TITLE: Effect of Antiretroviral Regimens on Bone Mineral Density of HIV-Infected Lactating Ugandan Women

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BACKGROUND

In healthy non-HIV infected women, it is known that bone density decreases transiently during lactation and then returns to levels prior to breast feeding. Bone mineral density loss of 1% to 3% per month has been reported in lactating women, much greater than the annual loss of 1%-3% seen in women with postmenopausal osteoporosis. Lactating women, in particular, have dramatic increases in bone turnover due to increases in bone resorption.

In addition, among HIV infected individuals, it is known that antiretroviral therapy (ART) may cause serial decrements in bone density over time. Based on studies from the US, low bone mineral density (BMD) including premature osteopenia and osteoporosis, is common among persons infected with HIV. Therefore a concern is whether there may be synergistic effects among HIV infected women on ART who are also l actating, which could lead to accelerated decreases in bone density during the breastfeeding period.

To address this research question, we assessed bone density using a Dual Energy X-ray Absorptiometry (DXA) scanner to provide preliminary, normative data describing any changes in bone density during lactation among a Ugandan population of HIV infected breastfeeding women.

METHODS

This research question was part of an operational research study designed to inform, promote and evaluate strategies aimed at promoting exclusive breast feeding for 6 months followed by continued breastfeeding for the next 6 months with the intro-duction of complementary foods among HIV infected women in a resource limited setting.

From February 2012 to November 2013, we evaluated BMD measurements among lactating HIV infected postpartum women enrolled in an operational randomized infant feeding trial in Kampala, Uganda. The women in the study received either zidovudine alone during pregnancy for prevention of mother-to-child transmission (PMTCT) of HIV/AIDS followed by nevirapine prophylaxis to the infant throughout the period of breastfeeding (Option A) or lifelong maternal triple antiretrovirals (ARVs) (tenofovir/lamivudine/efavirenz) offered to all pregnant or breastfeeding women living with HIV/AIDs regardless of CD4 count (Option B+) or requiring ART for their own health as per the Uganda Ministry of Health guidelines. Longitudinal BMD measurements using a Hologic Explorer Dual Energy X-ray Absorptiometry Bone Densitometer were taken at 2 weeks and 9 months postpartum.

Study Setting: Mulago National Referral Hospital and Makerere University – Johns Hopkins University (MU-JHU) Research Collaboration

Study Entry Criteria

- HIVpositive pregnant women in their late second or third trimester
- On ARVs for PMTCT as part of the PMTCT program (either of the recommended MOH PMTCT drug regimens); or ART if they qualified for HIV treatment, as recommended by the Uganda MOH guidelines
- ≥ 18 years
- Intention to breast feed
- Willingness to deliver at Mulago Hospital
- Living within Kampala and planning to stay within Kampala district for 9 months after delivery
- Willingness to participate during the post partum period
- Willingness to be home visited
- Provision of written informed consent

Analysis Outcomes

- Overall BMD measurements of the hip and spine presented as median T-scores at 2 weeks and 9 months post partum
- Comparison of BMD measurements of the hip and spine by ARV regimen (i.e. Option A versus Option B+/ ART)

Statistical Analysis

- Medians and inter-quartile ranges (IQR) are presented as a summary description of average and variation of some quantitative variables.
- Proportions were used to describe categorical variables presented.
- The statistical package used for analysis was Stata Version 10.1

RESULTS

218 HIV infected lactating women were enrolled at delivery and followed up through 9 months post partum. Fifty seven women were initiated on Option A while 161 women received Option B+ or ART.

Table 1:

Demographic Characteristics for HIV Infected Lactating Women by ARV Regimen

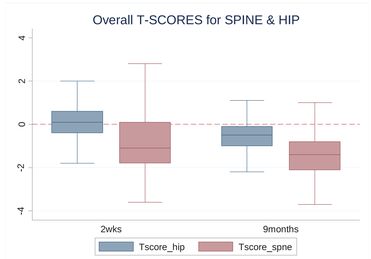
Demographic Characteristics	Option A N= 63	Option B+/ ART N = 155	p-Value
Maternal Age [yrs], median (IQR)	25 (22-28)	28(24-32)	0.003*
Maternal Weight [kgs], median (IQR)	67 (51-70)	65(60-72)	0.979
Maternal BMI, median (IQR)	25.8 (24.0-28.9)	26.1 (24.0-28.1)	0.780
Maternal CD4 Count ({cells/mm^3), median (IQR)	554.5 (454-682)	265(178-411)	0.0001*
Marital status, n (%)			
Not Married	7 (11.1)	36 (23.2)	
Married	56 (88.9)	119 (76.8)	0.042**
Education Level, n (%)			
None	0 (0)	14 (9.0)	
Primary Level	25 (40.3)	65 (41.9)	
Secondary Level	35 (56.5)	70 (45.2)	
Tertiary Level	2 (3.2)	6 (3.9)	0.044**
Maternal HIV WHO Stage			
Stage 1	56 (88.9)	95 (61.3)	
Stage 2	7 (11.1)	34 (21.9)	
Stage 3	0 (0)	20 (12.9)	
Stage 4	0 (0)	6 (3.9)	0.000**
Exclusively Breastfeeding at 6 months, n (%)			
Yes	43 (95.6)	126 (96.2)	
No	2 (4.4)	5 (3.8)	0.573

*p-values based on Kruskal Wallis Test
**p-values based on Fisher's Exact Test

- Women who were initiated on Option B+/ ART were significantly older than women who were initiated on Option A (Zidovudine)
- Women initiated on Option B+/ART had significantly lower CD4 counts when compared with women who were started on Option A who had CD4 counts >350 absolute counts /mm3
- The majority of the women in both groups had achieved either primary or secondary levels of education and most were married

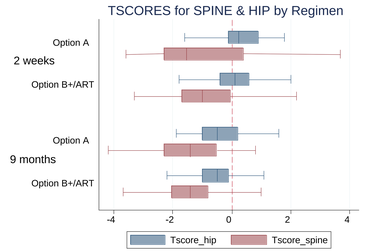
Overall Bone Mineral Density Measurements at 2 Weeks and 9 Months irrespective of ARV group (ZDV or triple ARVs)

- Overall, median T-score for the spine at 2 weeks was -1.1 and at 9 months was -1.4 (p=0.0001).
- Overall, median T-score for the hip at 2 weeks was 0.1 and at 9 months was -0.5 (p=0.0001).



Bone Mineral Density Measurements by ARV Regimen at 2 Weeks and 9 Months

- Among women who received Option A at 2 weeks, the median T-score of the spine was -1.55 compared with -1.00 among women who received Option B+/ART (p=0.405).
- Median T-score of the hip among women who received Option A at 2 weeks was 0.25 compared with 0.1 among women who received Option B+/ART (p=0.131).
- At 9 months, the standardized bone density measurements of the spine among women who received Option A was similar to that for women who received Option B+/ART at -1.4 (p = 0.961)
- Median T-score of the hip among women who received Option A at 9 months was -0.5 and it was the same among women who received Option B+/ART (p= 0.817)



Classification of Bone Mineral Density Measurements

There was a temporal decrement in bone mineral density measurements in the study population from 2 weeks to 9 months. At 2 weeks, 50% of the populations had normal bone density measurements. The other 50% would be considered osteopenic (36.63%) or osteoporotic (13.37%) using US norms. At 9 months, only 35.43% of the study population had normal bone density measurements using US norms. 48% of the study participants had osteopenia while 16.57% were found to be osteoporotic.

	2 Weeks n (%)	9 Months n (%)
Normal	101 (50)	62 (35.43)
Osteopenia	74 (36.63)	84 (48)
Osteoporosis	27(13.37)	29 (16.57)

Strengths

- Among the few studies conducted to describe bone density measurements among HIV infected lactating post partum women initiated on ART
- No other studies have compared findings for women on Option A versus Option B+/ART(i.e. ZDV during pregnancy versus maternal triple ARVs) during pregnancy and throughout the first year post partum

Limitations

- The study was not powered to detect differences in bone mineral density among HIV infected lactating post partum women initiated on either short course ART (Option A) or lifelong ART (Option B+/ART).
- Significant reduction in the numbers of women on Option A due to a change in Uganda Ministry of Health policy which occurred in 2012 when the MOH adopted Option B+.

With this policy shift beginning in October 2012, all HIV infected pregnant women were started on triple ARVs when diagnosed (Option B+) regardless of CD4 count or if they would have met criteria for ART for their own health based on MOH adult ART guidelines.

- Post partum women who were diagnosed as having osteopenia/osteoporosis at 2 weeks were started on calcium supplements which may have altered the incidence by 9 months resulting in fewer participants developing osteopenia /osteoporosis. However, for care, the women found to be osteopenic or osteoporotic based on US norms were given calcium dietary supplements.

Conclusions

- Significant decrements in BMD from 2 weeks to 9 months were observed in HIV infected and lactating women who received ARVs either for PMTCT or ART.
- There were no differences seen in the reduction of BMD among women who received short duration ARVs (Option A) when compared with women who received lifelong ART (Option B+/ART). However the study sample size was not powered to address this question.
- Further research is needed to establish BMD norms among non HIV-infected non-ARV exposed lactating women in resource limited settings; and also whether these decrements in BMD seen at 9 months resolve post cessation of breastfeeding.

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