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Growth and Bone Markers in Malawian Infants Pre- and Postnatally Exposed to Tenofovir

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BACKGROUND

Tenofovir (TDF) is known to affect bone metabolism, bone mass and bone turnover in HIV-infected patients.

In infants, pre- and postnatal exposure from mothers who receive TDF during pregnancy and breastfeeding might affect negatively bone metabolism and postnatal growth.

No data are available on bone metabolism markers and growth in breastfed children of mothers receiving TDF.

AIMS

- To evaluate growth indexes in a population of infants exposed to TDF in utero and during breastfeeding.
- To assess the levels of bone metabolism markers (formation and resorption) in TDF-exposed infants.
- To correlate bone markers levels with infant growth indexes

METHODS

Study population:
103 Malawian mother/child pairs enrolled in an option B-Plus–based program for prevention of HIV MTCT .

Treatment:
All women received TDF+3TC+EFV in pregnancy (started at a median gestational age of 23 weeks) and during breastfeeding (recommended until two years of age).

Measures:
Bone markers and growth status were assessed in infants at 6 and 12 months of age:
- bone formation: Serum Bone-specific alkaline phosphatase (**BAP**) (*Microvue BAP EIA* kit, Quidel corporation, San Diego, USA);
- bone resorption: C-terminal telopeptide of type I collagen (**CTX**) (*Serum CrossLaps ELISA, IDS* Ltd, UK);
- gender-adjusted weight-for-age z-scores (**WAZ**) and height-for-age z-scores (**HAZ**), calculated using the WHO Anthro (WHO Child Growth Standard, 2006).

Statistic analyses:
Demographic data were summarized with descriptive statistics. Levels of bone markers were compared by the Mann-Whitney U test. Potential correlations between levels of bone markers, growth indexes and duration of treatment were assessed by linear regression analyses. For all the analyses, p values below 0.05 were considered statistically significant. The analyses were performed using the SPSS software, version 20.0 (IBM, Somers, NY, USA).

RESULTS

Population

Mother/Child pairs *(n)*	103
ART duration in pregnancy *(median, weeks)*	15
Children, male *(%)*	48,5

Infant growth status

	6 months	12 months
Weight *(median, Kg)*	6.92	8.24
Height *(median, cm)*	64	71.7
Haemoglobin *(median, g/dl)*	10.1	9.9
WAZ mean (SD)	- 0.77 (1.33)	- 0.97 (1.22)
HAZ, mean (SD)	- 1.19 (1.25)	- 1.4 (1.23)

Malnutrition/Growth restriction

	6 months	12 months
WAZ< 10° percentile	30.1 %	39.2 %
HAZ < 10° percentile	43.7 %	56.9 %

Levels of bone markers

	6 months		12 months	
CTX * bone resorption marker (Median (IQR), ng/L)	320 ng/L	(225-565)	590 ng/L	(260-865)
BAP ** bone formation marker (Median (IQR), IU/ml)	278 IU/ml	(117-371)	186 IU/ml	(82-287)

* CTX normal range =202-2311 ng/L **BAP normal range = 43.5-208.1 IU/mL

Levels of bone markers by gender and growth status

Bone markers showed no differences by gender **(Fig. 1)** and by presence/absence of concomitant **(Fig.2)** and subsequent **(Fig.3)** growth restriction (WAZ or HAZ < 10th percentile).

Figure 1 Levels of bone markers by gender at 6 and 12 months

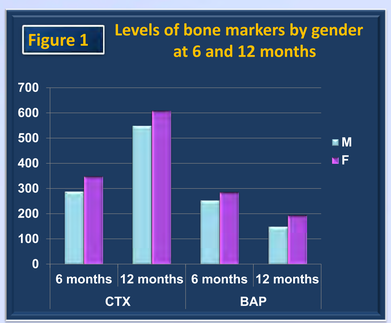


Figure 2 Levels of bone markers at 6 months and concomitant growth status

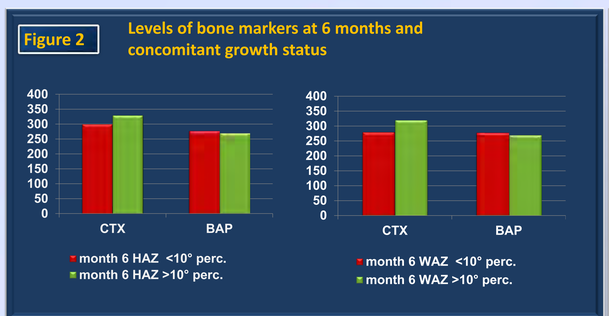
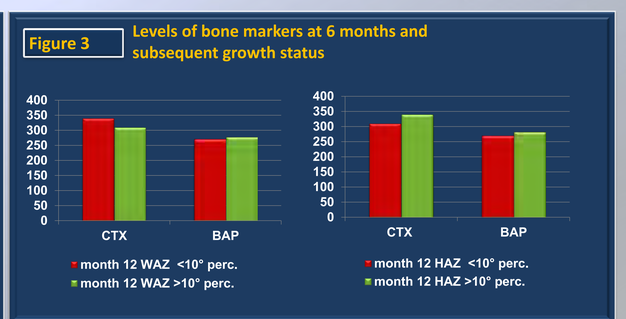


Figure 3 Levels of bone markers at 6 months and subsequent growth status

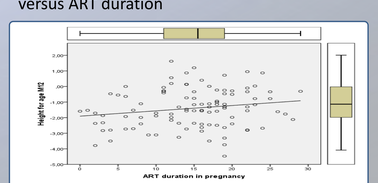


Infant growth (height difference between 6 and 12 months) was not correlated to BPA or CTX levels.

	N	Pearson's R	p
BAP Month 12 versus height difference between 6 and 12 months	102	0.072	0.470
CTX Month 12 versus height difference between 6 and 12 months	100	0.097	0.337

Growth parameters (HAZ and WAZ) at 6 and 12 months were not correlated to ART duration during pregnancy.

Graph shows Height for age Z-scores at month 12 versus ART duration



CONCLUSIONS

Levels of bone metabolism markers in TDF-exposed infants were reassuring: BAP levels (bone formation) slightly higher and CTX levels (bone resorption) similar to reference pediatric standards;

No association was observed between growth impairment and bone markers levels.

Malnutrition is likely to be predominant in determining growth restriction.