Preterm birth among women with ultrasound-based gestational age dating PROMISE 1077BF/FF

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BACKGROUND

More than 1.5 million women with HIV become pregnant every year. As such, it is important to understand the consequences of antiretroviral therapy (ART) on preterm birth (PTB).

The PROMISE trial found that ART decreased the rate of HIV transmission compared to zidovudine (ZDV) alone, but an unanticipated finding was a high frequency of PTB and its association with ART.

Because of the lack of universal prenatal ultrasound dating, the PROMISE trial utilized newborn clinical exam based on the New Ballard Score (NBS).

When the last menstrual period (LMP) is not reliable, prenatal ultrasound is the preferred method for determining gestational age because newborn examination is prone to misclassification

We analyzed the association between ART and PTB <37 and <34 weeks in a subset of PROMISE participants with fetal ultrasound.

METHODS

PROMISE 1077BF/FF compared the efficacy and safety of multiple evidence-based strategies for the prevention of mother-to-child HIV transmission among asymptomatic women with HIV with high CD4 cell counts.

Participants were randomized to one of three arms: (1) **ZDV alone:** ZDV plus intrapartum single-dose nevirapine, (2) **ZDV-based ART:** ZDV, lamivudine, and lopinavir–ritonavir, and (3) **TDF-based ART:** TDF, emtricitabine, and lopinavir–ritonavir

In the current analysis, we included participants with a pre-randomization ultrasound and documented NBS. Exclusion criteria included multiple gestation, congenital anomaly, and fetal demise.

Prenatal ultrasounds were documented within the medical record. The indication for sonography was not available. All sites used the Hadlock formula to estimate gestational age.

Our primary outcomes were PTB <37 weeks and PTB <34 weeks.

Our statistical analysis included:

- Multivariable logistic regression: To ensure that participants with ultrasound did not differ from randomized trial participants.
- Covariates included: maternal characteristics (e.g., age, BMI, and country), obstetric history (e.g., # of prior preterm births), and HIV disease severity (e.g., baseline plasma viral load).
- Sensitivity analysis: restricted to ultrasounds <24 weeks because third trimester ultrasound can be unreliable.
- Comparison to PROMISE trial: we compared our results to an earlier trial analysis with NBS to illustrate potential differences.

RESULTS

Among 3,423 trial participants, 724 (21%) had available data for NBS and prenatal ultrasound.

The median gestational age at ultrasound assessment was 24.0 weeks (IQR: 19.0, 28.8). Of these, 353 (49%) were performed before 24 weeks gestation.

All participants were recruited from one of three countries: South Africa, Uganda, and India.

Other participant characteristics were similar to those of the main PROMISE cohort (Table)

When this whole cohort was considered, 132 (18%) women met the PTB<37 weeks threshold; 38 (5%) met the PTB<34 weeks threshold.

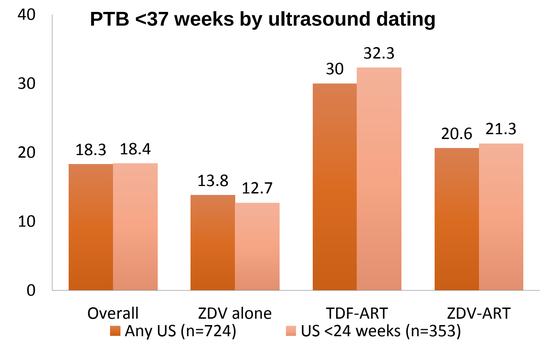
Both ART arms (ZDV- and TDF-based) had higher odds of PTB<37 weeks compared to ZDV alone. When the two ART arms were compared directly, there was a trend towards higher risk with TDF-based regimens; however, this did not reach statistical significance.

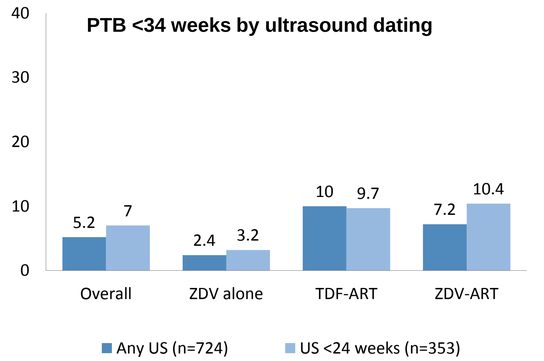
These associations remained mostly similar when the outcome was PTB<34 weeks.

When only US performed <24 weeks gestation were included, trends were mostly similar. The one difference was the TDF-ART vs. ZDV alone comparison, which was no longer statistically significant.

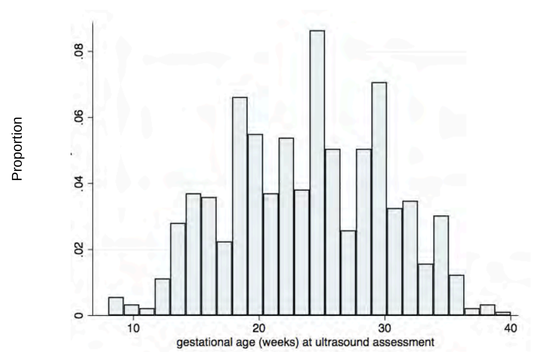
When compared to the parent study, we observed similar associations for PTB<37 weeks. With the PTB<34 weeks outcome, however, the TDF-ART vs. ZDV-ART comparison was not statistically significant.

	ZDV only	ZDV+3TC+LPV /r	TDF+FTC+ LPV/r
Age, years			
<20	154 (46.1)	146 (45.6)	27 (38.6)
20-30	112 (33.5)	106 (33.1)	26 (37.1)
>30	68 (20.3)	68 (21.3)	17 (24.3)
Country			
South Africa	192 (57.5)	177 (55.3)	25 (35.7)
Uganda	104 (31.1)	103 (32.2)	45 (64.3)
India	38 (11.4)	40 (12.5)	0 (-)
Gestational age at randomization			
Median (IQR)	25.8 (20.7, 30.4)	24.7 (20.0, 30.7)	26.4 (21.0, 30.8)
<24 weeks	134 (40.1)	143 (44.7)	28 (40.0)
24-28 weeks	70 (21.0)	62 (19.4)	13 (18.6)
>28 weeks	130 (38.9)	115 (35.9)	29 (41.4)
Gestational age at ultrasound			
<24 weeks	158 (47.3)	164 (51.3)	31 (44.3)
24-28 weeks	89 (26.7)	79 (24.7)	18 (25.7)
>28 weeks	87 (26.1)	77 (24.1)	21 (30.0)
History of prior PTB			
Nulliparous	72 (21.6)	65 (20.3)	10 (14.3)
Parous, no PTB	249 (74.6)	242 (75.6)	58 (82.9)
Parous, at least one PTB	13 (3.9)	13 (4.1)	2 (2.9)
Baseline CD4 cell count, cells/ul			
350-500	130 (38.9)	129 (40.3)	32 (45.7)
500-750	144 (43.1)	124 (38.8)	25 (35.7)
>750	60 (18.0)	67 (20.9)	13 (18.6)





Gestational age at ultrasound assessment



Association between ART and PTB <37 and <34 weeks by ultrasound

CURRENT SUBSET ANALYSIS	ZDV-ART vs. ZDV alone AOR (95% CI)	TDF-ART vs. ZDV alone AOR (95% CI)	TDF-ART vs. ZDV-ART AOR (95% CI)
PTB <37 weeks by ultrasound			
All ultrasound	1.67 (1.09 – 2.55)	2.72 (1.40 – 5.31)	1.65 (0.87 – 3.12)
Ultrasound <24 weeks	2.02 (1.07 – 3.80)	4.60 (1.61 – 13.08)	2.00 (0.77 – 5.22)
PTB <34 weeks by ultrasound			
All ultrasound	3.41 (1.48 – 7.86)	6.00 (1.77 – 20.34)	1.73 (0.66 – 4.56)
Ultrasound <24 weeks	5.00 (1.64 – 8.69)	3.22 (0.52 – 19.67)	0.71 (0.15 – 3.30)

Comparison to original trial analysis of the association between ART and PTB <37 and <34 weeks by NBS

ORIGINAL TRIAL ANALYSIS	ZDV-ART vs. ZDV alone AOR (95% CI)	TDF-ART vs. ZDV alone AOR (95% CI)	TDF-ART vs. ZDV-ART AOR (95% CI)
PTB <37 weeks by NBS			
Clinical trial*	1.75 (1.42 - 2.17)	1.70 (1.24 - 2.33)	0.97 (0.72 - 1.32)
PTB <34 weeks by NBS			
Clinical trial*	1.14 (0.71 - 1.85)	2.93 (1.66 - 5.16)	2.56 (1.47 - 4.46)

*These results are from a prior analysis of the clinical trial (Chi et al, CROI, 2016) that included 3,333 of 3,423 enrolled women, and excluded 90 singleton pregnancies whose fetus was stillborn (n=84) or a spontaneous abortion (n=6).

CONCLUSION

A subset analysis of PROMISE 1077BF/FF among HIV-infected women with US dating reconfirmed a significant association between ART started in pregnancy and PTB <37 and <34 weeks.

A significantly increased risk of PTB<34 weeks with ART was observed in the subset with US dating but not with newborn exam. This may be attributable to reduced misclassification with more accurate US gestational dating and warrants further research.

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