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Pregnancy outcomes of women conceiving on antiretroviral therapy (ART) compared to those commenced on ART during pregnancy.

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Key points

Globally more women living with HIV conceive on ART. This study reports an increased risk of low birth weight, spontaneous abortion, stillbirth and neonatal death for women conceiving on ART compared to those not on ART at conception.

Abstract

Background

Globally, the number of HIV-infected women of child-bearing age conceiving on ART is increasing. Evidence of ART safety at conception and during pregnancy and adverse pregnancy outcomes remains conflicting. The PROMISE 1077 breastfeeding (BF) and formula feeding (FF) international multisite trials provide an opportunity to examine the impact of ART at conception on pregnancy outcomes with subsequent pregnancies.

Methods

The PROMISE 1077BF/1077FF trials were designed to address key questions in the management of HIV-infected women who did not meet clinical guidelines for ART treatment during the time of the trials. After the period of risk of mother-to-child transmission was over, women were randomized to either continue or discontinue ART. We compared subsequent pregnancy outcomes of non-breastfeeding women randomized to continue ART following delivery, or breastfeeding women randomized to continue ART following breastfeeding cessation who conceived while on ART to women randomized to discontinue ART, who re-started ART after pregnancy was diagnosed.

Results

Pregnancy outcomes of 939 subsequent pregnancies of 826 mothers were recorded. The intention-to-treat analyses showed increased incidence of low birth weight (<2500gm) for women who conceived while on ART {relative risk 2.65 (95% CI 1.20, 5.81)}, and also a higher risk of spontaneous abortion, stillbirth, or neonatal death {hazard ratio 1.40 (0.99, 1.98)} compared to women who re-started ART after they were found to be pregnant during trial follow up.

Conclusions

We found an increased risk for adverse pregnancy outcomes in women conceiving on ART emphasising the need for improved obstetric and neonatal care for this group.

Keywords

Pregnancy outcomes conceiving on ART

PROMISE 1077BF and 1077FF are posted on ClinicalTrials.gov, with tracking number NCT01061151 (https://clinicaltrials.gov/ct2/show/NCT01061151).

Introduction

Universal antiretroviral therapy (ART) for all HIV-infected pregnant and breastfeeding women was offered since 2012 (Option B+) and rolled out more broadly since 2014 based on World Health Organisation (WHO) recommendations.(1) Increasingly, more HIV-infected women of child-bearing age are conceiving while on ART.(2) Evidence on the risk for adverse pregnancy outcomes with ART use at conception and during pregnancy is conflicting.(3,4,5) A meta-analysis of 11 studies by Uthman et al. demonstrated a significantly increased risk of preterm delivery (<37 weeks), very preterm delivery (< 32 or 34 weeks), and low birth weight (LBW, <2500g) when conceiving on ART compared to initiating ART during pregnancy.(6) The magnitude of the association of preterm delivery for women who conceived while on ART was stronger in low and middle income countries (LMIC) compared to high income countries. Preterm infants in LMIC, in addition, have an increased mortality risk.(7) However, studies of ART at conception have been observational and are subject to bias. Further research is necessary to understand these risks and to identify safest maternal ART regimens for optimized pregnancy and infant outcomes.

Clinical trial data from the international multisite PROMISE trials provide an opportunity to study this question using robust data from varied settings. The PROMISE 1077 breast feeding (BF) and 1077 formula feeding (FF) trials were designed to test the relative efficacy and safety of various proven antiretroviral (ARV) regimens for perinatal HIV prevention (PHP) of HIV among women who did not meet in-country guidelines for treatment at the time of the trial. The PROMISE 1077 HAART standard (HS) study, conducted in 8 countries, randomized 1653 asymptomatic HIV infected non-breastfeeding women with CD4 count >400 cells/ mm^3 who started ART during pregnancy to continue or discontinue ART within 42 days after delivery.(8) Subsequent pregnancies occurred in 277 (17%) women.(9) Spontaneous abortions and stillbirths were significantly more common among

women in the continue ART arm, compared to the discontinue arm. This study raises further questions around the risks of conception on ART.

The PROMISE 1077 BF and FF trials were conducted in 14 sites in 7 LMIC in India, Southern and Eastern Africa; and offer the opportunity to examine subsequent pregnancy outcomes in a larger cohort.(10) HIV-infected pregnant women with CD4 counts of at least 350 cells/mm^3 were evaluated on ART PHP regimens for maternal safety and efficacy in a randomised controlled trial. There were multiple comparisons at different time points: antenatal, postpartum, and post-breastfeeding, evaluating primary outcomes of safety and efficacy.(10, 11) This study evaluated subsequent pregnancy outcomes for PROMISE women who, after the period of risk of mother-to-child transmission was over, were randomized to either continue ART and were on ART at conception or discontinued ART and only restarted ART after they were found to be pregnant (ART re-initiation-in-pregnancy).

This secondary post-hoc analysis evaluates rates of spontaneous abortion, stillbirth, LBW and neonatal death by randomized arm among women with subsequent pregnancies. Associations of these outcomes with exposure to specific ART regimens were also determined. This PROMISE study is the largest cohort to be examined with longitudinal randomized ARV data available.

Methods

PROMISE 1077BF and 1077FF (Figures 1 and 2) was conducted at 14 sites in 7 countries (India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe). The study included open-label, parallel randomization components to address questions in the management of HIV-infected women with CD4 T-cell counts ≥350 cells/mm^3 and who did not meet clinical guidelines for ART initiation at the time of the study while also evaluating infant ARV prophylaxis during breastfeeding.(10) The postpartum preferred study maternal ART regimen was tenofovir, emtricitabine or lamivudine, and lopinavir/ritonavir (LPV/r). Regimens not provided by the study were allowed if they met the definition for combined ART of at least three or more drugs from two or more ARV classes. The trial

was performed in settings where breastfeeding was common, but allowed enrolment of both breastfeeding and formula feeding mothers. The postpartum (PP) randomizations differed by breastfeeding status. Formula-feeding women were randomized to continue or discontinue ART at delivery. Breastfeeding women and their infants were randomized to maternal ART or daily infant nevirapine (NVP) prophylaxis (no maternal ART) shortly after delivery. Another randomization at cessation of breastfeeding compared the effects on maternal health of continuing versus discontinuing ART. Follow up of all maternal participants continued until 96 weeks after the last delivery; infants were followed for two years. Maternal postpartum follow-up visits were around 1, 6, and 14 weeks after delivery and then every 12 weeks. Pregnancy tests were done when clinically indicated and for all women on efavirenz (EFV) beginning around 14 weeks postpartum and subsequently at 12 weekly intervals. Data presented includes all women randomized postpartum.

Women who became pregnant during follow-up in the PROMISE study, including women with more than one subsequent pregnancy, remained in the study and the pregnancy outcome of all pregnancies were recorded. Pregnancy outcomes included live births, live births followed by a neonatal death (≤28 days), ectopic pregnancies, induced and spontaneous abortions (<20 weeks), and stillbirths. Women receiving ART as part of the study continued to receive their study drugs, following additional informed consent. Women on a LPV/r regimen received a dose increase in the third trimester. Women not on a study ART regimen were treated according the local standard of care ART regimen. Data collected from women with subsequent pregnancies included demographic, clinical and laboratory data. Summary data of women included age, gravidity, and parity at the time of the estimated conception date of the first subsequent pregnancy. Pregnancy data included pregnancy complications, birth weight, gestational age at delivery, and type of delivery. Gestational age was based on an ordered hierarchal approach using ultra-sound, clinical exam, or LMP date. Diagnosis of subsequent pregnancy was based on urine or blood test or clinical examination. Body mass index was calculated based on the last maternal height and weight measured before the conception date. WHO clinical stage at baseline was the last classification given to a mother at or

before the estimated conception date, and CD4 and plasma HIV-RNA levels were the last available values. History of alcohol or smoking as reported at PROMISE entry and the hepatitis B surface antigen result prior to the first randomization. Summary data of infants include birth weight, sex, congenital abnormalities, and Apgar scores. Poor pregnancy outcomes included spontaneous abortion, stillbirth, neonatal death, and LBW.

In mid-2015, a change in the PROMISE protocols occurred due to the results of the START study, which demonstrated a significant benefit to receiving ART for people with high CD4 counts.(12) On July 7, 2015, PROMISE sites were notified that all maternal PROMISE participants should be recommended to take ART, breaking the randomizations. Analyses done by randomization arm in this study are thus limited to conceptions before July 7, 2015.

Ethics approval

The conduct of the study was approved by the respective local and collaborating Institutional Review Boards (IRBs) at each site. Written informed consent was obtained from all participating women.

Statistical analysis

Multiple imputation was used to include pregnancies in the analysis with known pregnancy outcomes but missing expected delivery date, gestational age, and LMP, while also accounting for the uncertainty in the missing term lengths. Gestational age was used to estimate each pregnancy's conception date, which determined the treatment designation in the analyses. The probability integral transform was used in the multiple imputation of missing conception dates.

Two types of analyses were conducted of pregnancy outcomes among women with repeat pregnancies: (1) by arm analyses in which data were restricted to pregnancies before July 7, 2015, and (2) time-to-event analyses that included all observed subsequent pregnancies. Both types evaluated the risk of spontaneous abortion, stillbirth, and neonatal death while the by arm analyses also separately evaluated the risk of LBW among live births. The first type of analysis used

generalized estimating equations to account for multiple repeat pregnancies, and was conducted with three strategies: (1) intention-to-treat (ITT); (2) excluding crossovers, those whose treatment at the time of estimated conception differed from the treatment assigned at randomization; and (3) as treated, analysis based on recorded regimen at estimated conception. The second analysis used Cox proportional hazards regression, clustered for multiple repeat pregnancies, and adjusted for country and previous adverse pregnancy outcome on study. The Cox models used ART exposure as a time-varying covariate, and regimens were grouped in two different ways: (1) a simple indicator for any ARV (compared to no ARVs) at a given time and (2) categorized based on the regimens. All analyses were conducted using SAS 9.4. Results were considered inconclusive if the 95% confidence interval (CI) included the null hypothesis of no difference.

Results

The 1077BF and 1077FF trials in breastfeeding and formula-feeding settings began enrolment in April and May 2011, respectively. Baseline characteristics by randomization arm for mothers are shown in Table 1. The last column in Table 1 includes all women with subsequent pregnancies. ART regimens at conception were approximately 30.8% protease inhibitor-based, 10.1% non-nucleoside reverse transcription inhibitor(NNRTI)-based, and 0.4% nucleoside reverse transcription inhibitor(NRTI)-only. The NNRTI-based regimen was primarily tenofovir, emtricitabine or lamivudine, and efavirenz. Pregnancy outcomes by subsequent pregnancy number are shown in Table 2. In total, there were 939 subsequent pregnancies recorded. Gestational ages were unknown in 36% to 64% of subsequent pregnancy outcomes that progressed to the second half of pregnancy. Therefore, a meaningful analysis with gestational age as an outcome was not possible, and the analyses focused on spontaneous abortions, stillbirths, neonatal deaths, and birth weight outcomes.

Subsequent pregnancy birth weights for the entire PROMISE follow-up subsequent pregnancy cohort are shown in Table 3A. Only live births were included in this analysis. Birthweights were available for 465 (72%) infants, of which 60 (13%) of the pregnancies resulted in LBW infants (<2500g). Table

3B shows subsequent pregnancy birth weights by comparison group and randomization arm for women with a conception date before July 7, 2015. There were 11 (17%) LBW infants among women in the ART at conception group, versus 5 (7%) in the ART re-initiated in pregnancy group. Among women randomized after cessation of breastfeeding, there were 8 (29%) LBW infants in the ART at conception versus 4 (14%) in the ART re-initiated in pregnancy groups.

Table 4 shows the analyses of LBW in the ART at conception versus ART re-initiation in pregnancy groups for those randomized at delivery and after breastfeeding. The analysis combining the groups randomized at delivery and after breastfeeding by intention to treat (ITT) and excluding crossovers both showed increased risk of LBW delivery in the ART at conception group with relative risks of 2.65 (95% CI 1.20, 5.81) and 2.94 (1.24, 6.98) respectively. The as-treated analysis RR was 2.47 (1.00, 6.14). When analysed separately as randomized at delivery and after breastfeeding the results were inconclusive since the 95% CIs included both increased and decreased relative risks.

Table 5 shows the result from the time-to-event analysis with a time-varying ART exposure indicator. Compared to ART re-initiation-in-pregnancy, the hazard rate of spontaneous abortion, stillbirth, or neonatal death among mothers in the ART at conception group was higher {HR=1.40 (0.99, 1.98)}. Table 5 also includes results with time-varying ART by regimen category. Comparing the ART at conception to the ART re-initiation in pregnancy groups, including NNRTI without a PI had a higher hazard rate of spontaneous abortion, stillbirth, or neonatal death {HR=1.48 (1.02, 2.14)}. Mothers on-ART at conception including LPV/r or on a nucleoside reverse transcribe inhibitor (NRTI) only regimen had higher hazard rates for the composite poor pregnancy outcomes, but the result was inconclusive. Country of residence did not have a large overall effect on the hazard ratios.

Discussion

The PROMISE 1077BF and 1077FF randomized trials, conducted in mid to low income countries (13) in sub-Saharan Africa and India, compared maternal health outcomes for women randomized to either continue or discontinue ART after the period of transmission risk for their infant.(10) Some women in PROMISE subsequently became pregnant again during study follow-up providing a unique opportunity to assess pregnancy outcomes among women who conceived while on ART compared to those who had discontinued ART. The post hoc analyses found that women who were on ART at the time of conception had an increased risk of adverse pregnancy outcomes compared to women not on ART the time of conception. This included a greater than two fold risk of delivering a low birth weight baby and a 1.4 fold increased risk of having either a spontaneous abortion, stillbirth, or neonatal death. In previous reports, the risk for LBW is increased with more advanced HIV disease.(14) However, the index study population were mainly WHO clinical stage I (>95%) asymptomatic HIV-infected women with high CD4 counts and low viral loads, suggesting that risk remains for all HIV-infected women conceiving on ART. The findings are important in high HIV prevalence countries in sub-Saharan Africa as more and more HIV-infected women conceive while receiving lifelong ART.

Our PROMISE findings are similar to some but not all prior published data. In a meta-analysis including 52 cohort studies, Xiao et al., found a significant association between HIV infection and LBW and preterm deliveries.(14) However, in a subgroup analysis, women receiving ARVs had a similar risk of LBW compared to those who did not.(15) This finding concurs with a meta-analysis by Kourtis et al., that found no association between ARV use during pregnancy and preterm delivery.(16) Kourtis et al. did, however, find a significant association between ART initiation pre-pregnancy or during the first trimester and prematurity, versus initiation in the second or third trimester, which supports our findings.(16) Likewise, the meta-analysis by Uthman et al., confirmed a significantly increased risk of preterm delivery, very preterm delivery, and low birth weight (LBW,

<2500g) when conceiving on ART compared to initiating ART during pregnancy.(6) The magnitude of the association of preterm delivery was stronger in the 5 LMIC compared to 5 high income countries. These findings, which included LBW, small for gestational age (SGA), and preterm delivery warrants their inclusion as outcome criteria in future trials including HIV-infected women. In addition, accurate gestational age determination needs to be a prerequisite to assess the contribution SGA babies in the LBW group.

The related PROMISE 1077HS trial provides data supporting the potential risks of ART exposure at the time of conception. PROMISE 1077HS was conducted in 56 sites in high and middle income countries where ART during pregnancy was standard of care as was formula feeding.(8) Women in PROMISE 1077HS were generally healthy with high CD4 counts, 90% had WHO clinical stage I disease and 55% were virally supressed.(9) There were 227 subsequent pregnancies during follow-up. PROMISE 1077HS did not report the incidence of preterm deliveries and LBW but found a significantly increased risk of stillbirth and/or spontaneous abortion among those women on ART at the time of conception compared to women who had discontinued ART.

Similar to the 1077HS results, the 1077BF/1077FF analyses found an increased risk of spontaneous abortion and stillbirths in subsequent pregnancies for women on ART at conception. In addition, we found an increased risk of LBW and neonatal death. We also noted some differences by type of ART regimen: Women on ART at conception including a NNRTI without a PI had a higher risk of spontaneous abortion, stillbirths, and neonatal deaths. For women on ART including a PI or NRTI-only regimen, the risk was also higher, but with a result that was inconclusive. In contrast, Stringer et al (PLOS 2018) did not find any significant difference in preterm birth by class of preconception ART in a meta-analysis including 3 ART trials.(17). An observational surveillance study from Botswana reported a significantly increased risk of preterm birth for infants born to mothers on LPV/r-based ART compared to those on EFV based ART.(18). These contrasting findings may be

related to differences in sample sizes or to differences in other background risk factors for preterm birth among these varied cohorts.

The overall incidence of spontaneous abortion were reported in 12% of this cohort, is similar to population based rates of 8 to 20% and to that reported in the PROMISE 1077HS study (15%).(9,19) The slight differences could be explained by higher very early spontaneous abortion detection in the 1077HS trial.

Missing gestational age and birth weight were limitations of this sub-study. However, strengths include that the data was collected in a carefully monitored trial and generalizability is increased by the multisite, multi-country design of the PROMISE trial.

Progress towards the UNAIDS 90-90-90 targets by 2020, has resulted in increasing numbers of HIV-infected women conceiving while on ART.(20) The benefit of ART in improving maternal health and reducing mother-to-child transmission have been proven beyond doubt in large randomized trials.(8,10) However, the PROMISE findings underscore the need for ongoing prospective monitoring of pregnancy outcomes as new ART regimens are rolled out, which include the recent WHO recommendations (IAS 2019) for use of Dolutegravir-based ART as the first line treatment regimen in resource limited settings.(21)

The Botswana Tsepamo Birth Outcomes Surveillance Study and the Antiretroviral Pregnancy Registry data serve as examples of combining ongoing research and surveillance during the ARV era.(22) Monitoring for possible adverse pregnancy outcomes related to ART will contribute towards improved care of HIV-infected women and their infants. In addition, the inclusion of pregnant women in trials evaluating new ARV drugs is crucial.(23)

Notes

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Disclaimer

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Conflict of interest

None of the authors have any conflict of interest to declare.

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Table 1: Baseline characteristics

		By Arm Analyses[1] (Conceptions prior to July 7, 2015 only)				Time-to-Event Analyses[2] (All conceptions)
		Randomized at delivery		Randomized after breastfeeding		All mothers (N=760)
		ART at conception (N=97)	ART re-initiation-in-pregnancy (N=121)	ART at conception (N=41)	ART re-initiation-in-pregnancy (N=41)	
Age (years) at estimated conception	N	96	121	41	41	755
	# missing	1	0	0	0	5
	Min-Max	19-41	19-39	21-37	21-39	19-43
	Median (Q1-Q3)	27 (24-31)	28 (25-32)	28 (25-32)	25 (23-28)	28 (24-31)
Country	India	2 (2%)	3 (2%)	3 (7%)	3 (7%)	39 (5%)
	Malawi	35 (36%)	43 (36%)	15 (37%)	17 (41%)	240 (32%)
	South Africa	26 (27%)	26 (21%)	9 (22%)	4 (10%)	188 (25%)
	Tanzania	2 (2%)	1 (1%)	0 (0%)	0 (0%)	10 (1%)
	Uganda	21 (22%)	23 (19%)	8 (20%)	10 (24%)	135 (18%)
	Zambia	0 (0%)	5 (4%)	0 (0%)	0 (0%)	15 (2%)
	Zimbabwe	11 (11%)	20 (17%)	6 (15%)	7 (17%)	133 (18%)
Race or ethnic group	Black African	95 (98%)	118 (98%)	38 (93%)	38 (93%)	719 (95%)
	Indian	2 (2%)	3 (2%)	3 (7%)	3 (7%)	40 (5%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Time (months)	N	96	121	41	41	755

between 1st PROMISE pregnancy outcome date and subsequent conception	# missing	1	0	0	0	5
	Min-Max	1-46	2-45	6-44	4-39	1-57
	Median (Q1-Q3)	16 (11-25)	18 (11-24)	22 (16-30)	23 (16-28)	22 (13-34)
BMI (kg/m²) at or before estimated conception	N	95	121	41	41	753
	# missing	2	0	0	0	7
	Min-Max	18-49	19-37	19-37	16-41	16-49
	Median (Q1-Q3)	26 (23-29)	26 (23-29)	26 (22-28)	25 (23-27)	26 (23-29)
WHO Stage at or before estimated conception	Clinical stage I	84 (88%)	112 (93%)	35 (85%)	36 (88%)	683 (90%)
	Clinical stage II	11 (11%)	8 (7%)	6 (15%)	4 (10%)	61 (8%)
	Clinical stage III	1 (1%)	1 (1%)	0 (0%)	1 (2%)	9 (1%)
	Clinical stage IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0%)
CD4 (cells/mm³) at or before estimated conception	N	96	121	41	41	755
	Min-Max	350-1,545	306-1,568	531-1,545	350-1,297	216-1,908
	Median (Q1-Q3)	818 (648-952)	600 (485-729)	771 (654-952)	710 (519-843)	692 (533-885)
Plasma HIV RNA (copies/mL) at or before estimated conception	N	96	121	41	41	755
	Min-Max	20-89,755	20-975,501	20-27,372	30-203,421	20-975,501
	Median (Q1-Q3)	40 (40-1,052)	3,726 (473-13,113)	40 (40-40)	565 (200-9,498)	200 (40-5,277)
	<400	62 (65%)	27 (22%)	37 (90%)	15 (37%)	413 (55%)
History of alcohol or smoking at	Yes, one	21(22%)	16 (13%)	4(10%)	8 (20%)	114 (15%)

PROMISE entry	Yes, both	1 (1%)	1 (1%)	0 (0%)	1 (2%)	11 (1%)
Hepatitis B Positive antigen result prior to first randomization in PROMISE		7 (7%)	8 (7%)	5 (12%)	1 (2%)	36 (5%)
Gravida prior to first subsequent pregnancy	1-2	52 (54%)	59 (49%)	22 (54%)	27 (66%)	413 (54%)
	3-4	39 (40%)	53 (44%)	15 (37%)	13 (32%)	296 (39%)
	5+	6 (6%)	9 (7%)	4 (10%)	1 (2%)	51 (7%)
Cohort Participation[3]	A	58	121	0	0	
	B	0	0	20	23	
	A+B	39	0	21	18	

Induced abortions, ectopic or other non-viable pregnancies, and missing outcomes were excluded. Variables reported "at or before estimated conception" were based on the average of imputed term lengths for mothers with missing gestational ages.

[1]Characteristics for mothers analysed in the by arm analyses, limited to those with estimated conception dates after the comparison group randomization, and prior to the protocol change on July 7, 2015.

[2]Characteristics for all PROMISE mothers with subsequent pregnancies.

[3]Mothers could be randomized after delivery and/or after breastfeeding cessation. A total of 39 mothers were overlaps, undergoing both randomizations.

Table 2: Pregnancy outcomes for all PROMISE subsequent pregnancies

		Subsequent pregnancy number[1]			
		1st (N=837)	**2nd (N=97)**	**3rd (N=5)**	**Total (N=939)**
Pregnancy outcome	Ectopic or other non-viable pregnancy	11 (1%)	0 (0%)	0 (0%)	11 (1%)
	Induced abortion	64 (8%)	10 (13%)	1 (33%)	75 (9%)
	Spontaneous abortion (< 20 weeks)	100 (13%)	6 (8%)	0 (0%)	106 (12%)
	Stillbirth (≥ 20 weeks)	25 (3%)	0 (0%)	0 (0%)	25 (3%)
	Live birth	558 (72%)	57 (72%)	2 (67%)	617 (72%)
	Live birth followed by neonatal death (≤ 28 days)	19 (2%)	6 (8%)	0 (0%)	25 (3%)
	Missing data	60	18	2	80

Outcomes are from 826 mothers, from any pregnancy that occurred after the first PROMISE pregnancy.

[1] 1st, 2nd, and 3rd subsequent pregnancies on PROMISE.

Table 3A: Birth weights among infants born from a PROMISE subsequent pregnancy

		Subsequent pregnancy number[1]			
		1st (N=577)	**2nd (N=63)**	**3rd (N=2)**	**Total (N=642)**
Birth Weight[2]	Very low birth weight (<1500g)	5 (1%)	2 (4%)	0 (0%)	7 (2%)
	Low birth weight (≥1500g-<2500g)	46 (11%)	7 (14%)	0 (0%)	53 (11%)
	Not a low birth weight (≥2500g)	363 (88%)	40 (82%)	2 (100%)	405 (87%)
	Live birth with missing birth weight	163 (28%)	14 (22%)	0	177 (28%)

Outcomes are from 600 mothers, from any live birth that occurred after the first PROMISE pregnancy.

[1] 1st, 2nd, and 3rd subsequent pregnancies on PROMISE.

[2] Percentages for known birth weights out of the total number of non-missing observations.

Table 3B: Birth weights among infants born from a PROMISE subsequent pregnancy with a conception date before July 7th, 2015, by comparison group

		Comparison group and randomization arm				
		Randomized at delivery		Randomized after breastfeeding		
		ART at conception (N=90	ART re-initiation in pregnancy (N=105)	ART at conception (N=39)	ART re-initiation in pregnancy (N=39)	Total (N=237)
Birth weight	Very low birth weight (<1500g)	0 (0%)	1 (1%)	2 (7%)	0 (0%)	3 (2%)
	Low birth weight (≥1500g-<2500g)	11 (17%)	4 (6%)	6 (22%)	4 (14%)	20 (13%)
	Not a low birth weight (≥2500g)	52 (83%)	63 (93%)	19 (70%)	24 (86%)	137 (86%)
	Live birth with missing birth weight	27	37	12	11	77

Outcomes are from 184 mothers in comparison group 2a and 71 mothers in 2b, with 34 mothers overlapping. The birth weights shown are limited to pregnancies with estimated conception dates before the protocol change on July 7, 2015.

Table 4: Risk of low birth weight among the on-ART at conception (cART) and the ART-re-initiation-in-pregnancy (pART) randomization groups by analysis type

Group[1]	Analysis Type[2]	Average count[3] of low birth weight cART	Average count of low birth weight pART	Percent[3] with low birth weight cART	Percent with low birth weight pART	Relative risk (95% CI) comparing cART to pART
A+ B	ITT	16	7	21.2%	8.0%	2.65 (1.20, 5.81)
	Excluding crossovers	14	7	26.6%	9.0%	2.94 (1.24, 6.98)
	As treated	14	9	22.3%	9.0%	2.47 (1.00, 6.14)
A	ITTITT	1117.9%	6 8.0%	2.24 (0.98, 5.11)	0.86%	2.24 (0.98, 5.11)
	Excluding crossovers	9	6	23.2%	9.1%	2.56 (0.98, 6.71)
	As treated	9	8	18.8%	9.0%	2.08 (0.76, 5.72)
B	ITT	10	3	25.0%	12.3%	2.03 (0.71, 5.79)
	Excluding crossovers	8	3	28.9%	13.4%	2.15 (0.60, 7.62)
	As treated	8	5	26.9%	14.5%	1.86 (0.51, 6.80)

Only live birth outcomes were analysed. Low birth weight is defined as < 2500 g.

[1] Randomization Group. A: Randomization at delivery. B: Randomization after breastfeeding.

[2] ITT: Intention to treat analysis. For the As Treated analyses, cART means on ART at conception and pART means re-initiated ART during pregnancy (rather than as randomized)

[3] Average counts are across 1000 imputations. Since dates were imputed and determine the treatment assignment, the treatment assignment could change across imputations. Percentages are based on the average counts of low birth weights across the imputations.

Table 5: Hazard ratios for adverse pregnancy outcomes comparing time-varying ART exposure or time-varying regimen group to no ART

Endpoint	ART Exposure and Regimen Group	Hazard Ratio (95% CI)
Spontaneous abortion, stillbirth, or neonatal death	No ART	Ref
	On ART at Conception	1.40 (0.99, 1.98)
	ART including boosted/non-boosted PI	1.24 (0.79, 1.93)
	ART including NNRTI with no PI	1.48 (1.02, 2.14)
	Only NRTIs	3.11 (0.73, 13.33)

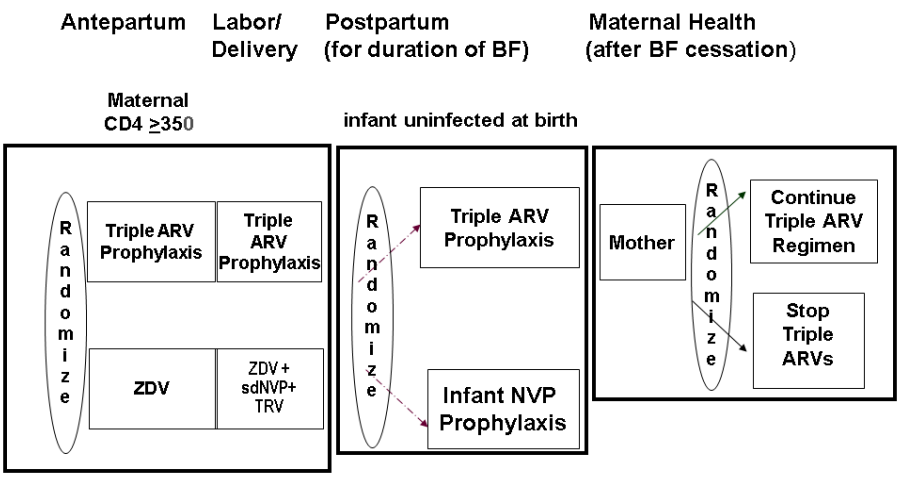
Results are based on 1000 imputations of missing gestational ages. Live births followed by neonatal deaths within 28 days were censored at the time of birth. Model was adjusted for country and for whether the mother's first PROMISE pregnancy resulted in a spontaneous abortion, stillbirth, neonatal death, or low birth weight (<2500 g).

Figure Legends:

Figure 1: Overall design of the PROMISE 1077BF trail including the Antepartum, Postpartum and Maternal Health components with 3 randomizations (n=3490)

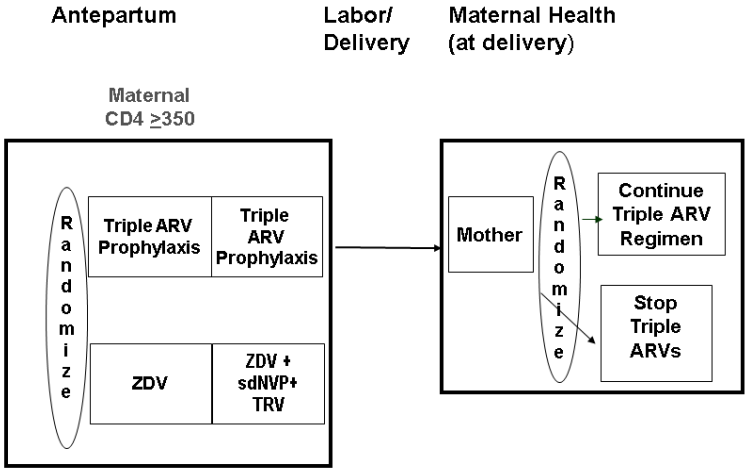
Figure 2: Overall design of the PROMISE 1077FF trial including the Antepartum, and Maternal Health components with 2 randomizations (n=284)

Figure 1



Sites: Zimbabwe, Uganda, Zambia, Malawi, South Africa, Tanzania, India

Figure 2



Sites: South Africa, India