

Preterm Birth, Breastfeeding, Antenatal ARV Regimen and 24-month HIV-free Survival

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Introduction and Background

Background:

- PROMISE 1077BF was a multi-site, randomized, open-label, perinatal trial comparing the relative safety/efficacy of ARV regimens during pregnancy and breastfeeding (BF) among HIV+ women not meeting treatment SOC criteria at trial entry. It was conducted at research sites in India, Southern and Eastern Africa.
- Randomized Trial took place between 2011 and 2015, with follow-up through 2017.
- Previous results found <1% HIV transmission but increased risk of adverse pregnancy outcomes including Higher risk of preterm (<37 weeks) delivery comparing ART to ZDV alone (**21% vs 13%**).

This raised concerns that an increased risk of prematurity might impact 24 month child survival.

Objectives:

- To assess 24-month HIV-free survival and overall survival in infants by Antepartum Component maternal study arm.
- To compare 24-month HIV-free survival and overall survival among live-born infants by gestational age at birth.

Hypotheses:

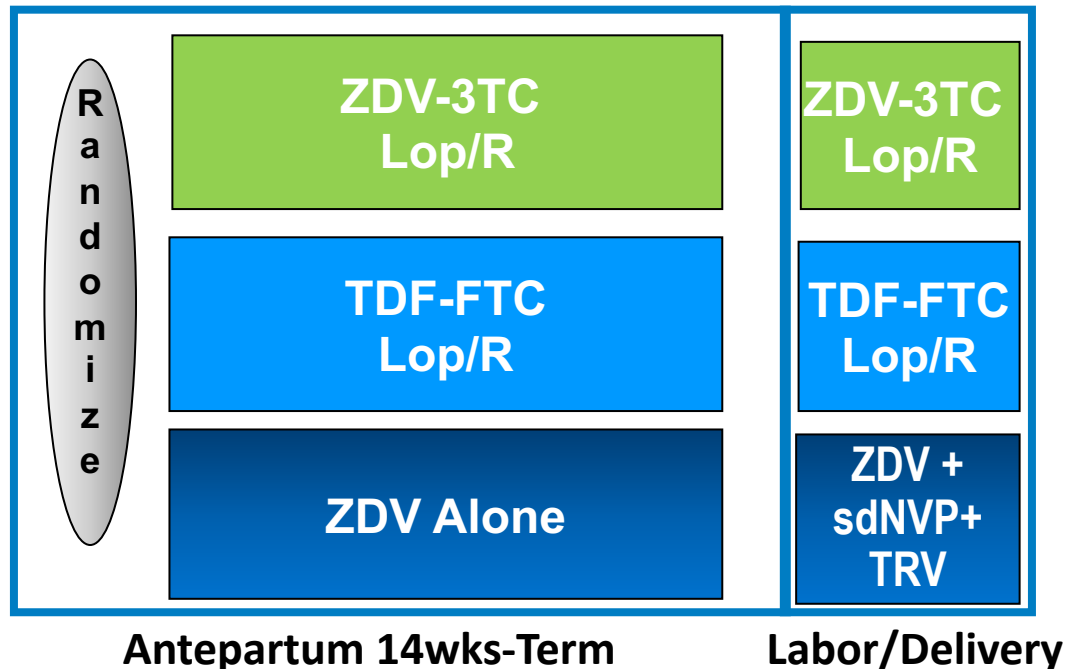
- Infants born to women randomized to antepartum Maternal ART will be at higher risk of death or HIV by age 24 months compared to those on whose mothers received antepartum ZDV alone.
- Preterm infants born at <37 weeks gestation, particularly those born at less than 34 weeks gestation will have lower 24 month HIV free survival when compared to term infants.

Study Analysis Methods

Study Population: Liveborn infants in 1077BF

Antepartum AP Trial Design:

- In Period I, HBV-/HIV+ pregnant women were randomized 1:1 to **ZDV alone or ZDV/3TC/Lop/R (ZDV-ART)** while HBV+/HIV+ women were randomized 1:1:1 to **ZDV alone, ZDV-ART, or TDF/FTC/Lop/R (TDF-ART)**. In Period II, pregnant enrollees were randomized 1:1:1 to the 3 regimens.



Primary Outcomes of Interest: HIV-free survival at age 24 months, based on:

Comparison Groups:

- Gestational age at delivery: **PT (<37 weeks) or Term (≥37 weeks)**
- Maternal antepartum ARV randomization
- Breastfeeding (BF) status

Statistical Analyses:

- Kaplan-Meier method was used to calculate survival probabilities and 95% confidence intervals (CIs).
- Cox proportional hazards regression with time-varying BF, adjusted for randomized ARVs, was used to calculate hazard ratios (HR) and 95% CIs.
- Survival analyses by ARV regimens compared AP ZDV and ZDV-ART regimens for combined **Periods I-II** and compared the 3 AP regimens for **Period II**.
- Survival analyses by gestational age (PT vs Term) included infants whose mothers were on any of the 3 AP regimens or late-presenting women.
- BF analyses included infants whose mothers planned to BF.

Analysis Results: Maternal ARV Regimen, Breastfeeding Duration And 24 Month HIV-free Infant Survival

- **Data analyses** included **3482** PROMISE infants (51% male; 97% African), median gestation 39 weeks
 - **2914** term infants; **568 (16%)** preterm <37 weeks of whom **104 (3%)** were very preterm <34 weeks.
- There were NO significant differences in overall 24 month HIV-free survival between antepartum ZDV or ZDV-ART for **Periods I-II** combined, adjusting for breastfeeding.
- In **Period II**, there was increased HIV free survival for infants whose mothers were on the ZDV-ART arm compared to the TDF-ART arm, adjusting for breastfeeding.
- Most infant deaths occurred early within the first few weeks after birth.
- **Time varying BF** among 2957 women was associated with decreased risk of infant HIV infection or death by age 24 months.

Hazard Ratios for HIV Free Survival

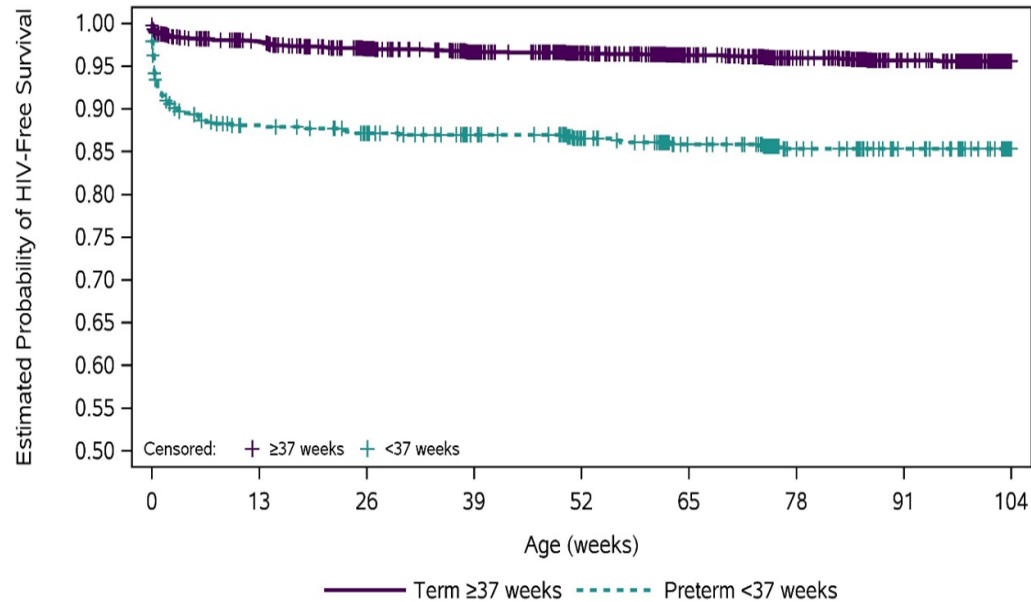
Comparison Periods I-II Combined	Unadjusted Hazard Ratio (95% CI)	P- value	Adjusted Hazard Ratio (95% CI)	P- value
BF vs Not BF	0.14 (0.09-0.21)	< 0.001	0.14 (0.09-0.20)	< 0.001
ZDV-ART vs ZDV alone	0.85 (0.61-1.20)	0.36	0.83 (0.59-1.16)	0.27
Comparison Period II	Unadjusted Hazard Ratio (95% CI)	P- value	Adjusted Hazard Ratio (95% CI)	P- value
BF vs Not BF	0.05 (0.03-0.09)	< 0.001	0.05 (0.03-0.08)	< 0.001
ZDV-ART vs ZDV alone	0.80 (0.38-1.66)	0.55	0.70 (0.34-1.46)	0.34
TDF-ART vs ZDV alone	1.59 (0.85- 2.97)	0.15	1.66 (0.89 - 3.11)	0.11
TDF-ART vs ZDV -ART	1.98 (1.02-3.88)	0.0450	2.37 (1.21-4.64)	0.0122

Analysis Results By Gestational Age at Delivery

Born at Term, <37 weeks and <34 weeks

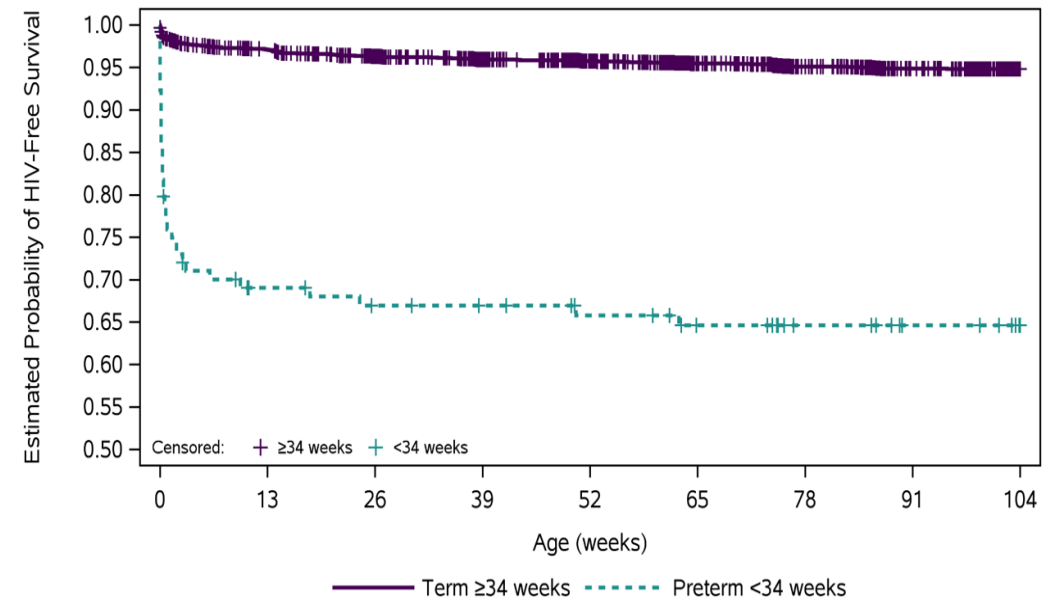
PT birth at <37 weeks was associated with decreased 24 month HIV-free survival: **0.85 (95%CI: 0.82-0.88)** vs Term **0.96 (95%CI: 0.95-96)**

PT birth at <34 weeks was associated with decreased 24 month HIV-free survival: **0.65 (95%CI: 0.54-0.73)** vs Term **0.95 (95%CI: 0.94-96)**



	Number at Risk								
≥37 weeks	2914	2777	2687	2455	2242	2025	1842	1653	1300
<37 weeks	568	481	466	437	395	350	308	283	231

	HIV-Free Survival Probability (95% CI)			
	26 weeks	52 weeks	78 weeks	104 weeks
≥37 weeks	0.97 (0.96, 0.98)	0.97 (0.96, 0.97)	0.96 (0.95, 0.97)	0.96 (0.95, 0.96)
<37 weeks	0.87 (0.84, 0.90)	0.87 (0.83, 0.89)	0.85 (0.82, 0.88)	0.85 (0.82, 0.88)



	Number at Risk								
≥34 weeks	3378	3191	3090	2831	2580	2323	2106	1897	1498
<34 weeks	104	67	63	61	57	52	44	39	33

	HIV-Free Survival Probability (95% CI)			
	26 weeks	52 weeks	78 weeks	104 weeks
≥34 weeks	0.96 (0.96, 0.97)	0.96 (0.95, 0.96)	0.95 (0.94, 0.96)	0.95 (0.94, 0.96)
<34 weeks	0.67 (0.57, 0.75)	0.66 (0.56, 0.74)	0.65 (0.54, 0.73)	0.65 (0.54, 0.73)

Analyses Conclusions

- In Periods I-II combined, there were no significant differences in overall 24 month HIV-free survival between antepartum ZDV or ZDV-ART regimens, adjusting for breastfeeding; however in Period II, infants born to mothers on ZDV-ART had higher HIV free survival compared to mothers on TDF-ART during pregnancy, adjusting for breastfeeding.
- Preterm birth <37 weeks and <34 weeks were significantly associated with lower 24 month HIV-free survival, while Breastfeeding was associated with increased HIV-free survival.
- These analyses extend our understanding of the longer term safety of maternal ARV regimens administered during pregnancy and maternal breastfeeding on longer term outcomes for HIV exposed infants.
- Finding the optimal ART interventions to decrease risk of PT birth for HIV+ pregnant women and prevent related infant deaths remains a high priority; as does support for breastfeeding among HIV+ mothers in resource limited settings with high background early child mortality.

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