HS) study was a randomized trial designed to examine nonbreastfeeding women with $CD4^+$ T-cell counts ≥400 cells/μL in regard to the risks and benefits of continued triple-drug ART compared to stopping ART after delivery, and reinitiating for $CD4^+$ T-cell counts <350 cells/

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μL. The trial was planned for settings where triple-drug ART was the standard of care for the prevention of perinatal HIV transmission in 2009. The PROMISE HS study design provides a unique opportunity to explore the relationship between ART and pregnancy outcomes for women who were randomized to stop or continue ART after an index delivery and who had a subsequent pregnancy. Using post hoc analyses, we sought to evaluate rates of spontaneous abortion and stillbirth by randomized arm among women with subsequent pregnancies in PROMISE HS, and to evaluate associations of these outcomes with exposure to specific ART regimens. PROMISE is the only study that has followed women for subsequent pregnancies in a randomized, longitudinal manner.

METHODS

PROMISE HS was conducted by the International Maternal, Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network in collaboration with the AIDS Clinical Trials Group (ACTG) Network. PROMISE HS was a randomized strategy trial conducted among clinically stable HIV-infected pregnant women, antiretroviral-naive except for prior use in pregnancy, without other indications for ART based on local guidelines, who received triple-drug ART during pregnancy for the purpose of preventing mother-to-child transmission of HIV. Fifty-six sites in Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand, and the United States participated between December 2011 and November 2014. Women ≥18 years of age or who had attained the minimum age of independent consent as defined by the local institutional review board were eligible to enroll if they had documentation of a $CD4^+$ T-cell count ≥400 cells/μL within 120 days of the start of ART during the current pregnancy and evidence that $CD4^+$ T-cell count remained ≥400 cells/μL within 45 days prior to entry while on ART. Participants could not have a clinical indication for ART, including any World Health Organization (WHO) clinical stage 3 or 4 condition, or any clinically significant illness within 30 days prior to entry. Detailed study methods, including a CONSORT (Consolidated Standards of Reporting Trials) diagram, have been recently published with primary outcome data [2]. The study was approved by the institutional review board or ethics committee at each participating site and written informed consent was obtained from all participants.

The trial evaluated 2 strategies for the management of ART among postpartum women within 42 days after delivery: continue ART (CTART) or discontinue ART (DCART) and restarting when clinically indicated (including for a subsequent pregnancy). In step 1 of the trial, participants were randomized to either continue or discontinue ART. Participants in step 1 entered step 2 and started ART if they met 1 of the following criteria: (1) developed an AIDS-defining/WHO stage 4 illness; (2) had a confirmed $CD4^+$ T-cell count <350 cells/μL; (3) developed a clinical condition considered an indication for ART by country-specific guidelines; or (4) otherwise required ART as determined in consultation with the study clinical management committee.

The preferred study-supplied ART regimen was lopinavir/ritonavir plus fixed-dose combination emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF). This regimen was chosen because it was the preferred regimen for use in pregnancy by the United States Department of Health and Human Services guidelines at the time the study was designed [14]. Additional study-supplied antiretrovirals (ARVs) included lamivudine (3TC), zidovudine (ZDV), fixed-dose combination 3TC/ZDV, TDF, fixed-dose combination FTC/TDF/rilpivirine, atazanavir, raltegravir, and ritonavir. Study clinicians, in conjunction with participants, were allowed to determine the optimal drug combination for each participant.

Participants were seen for evaluations at 4 weeks and at 12 weeks, and every 12 weeks thereafter. HIV viral load was used to maximize the benefits of ART and to determine when treatment should be changed. Pregnancy testing was performed at each 12-week follow-up visit. Women randomized to stop ART who became pregnant were restarted on ART per the local country guidelines. Information on the pregnancy outcomes (live birth, induced abortion <20 weeks, spontaneous abortion <20 weeks' gestation, and stillbirth ≥20 weeks' gestation) was collected for all women who developed a pregnancy during study follow-up. Estimated date of delivery was determined by the site based on any one of the following: last menstrual period, initial obstetric ultrasound, conception date based on assisted reproduction, or physical examination (if no other method for dating was available). This analysis includes pregnancies identified before 7 July 2015, when participants were informed about the Strategic Timing of AntiRetroviral Treatment (START) trial results [15] and all participants were offered ART. Only the first subsequent pregnancy was included in the analysis.

Statistical Methods

Relative risks and Fisher exact tests were used to compare subsequent pregnancy outcomes by arm. By-arm analyses were performed using 3 different strategies: (1) intent-to-treat (ITT); (2) excluding women who crossed over to the other arm (ie, women in the DCART arm who started ART prior to their subsequent pregnancy and those in the CTART arm who discontinued ART prior to their subsequent pregnancy); and (3) performing an as-treated analysis comparing pregnancy outcomes among all women with a subsequent pregnancy who conceived on ART compared to those who did not conceive on ART.

After observing by-arm differences, we investigated ART regimen exposure and the timing of ART drug initiation. These analyses used Cox proportional hazards regression to model the time from conception to the composite outcome of spontaneous abortion or stillbirth. The Cox models adjusted for country as a confounder. The date of conception was

estimated by subtracting 40 weeks from the expected delivery date. Sixty-three women did not have an expected delivery date recorded in the database. For these women, the length of pregnancy was imputed using the observed length of pregnancy averages. For the analysis by regimen, women were grouped by ART with boosted/nonboosted protease inhibitor (PI), ART with nonnucleoside reverse transcriptase inhibitor (NNRTI) and no PI, ART with nucleoside reverse transcriptase inhibitor (NRTI) only (CTART group only), and no ART (DCART only). We performed Cox regression models that included both ART at conception and ART exposure as a time-varying covariate. Finally, additional Cox analyses were performed combining both arms and looking at ART regimens for the combined cohort and comparing the randomized arms adjusted for regimen.

P values <.05 were considered to be statistically significant. Analyses were conducted using SAS version 9.2 software.

RESULTS

Seventeen percent of the study cohort experienced a subsequent pregnancy during follow-up (277/1652) and the number of subsequent pregnancies was similar between arms (CTART: 144/827; DCART: 133/825). Among the 277 women with an initial subsequent pregnancy, 266 (96%) had a pregnancy outcome recorded. Outcome data were not available for 4 women in the CTART arm and 7 in the DCART arm. Among the 266 women with outcome data, there were 200 (75%) live births, 40 (15%) spontaneous abortions, 18 (7%) induced abortions, and 8 (3%) stillbirths. At the time of estimated conception, the median age of women with a subsequent pregnancy was 27 years (interquartile range [IQR], 24–31 years), the median $CD4^+$ T-cell count was 638 cells/μL (IQR, 492–833 cells/μL), the majority (95%) were WHO clinical stage I, and 65% had a viral load <400 copies/mL. The median number of weeks on study at the time of pregnancy was 59 (IQR, 35–109 weeks). Participant characteristics at the time of estimated conception are summarized in Table 1.

Spontaneous abortion and stillbirth event percentages were each higher in the CTART arm compared to the DCART arm. Of the 40 spontaneous abortions, 27 of 140 (19.3%) were in the CTART arm and 13 of 126 (10.3%) were in the DCART arm. There were 8 stillbirths, 6 of 140 (4.3%) in the CTART arm, and 2 of 126 (1.6%) in the DCART arm. When spontaneous abortions and stillbirths were combined, there was a statistically significant difference, with 33 of 140 (23.6%) in the CTART arm and 15 of 126 (11.9%) in the DCART arm (relative risk [RR], 2.0 [95% confidence interval {CI}, 1.1–3.5]; *P* = .02; Table 2). The RR for the cross-over analysis (RR, 1.8 [95% CI, 1.0–3.2]) and the RR for the as-treated analysis (RR, 1.4 [95% CI, .8–2.4]) were reduced compared to the ITT analysis and did not reach statistical significance (Table 2).

Fourteen of 140 women (10.0%) in the CTART arm stopped ART and therefore were not on treatment at the time of conception. Among the remaining women in CTART, the median time on ART at the time of conception was 60 weeks (IQR, 31–106), and 86% were on a boosted/nonboosted PI regimen vs 6% on NNRTI-based therapy (Table 3). After pregnancy diagnosis (first regimen during pregnancy), there was frequent use of PIs in the CTART arm (89% PI vs 7% NNRTI). Sixteen of 126 women (13.0%) in the DCART arm started ART prior to conception, either for their own health or based on personal preference. Among women in the DCART arm restarting treatment for their subsequent pregnancy, 53% were on a PI (Table 3). The median gestational age at ART start in the DCART group was 16 weeks (IQR, 10–21 weeks).

Table 4 displays Cox regression models for the composite outcome of spontaneous abortion and stillbirth for women by specific ART categories. In the CTART arm, the relative risk (hazard) for spontaneous abortion or stillbirth was higher in women on NNRTIs compared to women on boosted/nonboosted PIs (hazard ratio [HR], 4.70 [95% CI, 1.34–16.53]; *P* = .02). It is important to note that there were few women on NNRTI (n = 12), and as a result the range of the CI is large, indicating a large amount of uncertainty. In the DCART arm, there was no apparent difference between ART with boosted/nonboosted PI vs no ART at conception. There were no spontaneous abortions or stillbirths in the DCART women on NNRTI with no PI (n = 5); therefore, an estimate of the HR was not possible. In additional models that used both ART at conception and subsequent ART over time (time-varying effect), the HR for spontaneous abortion or stillbirth remained significant for women on NNRTI compared to women on boosted/nonboosted PI (HR, 5.99 [95% CI, 1.99–18.05]; *P* = .001). In an analysis that combined both arms and categorized women by different ART regimens, there were no apparent differences on the composite outcome of spontaneous abortion and stillbirth between ART with a boosted/nonboosted PI at conception compared to NNRTI. In a Cox model evaluating the outcomes by randomized arm (CTART vs DCART) and adjusting for ART regimen, the HRs were 3.44 (for exposure at conception) and 3.04 (for time-varying exposure) with *P* values of .009 and .006, respectively, indicating that the difference between the arms was not explained by ART regimen.

DISCUSSION

In the ITT analysis, our data suggest that conception on ART may be associated with higher rates of the adverse pregnancy outcomes of spontaneous abortion and stillbirth; however, the as-treated results were not statistically significant. The RRs and 95% CIs are in the same direction and magnitude in both 2 approaches to the data, changing from 2.0 (95% CI, 1.1–3.5) in

Table 1. Baseline Characteristics of Women in the Promoting Maternal and Infant Safety Everywhere Highly Active Antiretroviral Therapy Standard (PROMISE HS) Study With a Subsequent Pregnancy During Follow-up (N = 266)

		Randomization Arm		
		Continuation of ART	Discontinuation of ART	Total
Characteristic	Variable	(n = 140)	(n = 126)	(N = 266)
Country	Argentina	5 (4)	7 (6)	12 (5)
	Botswana	48 (34)	45 (36)	93 (35)
	Brazil	37 (26)	37 (29)	74 (28)
	China	5 (4)	2 (2)	7 (3)
	Haiti	10 (7)	6 (5)	16 (6)
	Thailand	15 (11)	14 (11)	29 (11)
	United States	20 (14)	15 (12)	35 (13)
Age at time of estimated conception, y		(n = 140)	(n = 126)	(n = 266)
	Median (Q1–Q3)	27 (23–31)	28 (24–31)	27 (24–31)
	Min–Max	19–41	19–45	19–45
BMI at time of estimated conception, kg/m^2		(n = 138)	(n = 123)	(n = 261)
	Min–Max	14.3–58.5	15.0–49.6	14.3–58.5
	Median (Q1–Q3)	22.4 (19.7–26.7)	23.9 (19.9–30.1)	22.8 (19.9–27.6)
WHO stage at time of estimated conception	Clinical stage I	135 (96)	119 (94)	254 (95)
	Clinical stage II	4 (3)	3 (2)	7 (3)
	Clinical stage III	1 (1)	4 (3)	5 (2)
CD4$^+$ cell count at time of estimated conception, cells/μL		(n = 138)	(n = 123)	(n = 261)
	Min–Max	215–1577	200–1704	200–1704
	Median (Q1–Q3)	730 (606–890)	525 (404–682)	638 (492–833)
Plasma HIV RNA at time of estimated conception, copies/mL	<400	107 (78)	27 (39)	134 (65)
	400–1000	4 (3)	8 (12)	12 (6)
	>1000–100 000	23 (17)	30 (43)	26 (16)
	>100 000	3 (2)	4 (6)	7 (3)
Alcohol use at study entry	≤1 drink /mo	103 (84)	95 (85)	198 (84)
	2–3 drinks/mo	10 (8)	8 (7)	18 (8)
	1–2 drinks/wk	6 (5)	6 (5)	12 (5)
	>3 drinks/wk	3 (2)	3 (3)	6 (3)
Cigarette use at study entry	Yes	19 (14)	16 (13)	35 (13)
	No	121 (86)	110 (87)	231 (87)
Marijuana use at study entry	Never used	106 (90)	94 (86)	200 (88)
	>1 y ago	6 (5)	13 (12)	19 (8)
	Within past y until 1 mo ago	2 (2)	0 (0)	2 (1)
	Within the past mo	4 (3)	2 (2)	6 (3)
Cocaine use at study entry	Never used	112 (95)	103 (94)	215 (95)
	>1 y ago	3(3)	5 (5)	8 (4)
	Within past y until 1 mo ago	3 (3)	0 (0)	3 (1)
	Within the past mo	0 (0)	1 (1)	1 (0)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; WHO, World Health Organization.

the ITT to 1.4 (95% CI, .8–2.4) in the as-treated analysis. While these results may signal the possibility of an increase in adverse outcomes for women who conceive on ART, the relatively low rates of adverse pregnancy outcomes must be weighed against the tremendous benefit of lifelong, uninterrupted ART. The PROMISE HS study provides a unique opportunity to detect spontaneous abortion because women received pregnancy testing every 12 weeks, at the time of routine visits. Few studies in HIV-infected women have characterized rates of spontaneous abortion and this outcome has not been reported from other treatment studies in which HIV-infected women were randomized to a study arm that included no ART.

Prior data on rates of spontaneous abortion among women with HIV have been conflicting [16, 17]. Cohort studies from Zambia and South Africa have reported associations between advanced maternal HIV disease (CD4$^+$ T-cell counts <350

Table 2. Pregnancy Outcomes by Treatment Arm and Relative Risk and 95% Confidence Intervals for the Combined Outcome of Spontaneous Abortion or Stillbirth, Secondary Analysis Excluding Women Who Were Off Their Randomized Arm at the Time of Conception, and Secondary Analysis Using an As-Treated Approach

Analysis	CTART	DCART	*P* Value	RR (95% CI) of SA or SB Comparing CTART to DCART
Intent-to-treat				
Live birth	100	100	.16	
SA (<20 wk)	27	13	.06	
SB	6	2	.29	
SA or SB	33	15	.02	2.0 (1.1–3.5)
Crossover excluded				
Live birth	90	85		
SA (<20 wk)	23	13	.21	
SB	6	1	.13	
SA or SB	29	14	.06	1.8 (1.0–3.2)
As-treated	Conceived on ART	Did Not Conceive on ART	*P* Value	RR (95% CI) of SA or SB: Conceived on ART vs Off ART
Live birth	105	95		
SA (<20 wk)	23	17	.73	
SB	7	1	.07	
SA or SB	30	18	.20	1.4 (.8–2.4)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; CTART, continue ART arm; DCART, discontinue ART arm; RR, relative risk; SA, spontaneous abortion; SB, stillbirth.

Table 3. Antiretroviral Therapy Regimens by Arm, 12 Weeks Before Estimated Conception and First Regimen After Conception

	PROMISE HS Randomization Arm	
ART Category	Continuation of ART	Discontinuation of ART
12 wk before estimated conception		
ART including boosted/nonboosted PI[a]	120 (86)	14 (11)
ART including NNRTI[b] with no PI	8 (6)	5 (4)
ART with NRTI only (includes 1, 2, or 3 NRTIs)	3 (2)	0 (0)
ART including integrase with no PI	1 (1)	0 (0)
No ARVs	8 (6)	107 (85)
Total	140	126
First regimen after conception		
ART including boosted/nonboosted PI[c]	124 (89)	67 (53)
ART including NNRTI[d] with no PI	10 (7)	34 (27)
ART with NRTI only (includes 1, 2, or 3 NRTIs)	3 (2)	1 (1)
ART including integrase with no PI	1 (1)	1 (1)
No ARVs	2 (1)	23 (18)
Total	140	126

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PROMISE HS, Promoting Maternal and Infant Safety Everywhere highly active antiretroviral therapy standard.

[a]Continue ART arm: 59 on zidovudine (ZDV)/lamivudine (3TC)/ritonavir (RTV)/lopinavir (LPV) and 37 on tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/LPV/RTV; 24 other PI. Discontinue ART arm: 4 on ZDV/3TC/RTV/LPV and 5 on tenofovir/FTC/LPV/RTV; 5 other PI.

[b]Continue ART arm: 7 women were on efavirenz (EFV) and 1 on rilpivirine (RPV). Discontinue ART arm: 2 women on EFV and 3 on RPV.

[c]Continue ART arm: 59 on ZDV/3TC/RTV/LPV and 35 on tenofovir/FTC/LPV/RTV; 30 other PI. Discontinue ART arm: 46 on ZDV/3TC/RTV/LPV and 9 on tenofovir/FTC/LPV/RTV; 12 other PI.

[d]Continue ART arm: 8 women were on EFV and 2 on RPV. Discontinue ART arm: 31 women on EFV and 3 on RPV.

cells/μL) and risk for spontaneous abortion. These African studies did not include HIV-uninfected comparison groups [18, 19]. A limited number of studies have evaluated specific ARV regimens and the risk of spontaneous abortion. In a retrospective study of West African women on efavirenz or nevirapine (NVP) in the first trimester, spontaneous abortion occurred in 5.2%, with no difference in rates by regimen [20]. In a randomized study of elvitegravir/cobicistat/FTC/TDF compared to ritonavir-boosted atazanavir plus FTC/TDF, spontaneous abortion occurred in 25% of participants who conceived on ART, with events evenly divided by arm [21]. The rate of spontaneous abortion in WAVES was higher than the observed rate in the CTART arm of PROMISE HS (19%). Like PROMISE HS, this study performed frequent pregnancy testing in participants and was likely able to detect pregnancy losses that may have never come to medical attention outside of a clinical trial setting.

Rates of spontaneous abortion in our study are similar to rates in the HIV-uninfected general population, which have been reported in the range of 13%–26% for early pregnancy [22, 23]. An important HIV-uninfected comparison group for PROMISE HS consists of women who conceived on preexposure prophylaxis (PrEP) as part of a randomized study in serodiscordant couples in Kenya and Uganda [24]. In this clinical trial, which included frequent pregnancy testing, approximately one-third of women (26.7%) had a spontaneous abortion. PrEP was discontinued as soon as a pregnancy was identified and there were no statistically significant differences by treatment vs placebo. In our study, rates of spontaneous abortion, while higher in the CTART than DCART arm (19% vs 10%,

Table 4. Cox Proportional Hazard Ratios for the Composite Outcome of Spontaneous Abortion and Stillbirth Comparing Antiretroviral Therapy (ART) Exposure for the Continue ART Arm and for the Discontinue ART Arm

	Exposure at the Estimated Conception Date		Time-Varying Exposure from the Estimated Conception Date	
Arm and Comparison Group	Hazard Ratio (95% CI)	*P* Value[a]	Hazard Ratio (95% CI)	*P* Value[a]
Continue ART				
ART including boosted/non-boosted PI	Ref		Ref	
ART including NNRTI with no PI	4.70 (1.34–16.53)	.02	5.99 (1.99–18.05)	.001
Only 1, 2, or 3 NRTIs	1.89 (.23–15.35)	.55	1.51 (.19–11.74)	.69
Discontinue ART				
ART including boosted/non-boosted PI	Ref		Ref	
No ARVs	1.90 (.24–14.81)	.54	1.35 (.37–4.86)	.65
ART with NNRTI with no PI[b]	Not applicable	.13	Not applicable	NA
Multivariable model with both arms				
ART including boosted/non-boosted PI	Ref		Ref	
ART including NNRTI with no PI	2.88 (.93–8.94)	.067	2.32 (.80–6.71)	.12
Only 1, 2, or 3 NRTIs	2.17 (.28–16.88)	.46	1.52 (.20–11.50)	.69
No ARVs	2.15 (.85–5.41)	.11	1.94 (.82–4.60)	.13
Discontinue ART arm	Ref		Ref	
Continue ART arm	3.44 (1.36–8.69)	.009	3.05 (1.37–6.79)	.006

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Analyses were adjusted for country: Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand, and United States.

[b]In the discontinue ART arm, there were no spontaneous abortions or stillbirths in the ART with NNRTI with no PI group; therefore, an estimate of the hazard ratio was not possible. The *P* value was based on a log-rank test comparing the ART with NNRTI with no PI vs ART including boosted/nonboosted PI.

respectively), were lower compared to the rate in the HIV-uninfected women in Partners PrEP.

Rates of stillbirth have been evaluated in modern HIV-infected cohorts. In a large observational study from Zambia, the crude rate of stillbirth was 22 per 1000 live births with no difference in rates between HIV-infected and -uninfected women [25]. Among HIV-infected women, those who did not have any ARV exposure had a higher odds of stillbirth (adjusted odds ratio [aOR, 2.4 [95% CI, 2.0–3.0]). Similar outcomes were seen in South Africa where expanded coverage of ART resulted in a decrease in stillbirth over time (2011–2014) from 3.7% to 2.7%, rates both significantly lower than those seen in women with no ART (13.5%) [26]. In another African cohort comprised of women from South Africa and Zambia who conceived on predominately NNRTI-based ART, the rate of stillbirth was 2.0% [27]. In a large cohort of women in Botswana, women receiving ART (87% NVP-based) had higher odds of stillbirth compared with women receiving ZDV alone (aOR, 2.5 [95% CI, 1.6–3.9]) and this difference persisted after adjustment for $CD4^+$ T-cell count, maternal age, parity, maternal hypertension, and anemia [8]. Another large observational cohort from Botswana showed higher rates of stillbirth in HIV-infected vs -uninfected women (3.4% vs 2.1%), with the highest rate in HIV-infected women exposed to NVP/ZDV/3TC (6.1%) and the lowest rate in women on efavirenz/TDF/FTC (2.4%) [28]. Stillbirth rates in women on ART from these African cohorts are similar to those in PROMISE HS (3% overall).

There are limitations to this study. We are missing pregnancy outcome data on 11 women, and it is possible that the lack of inclusion of adverse events in this subgroup could bias our results. We did not capture the full spectrum of pregnancy and infant outcomes including preterm labor, preterm delivery, and low birth weight, as these were not recorded in the data collection forms. Women in the study may have been uncomfortable disclosing elective abortions and these events may have been classified as spontaneous abortions. The study did not collect information on prior history of adverse pregnancy outcomes or gravity/parity and therefore we could not adjust our findings for these factors. We had a small number of women on NNRTI- and integrase-based ART, limiting our ability to compare risks of conception by these regimen types.

CONCLUSIONS

In this prospective study of women with CD4 counts >400 cells/μL, women randomized to continue ART who subsequently conceived were more likely to have spontaneous abortion or stillbirth compared to women randomized to stop ART; however, the findings did not remain statistically significant in the as-treated analysis, in which women were categorized by their ART status at conception. Event rates were similar to those reported from

other studies in modern HIV-infected cohorts, and rates of spontaneous abortion we observed were very similar or lower than those reported in HIV-negative women. These relatively low risks of adverse pregnancy outcomes must be weighed against the tremendous benefit of lifelong, uninterrupted ART. More data are needed on pregnancy outcomes among women who conceive on ART, particularly with newer regimens. Randomized clinical trials of newer ART regimens provide an opportunity to follow women who conceive on study to learn about safety and efficacy of treatment throughout the life span.

Notes

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