Impact of maternal antiretroviral therapy (ART) versus infant nevirapine prophylaxis on somatic growth of breastfeeding infants in the PROMISE trial

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1. PROMISE TRIALS

BACKGROUND

PROMISE was a randomized controlled trial conducted in 14 countries around the globe that began in 2010. The aim was to determine the optimal antiretroviral strategy to prevent vertical transmission of HIV and maintain maternal and infant health.

The breastfeeding version of PROMISE (1077BF) was designed for countries where maternal triple ART during breastfeeding (BF) was not standard when the study began.

PROMISE 1077BF was conducted in 7 countries in Africa and India (Figure 1).

FIGURE 1. Breastfeeding Version of PROMISE Study Sites

INFANT ARV EXPOSURE

The use of combination antiretroviral (ARV) regimens by HIV-infected women while pregnant and breastfeeding is increasing as more women initiate life long ART globally. Monitoring continues for evidence of clinically important adverse fetal/infant effects in infants exposed to ARVs in utero and through breastfeeding.

2. STUDY TREATMENT

BREASTFEEDING VERSION OF PROMISE

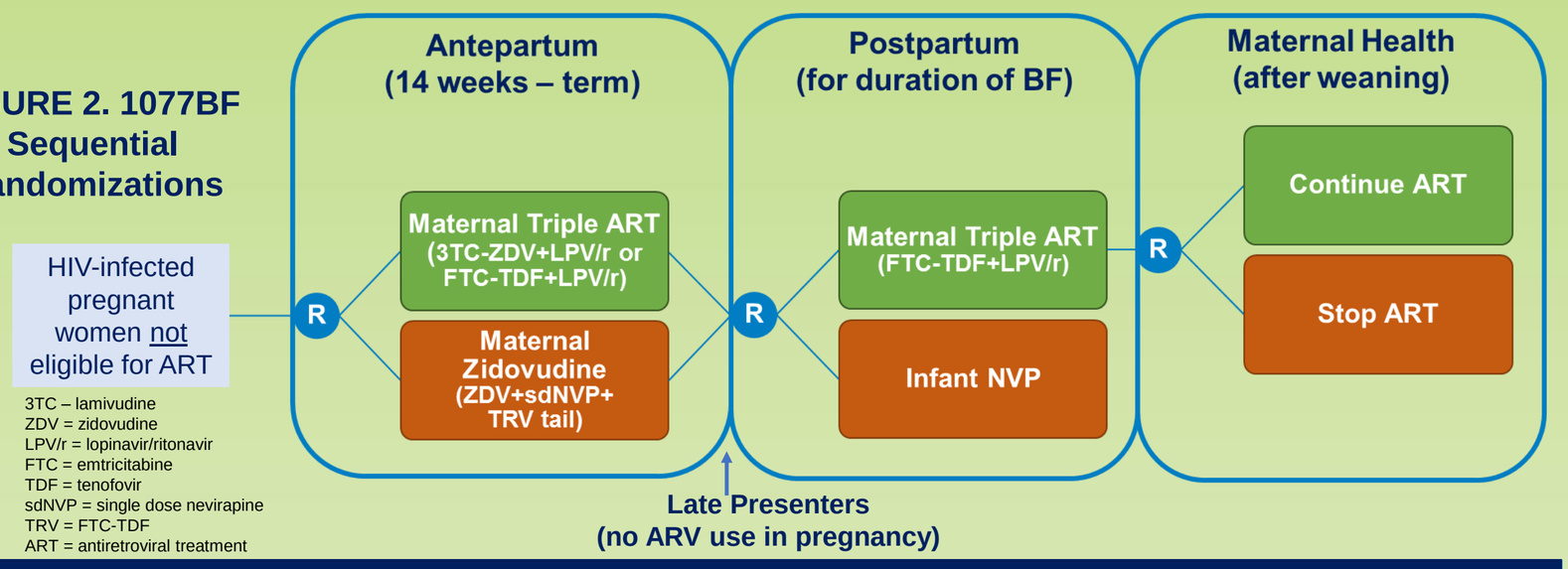
To address concerns about the potential adverse impact of ARV exposure on infant growth, we evaluated the effect of postnatal ARV exposure on somatic growth of healthy HIV-exposed uninfected breastfed infants (HEUs) within the Breastfeeding version of the PROMISE trial (1077BF).

Eligible HIV-infected pregnant women who did not meet local criteria to initiate ART were randomized with their healthy fetus/infants to different antiretroviral strategies to assess prevention of vertical transmission during pregnancy and post-delivery, infant safety, and maternal health.

The 1077BF trial involved 3 sequential randomisations to assess the different ARV strategies (Figure 2) for eligible healthy mother-infant pairs. Infants with birth weight below 2000g were excluded.

All infants received standard of care nevirapine prophylaxis from birth through week 6 of life.

FIGURE 2. 1077BF Sequential Randomizations



3TC – lamivudine
ZDV = zidovudine
LPV/r = lopinavir/ritonavir
FTC = emtricitabine
TDF = tenofovir
sdNVP = single dose nevirapine
TRV = FTC-TDF
ART = antiretroviral treatment

3. METHODS

GROWTH ASSESSMENTS

Length/height, weight, and head circumference were measured using standard methods at birth and postpartum. Infant feeding method and infant HIV infection status were monitored throughout follow-up.

STATISTICAL METHODS

We studied the effect of the postpartum randomization on infants' growth using an intention-to-treat approach and World Health Organisation z-scores at birth, age 10, 26 weeks (primary time point), 74 and 104 weeks:

- Length-for-age (LAZ, primary outcome)
- Weight-for-age (WAZ)
- Head circumference-for-age (HCAZ)

Data were censored at the time the PROMISE study sites were notified of the START study results on 6 July 2015.

Student T-tests were used to compare randomized ARV exposure LAZ, WAZ and HCAZ. The primary outcome was further analysed by ARV exposure *in utero* in linear regression model.

4. RESULTS

POSTPARTUM ENROLMENT

Mothers (n=2431) and their infants (n=2444; 13 sets of twins) were randomised within 14 days after delivery to:

- Maternal triple ART, n=1227 infants
- Infant Nevirapine prophylaxis, n=1217 infants

This included 128 mothers who entered PROMISE as Late Presenters in labour or soon after delivery.

Median follow-up was to 104 weeks of age. Ten percent of infants (236) prematurely discontinued study follow-up, 38 due to death (2%).

BASELINE CHARACTERISTICS

Maternal and infant baseline characteristics were comparable between study arms (Table 1).

TABLE 1. Baseline Characteristics

Mothers' (n=2431)	Value
Race Black African	2346 (97%)
Median Age (Q1-Q3)	26.6 years (23.2-30.3)
ARV use in pregnancy:	
No ARV use (Late Presenters)	128 (5%)
ZDV/3TC/LPV/r	1005 (41%)
TDF/FTC/LPV/r	289 (12%)
ZDV in pregnancy +sdNVP+TRV tail	1009 (42%)
Median BMI (Q1-Q3)	24.7 (22.2-27.9)
Median CD4 pre-ART (Q1-Q3)	535 cells/mm^3 (438-671)
Median viral load post delivery (Q1-Q3)	324 copies/mL (40-1434)

Infants' (n=2444)	Value
Median weeks of gestation (Q1-Q3)	39 weeks (38-40)
Median birth weight (Q1-Q3)	2900g (2600-3200)

INFANT GROWTH MEASUREMENTS

Table 2 shows mean length, weight and head circumference measurements (95% Confidence Interval – 95%CI and the number (%) of infants with LAZ below -2 standard deviations.

Mean LAZ (primary outcome) was -0.93 (95% CI -1.02, -0.83) in the maternal triple ART arm and -0.86 (-0.95, -0.77) in the infant nevirapine arm.

There was no significant difference between the arms:

- LAZ at week 26 (mean difference -0.07 (95%CI -0.20, 0.06), p-value=0.30), or for secondary outcomes of:
- WAZ (mean difference 0.01 (95%CI -0.09, 0.10), p-value=0.90) and
- HCAZ (mean difference -0.08 (95%CI -0.19, 0.02), p-value=0.13).

There was no significant evidence that the postpartum randomization ARV exposure effect on LAZ at week 26 differed by the four *in utero* ARV exposure groups (p-value=0.56). Similarly, there was no significant difference between the arms for LAZ, WAZ or HCAZ secondary outcomes at week 74 (p-value>= 0.18) (Figure 3).

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FIGURE 3. WHO Z-scores by postpartum visit (mean, 95%CI)

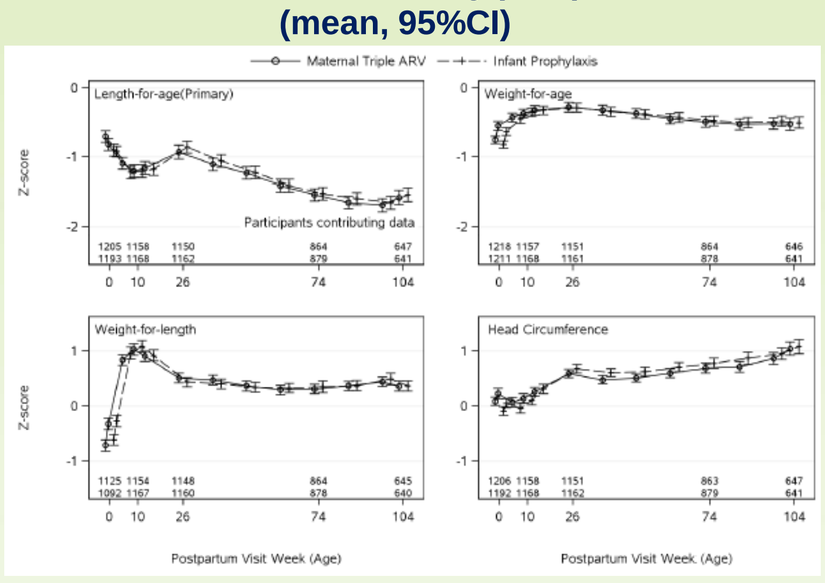

TABLE 2. Infant Growth Parameters (Mean, 95%CI) by Postpartum Week

Study visit Week (Age)	N (for length)	Length in cm (Mean, 95%CI)	Weight in kg (Mean, 95%CI)	Head Circumference in cm (Mean, 95%CI)	LAZ <-2 (N, %)
Week 0 (day 0-5)	2398	48.31 (48.2-48.42)	2.94 (2.92-2.95)	34.35 (34.28-34.42)	-
Week 10	2326	56.28 (56.14-56.41)	5.41 (5.38-5.44)	39.31 (39.24-39.39)	640 (27.5%)
Week 26	2312	64.75 (64.61-64.90)	7.45 (7.40-7.49)	43.59 (43.52-43.66)	476 (20.6%)
Week 74	1743	76.35 (76.17-76.53)	9.92 (9.86-9.99)	47.65 (47.56-47.74)	586 (33.6%)
Week 104	1288	82.35 (82.12-82.57)	11.24 (11.16-11.33)	49.21 (49.09-49.34)	437 (33.9%)

5. CONCLUSIONS

WHAT THESE DATA SHOW

Growth outcomes in breastfed HEUs through age 74 weeks did not differ significantly between infants who received Nevirapine prophylaxis during the period of breastfeeding and those whose mothers received predominantly tenofovir-containing triple ART.

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