29

Changes in Bone Turnover Markers after Delivery in Breastfeeding Mothers with and without ART

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BACKGROUND

- In the postpartum component of the IMPAACT PROMISE[1] trial, breastfeeding mothers with HIV and their infants were randomized to either a maternal TDF-based ART regimen (**Maternal ARV**) or infant nevirapine prophylaxis without maternal ART (**Infant NVP**) to prevent HIV transmission through breastmilk.
- Women in the Maternal ARV arm experienced greater decline in bone mineral density (BMD) from postpartum Week 1 to Week 74 than women in the Infant NVP arm.[2]
- The underlying mechanism of observed differences in percent change in BMD not fully established.
- We compared **the trajectory of bone turnover biomarkers** between arms and evaluated their association with **change in BMD**.

METHODS

- 400 women were enrolled in the PROMISE P1084s substudy[3] from 8 sites in 4 African countries with capacity for BMD evaluation and no prior exposure to TDF ART.
- Urine and serum samples were collected at **Entry** and postpartum **weeks 6, 26, and 74**.
- Assayed:
  - Markers of bone resorption:
    - urinary deoxypyridinoline to creatinine (**uDPD**)
    - serum C-terminal telopeptides (**CTX**)
  - Marker of bone formation:
    - **osteocalcin**

AT postpartum Weeks 6 and 26, the Maternal ART arm had higher mean uDPD, CTX, and osteocalcin compared with the Infant NVP arm.

STATISTICAL METHODS

- **Compared** uDPD between arms at Week 74 using a two-sided Student's t-test (primary)
- **Described** the postpartum trajectories of biomarkers using spaghetti plots and LOESS regression
- **Compared** biomarkers longitudinally using generalized estimating equation (GEE) models that accounted for repeated measures
- **Evaluated** the association between biomarkers at Entry and percent change in lumbar spine and hip BMD from Entry to Week 74 using adjusted linear regression models

RESULTS

- 398 women were included, 2 Maternal ART women were excluded for not initiating TDF-ART.
- Baseline characteristics were similar across arms.
- Breastfeeding duration (median 62 weeks) and contraception uptake (64%) were also comparable across arms.
- At Week 74, the mean uDPD was not significantly different between arms **(0.6 nmol/mmol (-0.1, 1.3), P = 0.17).**
- **Lumbar spine BMD** percent change was positively associated with uDPD and osteocalcin; there was no apparent association with CTX.
- **Hip BMD** percent change was positively associated with osteocalcin; there was no apparent association with uDPD or CTX.

TABLE 1. Baseline Characteristics

Characteristic	Maternal ARV (N=200)	Infant NVP (N=198)	Overall (N=398)
Age (years) Median (Q1, Q3)	26.3 (23.4, 29.5)	26.7 (23.2, 31.3)	26.5 (23.3, 30.2)
WHO Clinical Stage I	187 (94%)	185 (93%)	372 (93%)
CD4 Cell Count (cells/mm^3) Median (Q1, Q3)	737.0 (571.0, 935.0)	695.0 (581.0, 896.0)	714.0 (575.0, 911.0)
HIV RNA level <400 copies/mL	110 (55%)	104 (53%)	214 (54%)
Calculated CrCl (mL/min) Median (Q1, Q3)	133.6 (117.3, 158.4)	135.7 (115.9, 151.1)	134.4 (116.6, 155.8)

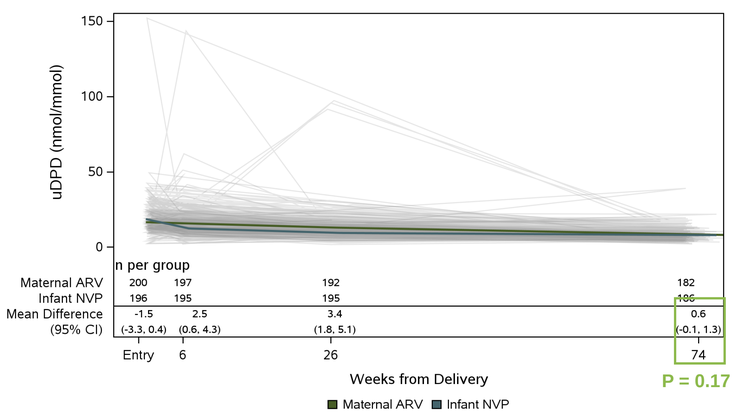

FIGURE 1. Urinary deoxypyridinoline to creatinine (uDPD)

- For the Maternal ART arm (shown in green), mean uDPD decreased gradually from Entry to Week 74.
- For the Infant NVP arm (shown in blue), mean uDPD decreased sharply from Entry to Week 6.

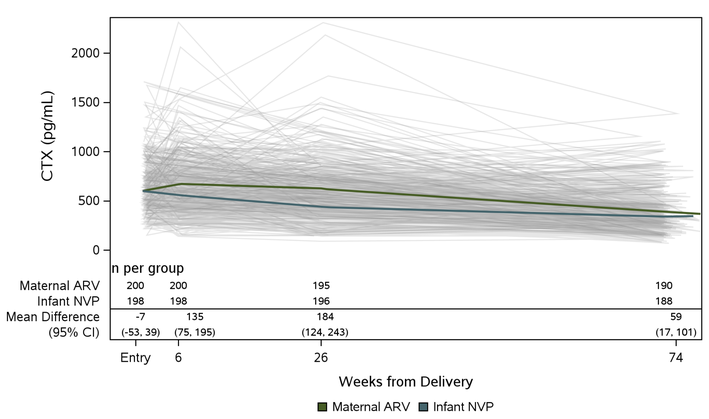

FIGURE 2. Serum C-terminal telopeptides (CTX)

- For the Maternal ART arm, mean CTX increased from Entry through Week 26.
- For the Infant NVP arm, mean CTX decreased across visits.

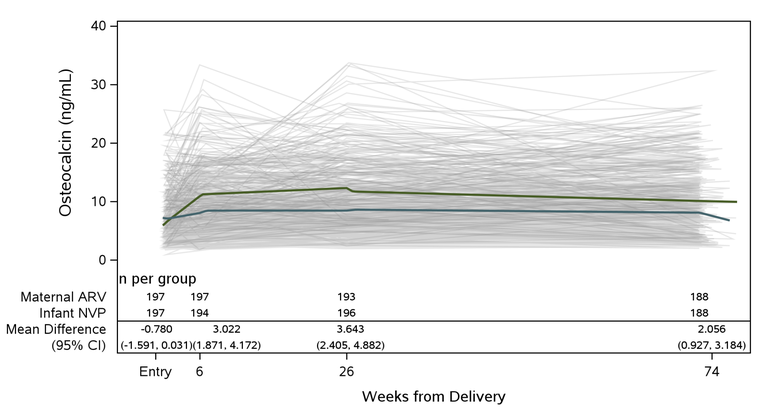

FIGURE 3. Osteocalcin

- For the Maternal ART arm, mean osteocalcin increased from Entry through Week 26.
- For the Infant NVP arm, mean osteocalcin slightly increased across visits.

TABLE 2. Associations between percent change in BMD and bone biomarkers at Entry*

BMD Outcome Measure	Bone Biomarker	N	Adjusted Coefficient[1] (95% CI)
Lumbar Spine	uDPD (nmol/mmol)	336	0.104% (0.008, 0.200)
	CTX (pg/mL)	337	0.003% (<0, 0.006)
	Osteocalcin (ng/mL)	335	0.255% (0.088, 0.423)
Hip	uDPD (nmol/mmol)	335	0.008% (-0.068, 0.083)
	CTX (pg/mL)	336	0.001% (<0, 0.004)
	Osteocalcin (ng/mL)	334	0.159% (0.028, 0.290)

[1]Models were adjusted for postpartum randomization arm, maternal age at baseline, country, HIV viral load at baseline, maternal weight at baseline, parity, and antepartum ARV exposure at postpartum entry

***Adjusted coefficient represents the mean percent increase in BMD outcome measure per unit increase in bone biomarker at Entry.**

CONCLUSIONS

- Compared with the Infant NVP arm, the Maternal ART arm had higher mean uDPD, CTX, and osteocalcin through Week 26.
- These results could indicate the underlying mechanism for the greater percent change in BMD observed with postpartum Maternal ART, but the clinical significance of these changes remains to be determined.

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