Subsequent Pregnancy Outcomes in Women During Follow-up in PROMISE 1077HS

Jose H Pilotto[1], Sean Brummel[2], Risa M Hoffman[3], Paula Britto[2], Gaerolwe Masheto[4], Linda Aurpibul[5], Nahida Chakhtoura[6], Karin Klingman[7], Judith S Currier[3]

1 Oswaldo Cruz Foundation/Fiocruz & HGNI, Rio de Janeiro, Brazil; 2 Harvard T.H. Chan School of Public Health, Boston, MA, USA 3 David Geffen School of Medicine at University of California Los Angeles, Division of Infectious Diseases, Los Angeles, CA, USA; 4 Botswana Harvard AIDS Institute Partnership, Gaberone, Botswana; 5 Chiang Mai University, Chiang Mai, Thailand; 6 NICHD, Bethesda, MD, USA; 7 DAIDS, NIAID/NIH, DHHS, Bethesda, MD, USA

ABSTRACT

BACKGROUND

Rates of adverse pregnancy outcomes for women who conceive on ART may be increased, but data are conflicting.

METHODS

In PROMISE 1077HS, asymptomatic HIV+, non-breastfeeding women with pre-ART CD4 cell count ≥400 cells/mm3 who started ART during pregnancy were randomized up to 42 days after delivery to continue (cART) or discontinue ART (dART). LPV/RTV with TDF/FTC or ZDV/3TC was the preferred study regimen. Sixty sites in Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand and the US participated between 12/2011-11/2014. Women randomized to dART were recommended to restart if a subsequent pregnancy occurred or for clinical indications. This analysis includes outcomes for all subsequent pregnancies that occurred prior to offering all women ART in 7/2015. We compared subsequent pregnancy outcomes among women in the cART versus dART arm using Fisher's exact test (post hoc analysis).

RESULTS

Subsequent pregnancies occurred in 277/1652 (17%) women (cART: 144/827, dART: 133/825). A pregnancy outcome was recorded for 266 women with median age 27.4 years (IQR 23.7, 31.1) at pregnancy diagnosis and median CD4 688 cells/mm3 (IQR 529, 867) recorded at 2 months prior pregnancy diagnosis. Two hundred (75%) live births were included, 40 (15%) spontaneous abortions (<20 weeks gestation), 18 (7%) induced abortions (<20 weeks gestation) and 8 (3%) stillbirths (≥20 weeks gestation). At 12 weeks prior to pregnancy diagnosis, 86% (120/140) in the cART group were on a boosted/non-boosted PI regimen versus 6% (8/140) NNRTI. In the dART arm, 19/126 (15%) restarted ART prior to pregnancy diagnosis: 74% (14/19) were on a PI regimen versus 26% (5/19) NNRTI. After pregnancy diagnosis (first regimen during pregnancy), there was frequent use of PIs in the cART arm (89% (124/140) PI versus 7% (10/140) NNRTI) and among those restarting ART in the dART arm (53% (67/126) PI versus 27% (34/126) NNRTI). Spontaneous abortions were more common in the cART arm (cART: 19.3% (27/140), dART: 10.3% (13/126); p=0.06), as were stillbirths (cART: 4.3% (6/140), dART: 1.6% (2/126); p=0.29). When stillbirths and spontaneous abortions were combined, there was a statistically significant higher rate in the cART arm (cART: 23.6% (33/140), dART: 11.9% (15/126); p=0.02).

CONCLUSION

Women randomized to continue ART after their index pregnancy who subsequently conceived were more likely to have spontaneous abortion or stillbirth compared to women randomized to stop ART.

BACKGROUND

More than 1 ½ million HIV-infected women will become pregnant and deliver babies annually, and the majority of these women now receive ART antepartum[1]. As the availability of ART expands globally and more women conceive on ART, it is imperative that we collect adequate safety and efficacy data for pregnancy outcomes.

Previous studies have shown higher rates of adverse pregnancy outcomes (preterm birth, stillbirth, small for gestational age, and in some instances spontaneous abortion) associated with HIV infection and/or with ART in pregnancy[2] and some regimens may be safer than others with regard to adverse pregnancy outcomes[3,4].

The PROMISE 1077HS study design provided 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, who had a subsequent pregnancy.

METHODS

PROMISE 1077HS was an open-label, randomized clinical trial evaluating two strategies for the management of ART among postpartum women within 42 days after delivery: continuing ART (cART) or discontinuing ART (dART) and restarting when clinically indicated (Figure 1). 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 one of the following criteria:

1) Developed an AIDS-defining/WHO Stage 4 illness,
2) Had a confirmed CD4+ T-cell count <350 cells/mm^3,
3) Developed a clinical condition (other than pregnancy) considered an indication for ART by country-specific guidelines or otherwise required ART as determined by the clinical management committee.

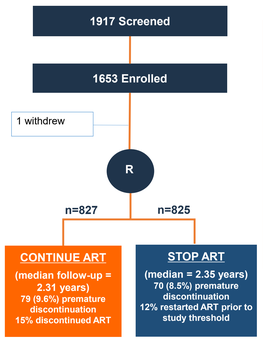
Women randomized to stop ART who became pregnant were restarted on ART per the local country guidelines. Pregnancy testing was performed at each follow-up visit. Information on the initial subsequent pregnancy outcomes was collected for all women who developed a pregnancy during study follow-up.

We used Fishers exact test to compare subsequent pregnancy outcomes by arm. The date of conception was estimated by subtracting 40 weeks from the estimated date of delivery. Sixty-three women did not have expected date of delivery recorded and, for these women, we imputed length of pregnancy using the observed length of pregnancy averages for a given pregnancy outcome.

The preferred study supplied ART regimen was Lopinavir/Ritonavir (LPV/RTV) plus fixed dose combination Emtricitabine/Tenofovir(FTC/TDF). This regimen was chosen because it was the preferred regimen for use in pregnancy by the DHHS guidelines at the time the study was designed. Additional study-supplied antiretrovirals (ARVs) included: Lamivudine/Zidovudine (3TC/ZDV), Lamivudine (3TC), Zidovudine (ZDV), Tenofovir disoproxil fumarate (TDF), fixed dose combination Emtricitabine/Tenofovir disoproxil fumarate/Rilpivirine (FTC/TDF/RPV), Atazanavir (ATV), Raltegravir (RAL), and Ritonavir (RTV).

PROMISE COUNTRIES
Argentina
Botswana
Brazil
China
Haiti
Peru
Thailand
United States

FIGURE 1. PROMISE 1077HS study design



RESULTS

TABLE 1. Characteristics of women with a subsequent pregnancy

Characteristic		Randomization Arm: Continuation of ART (N=140)	Discontinuation of ART (N=126)	Total (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%)
	USA	20 (14%)	15 (12%)	35 (13%)
Age at time of estimated conception (years)	N	140	126	266
	Min-Max	18-40	18-42	18-42
	Median (Q1-Q3)	27 (23-31)	28 (24-31)	27 (24-31)
	# missing	0	0	0
BMI at time of estimated conception (kg/m^2)*	N	138	123	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)
	# missing	2	3	5
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/mm^3)	N	138	123	261
	Min-Max	215-1577	200-1704	200-1704
	Median (Q1-Q3)	730 (606-890)	525 (404-682)	638 (492-833)
	# missing	2	3	5
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 - <10000	14 (10%)	19 (28%)	33 (16%)
	10000 - <100000	9 (7%)	11 (16%)	20 (10%)
	100000 - <2000000	3 (2%)	3 (4%)	6 (3%)
	≥200000	0 (0%)	1 (1%)	1 (0%)
	# missing	3	57	60

- Subsequent pregnancies occurred in 277/1652 (17%) women (cART: 144/827, dART: 133/825).
- A pregnancy outcome was recorded for 266 women with median age 26 years (IQR 22-30) and median CD4 638 cells/mm^3 (IQR 492-833) at estimated conception. At the time of conception, the majority (95%) were WHO clinical stage I. 65% of women were virologically suppressed (<400 copies/mL), 6% had between 400-1,000 copies/mL and 29% had a viral load of 1,000 copies/mL. Participant characteristics are summarized in Table 1.
- Two hundred (75%) live births were included:
  - 40 (15%) spontaneous abortions (<20 weeks gestation)
  - 18 (7%) induced abortions (<20 weeks gestation)
  - 8 (3%) stillbirths (≥20 weeks gestation)

- Subsequent pregnancy outcomes by arm are summarized below in Table 2.
  - **Spontaneous abortions were more common in the cART arm.**
  - **When stillbirths and spontaneous abortions were combined, there was a higher rate in the cART arm.**

TABLE 2. Pregnancy outcomes recorded for the initial subsequent pregnancy

	HS Randomization Arm: Continuation of HAART (N=140)	Discontinuation of HAART (N=126)	P-value
Live Birth	100 (71%)	100 (79%)	
Spontaneous Abortion (<20 weeks)	27 (19%)	13 (10%)	0.06
Stillbirth (IUFD ≥ 20 weeks)	6 (4%)	2 (2%)	0.29
Spontaneous Abortion or Stillbirth	33 (24%)	15 (12%)	0.02

- Subsequent pregnancy outcomes by country are summarized below in Table 3.
  - Spontaneous abortions were more frequent in Haiti and Thailand, followed by Botswana, Brazil, and the US.
  - Stillbirths were most common in China, followed by Argentina and Botswana.

TABLE 3. Pregnancy outcomes recorded for the initial subsequent pregnancy – by country

	Country: Argentina (N=12)	Botswana (N=93)	Brazil (N=74)	China (N=7)	Haiti (N=16)	Thailand (N=29)	USA (N=35)	Total (N=266)
Live Birth	11 (92%)	68 (73%)	60 (81%)	3 (43%)	11 (69%)	23 (79%)	24 (69%)	200 (75%)
Spontaneous Abortion (<20 weeks)	0 (0%)	15 (16%)	11 (15%)	0 (0%)	4 (25%)	6 (21%)	4 (11%)	40 (15%)
Induced Abortion (<20 weeks)	0 (0%)	4 (4%)	3 (4%)	3 (43%)	1 (6%)	0 (0%)	7 (20%)	18 (7%)
Stillbirth (IUFD≥ 20 weeks)	1 (8%)	6 (7%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	8 (3%)

TABLE 4. ART regimens 12 weeks before estimated conception (upper panel) and first regimen after pregnancy diagnosed (lower panel)

	HS Randomization Arm: Continuation of ART		Discontinuation of ART		TOTAL
ART Category	N	(%)	N	(%)	N
ART including boosted/non-boosted PI*	120	(86%)	14	(11%)	134
HAART including NNRTI with no PI	8	(6%)	5	(4%)	13
ART with NRTI only (includes 1, 2, or 3 NRTIs)**	3	(2%)	0	(0%)	3
ART including Integrase with no PI	1	(1%)	0	(0%)	1
No ARVs^	8	(6%)	107	(85%)	115
Total	140	(100%)	126	(100%)	266

	HS Randomization Arm: Continuation of ART		Discontinuation of ART		TOTAL
ART Category	N	(%)	N	(%)	N
ART including boosted/non-boosted PI*	124	(89%)	67	(53%)	191
ART including NNRTI with no PI	10	(7%)	34	(27%)	44
ART with NRTI only (includes 1, 2, or 3 NRTIs)**	3	(2%)	1	(1%)	4
ART including Integrase with no PI	1	(1%)	1	(1%)	2
No ARVs^	2	(1%)	23	(18%)	25
Total	140	(100%)	126	(100%)	266

* Four women were on PI combined with NNRTI, and 3 women were on PI combined with Integrase
** Two including TDF and one not on TDF
^ These women were not on any ART 12 weeks prior to pregnancy

- 12 weeks prior to pregnancy diagnosis, 86% of women in the cART group were on a boosted/non-boosted PI regimen versus 6% on NNRTI (Table 4, upper panel). After pregnancy diagnosis (first regimen during pregnancy), there was frequent use of PIs in the cART arm (89% PI versus 7% NNRTI).
- In the dART arm, (15%) restarted ART prior to pregnancy diagnosis. Of these women, 74% were on a PI-based regimen versus 26% NNRTI. Among those in the dART arm restarting ART for pregnancy, 53% were on PI versus 27% on NNRTI (Table 4, lower panel and Figure 2).
- Across the cohort, use of integrase-containing regimens during pregnancy was rare (<1%) as were regimens with NRTIs only (1.5%).

FIGURE 2. ART use in the initial subsequent pregnancy among women randomized to discontinue therapy

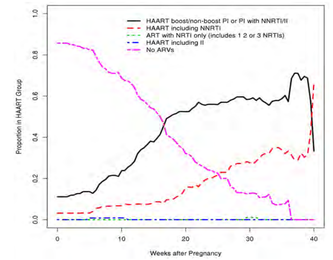


TABLE 5. Pregnancy outcome by ART category at time of estimated conception for the cART arm (upper panel) and dART arm (lower panel).

	Pregnancy Outcome cART Arm (N=140): Live Birth		Spontaneous Abortion (<20 weeks)		Induced Abortion (<20 weeks)		Stillbirth (IUFD ≥ 20 weeks)		TOTAL
ART Category	N	(%)	N	(%)	N	(%)	N	(%)	N (%)
ART including boosted/non-boosted PI	84	(74%)	18	(16%)	5	(4%)	6	(5%)	113 (81%)
ART including NNRTI with no PI	3	(38%)	4	(50%)	1	(13%)	0	(0%)	8 (6%)
ART with Integrase (no PI)	1	(100%)	0	(0%)	0	(0%)	0	(0%)	1 (<1%)
ART with NRTI only	2	(67%)	1	(33%)	0	(0%)	0	(0%)	3 (2%)
No ART in the 12 weeks prior to pregnancy	10	(67%)	4	(27%)	1	(7%)	0	(0%)	15 (11%)

	Pregnancy Outcome dART Arm (N=126): Live Birth		Spontaneous Abortion (<20 weeks)		Induced Abortion (<20 weeks)		Stillbirth (IUFD ≥ 20 weeks)		TOTAL
ART Category	N	(%)	N	(%)	N	(%)	N	(%)	N(%)
ART including boosted/non-boosted PI	12	(86%)	0	(0%)	1	(7%)	1	(7%)	14 (11%)
ART including NNRTI with no PI	3	(75%)	0	(0%)	1	(25%)	0	(0%)	4 (3%)
No ART in the 12 weeks prior to pregnancy	85	(79%)	13	(12%)	9	(8%)	1	(1%)	108 (86%)

- Table 5 describes subsequent pregnancy outcome by ART category in each of the arms:
  - Among 113 in the cART arm (upper panel) on a regimen that included a boosted or non-boosted PI, 16% had a spontaneous abortion and 5% experienced stillbirth; only 8 women in the cART arm were on NNRTI without PI and half of these had a spontaneous abortion and none experienced stillbirth.
  - In the cART arm, 15 women with a subsequent pregnancy were not on ART at the time of conception. In this group 27% had a spontaneous abortion.
  - In the dART arm (lower panel), the majority of women were off ART at conception (79%) and, of these, 12% had a spontaneous abortion and 1% stillbirth.

CONCLUSIONS

- Women randomized to continue ART who subsequently conceived were more likely to have spontaneous abortion or stillbirth compared to women randomized to stop ART.
- Pregnancy testing was performed frequently in PROMISE allowing for pregnancy to be detected early and allowing the opportunity to capture complete data on early pregnancy losses. These early pregnancy losses may be missed in clinical practice, as women may not be aware of pregnancy and/or present for medical attention.
- We did not capture other pregnancy outcomes and/or infant outcomes including preterm labor, preterm delivery, very preterm delivery, low birth weight, and very low birth weight, and we had a small number of women on NNRTI- and integrase-based ART limiting our ability to evaluate associations with specific regimens and individual pregnancy complications.
- More data are needed on pregnancy outcomes among women who conceive on ART, particularly with newer regimens. Randomized clinical trials of ART can provide an opportunity to follow women who conceive on study, to learn about outcomes.

ACKNOWEDGEMENTS

The 1077 PROMISE study team gratefully acknowledges the dedication and commitment of the 1652 participants without whom this study would not have been possible. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). Overall support for the AIDS Clinical Trials Group (ACTG) 5UM1AI068636.

REFERENCES

1. IATT Dashboard for Monitoring Progress Towards EMTCT Goals. 2015; 1–6. http://www.emtct-iatt.org/wp-content/uploads/2015/09 Accessed 18 April 2016.
2. Chen JY, Ribaudo HJ, Souda S, et al. Highly Active Antiretroviral Therapy and Adverse Birth Outcomes Among HIV-Infected Women in Botswana. Journal of Infectious Diseases 2012; 206: 1695–705.
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. Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. Journal of Infectious Diseases 2011; 204: 506–14.

Presented at CROI
Seattle, February 2017
Poster Number:772