

Short term bone loss in HIV infected premenopausal women

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ABSTRACT (T-138)

Background Low bone density (BMD) is prevalent among HIV+ women. Data on short term bone loss, fracture risk and impact of antiretrovirals is limited.

Methods In 100 HIV+ and 68 HIV- premenopausal women enrolled in the Women's Interagency HIV Study (WIHS), BMD was measured by dual xray absorptiometry at the femoral neck (FN) and lumbar spine (LS) at baseline and 2 yrs. Baseline serum levels of bone formation (osteocalcin (OC) and bone alkaline phosphatase (BAP)) and bone resorption (N-telopeptide (NTX)) markers, and pro-resorptive cytokines (IL-6, TNF- α , and RANKL) were determined.

Results HIV+ women were older than HIV- (40 \pm 5 v 36 \pm 7 yrs, p<0.01 and fewer had irregular periods (11% v 22%, p=0.05) but were similar with regard to race, BMI, prevalence of smoking, alcohol use, heroin use, diabetes, calcium and vitamin D deficiency. HIV+ women had lower baseline LS BMD than HIV- (1.25 \pm 0.2 v 1.31 \pm 0.2 g/cm², p=0.05) and lower FN BMD (1.05 \pm 0.1 v 1.10 \pm 0.2 g/cm², p=0.03). FN BMD was lowest in HIV+ women on PI based HAART (HIV+PI+) (0.99 \pm 0.1 g/cm²). Baseline serum bone turnover marker and cytokine levels were similar between HIV+ and HIV-. Annual % change in BMD was similar in HIV+ and HIV- at FN (-0.64 \pm 0.3 v -0.40 \pm 0.3%, p=0.50) and LS (-0.73 \pm 0.3 v -0.48 \pm 0.3%, p=0.54), after adjusting for age, BMI, and baseline BMD in mixed model analysis. Among HIV+, NTX levels were higher among HIV+PI+ in comparison to those not receiving ART (14.9 \pm 6.9 v 11.4 \pm 3.5 nmol BCE/L, p=0.03) and BAP lower among HIV+PI+ in comparison to HIV+PI- (28.8 \pm 10.8 v 36.2 \pm 14.1 U/L, p=0.03); however annual % change in BMD was similar between all treatment groups. Lastly, over a 2 year follow up, occurrence of new self-reported fragility fractures was similar between the two groups (3%).

Conclusions In premenopausal HIV+ women, baseline BMD was lower than comparable HIV- women but rates of short term bone loss at the LS and FN and fragility fracture were similar. In HIV+ women on PI based HAART, elevated bone resorption and depressed bone formation markers did not translate to increased bone loss.

INTRODUCTION

• Low BMD is a complication of HIV which may be related to upregulation of bone resorbing cytokines, nutritional and hormonal status, and exposure to certain antiretrovirals.

• There are very few controlled longitudinal studies of BMD in HIV infected women. In a recently published study of predominantly premenopausal women, short term changes in BMD were not significantly different between HIV+ and matched healthy controls (Dolan et al., JCEM, 2005)

METHODS

- Longitudinal analysis of a bone density (BMD) substudy in the Women's Interagency HIV Study (WIHS)
- WIHS is a multicenter prospective study of 3770 (2794 HIV+, 976 HIV-) women
- BMD substudy enrolled 426 (247 HIV+, 152 HIV-) women from 2001-2005. Exclusion criteria included: Type I DM, weight>264 lbs, osteoporosis, and exogenous hormones or corticosteroids use
- Longitudinal analysis limited to young premenopausal women, age < 48, with \geq 2 BMD analyses separated by median of 2 yrs and no history of bilateral oophorectomy, thyroid disease, or anticonvulsant use
- Baseline stored sera analyzed for bone turnover markers (bone alkaline phosphatase, osteocalcin, N-telopeptide), pro-resorptive cytokines (TNF- α , IL-6 and Receptor Activator of NF κ B Ligand (RANKL)), and plasma for 25OHD
- BMD of lumbar spine and femoral neck assessed by DXA (Lunar Prodigy)
- Baseline BMD and biochemical indices compared between HIV+ and HIV- women and multivariate model of variables associated with BMD presented
- Annual % change in BMD over 2 years and correlations compared

RESULTS

Table 1. Baseline demographic and medical data (mean \pm SD)

| | HIV- (N=68) | HIV+ (N=100) |
|-------------------------------------|-------------------------------|----------------|
| Age* | 36 \pm 7 | 40 \pm 5 |
| Race: % White / Black / Latina | 25 / 56 / 19 | 18 / 61 / 21 |
| Weight (Kg) | 79 \pm 17 | 75 \pm 18 |
| BMI (kg/m ²) | 30.2 \pm 6.5 | 28.8 \pm 6.6 |
| Smoking % | 65 | 59 |
| Opiate use % | 6 | 4 |
| Cocaine use % | 18 | 14 |
| Alcohol use % | 56 | 45 |
| Number pregnancies | 5.2 \pm 3 | 4.4 \pm 3 |
| Irregular periods %* | 22 | 11 |
| Calcium / Vitamin D supplement | 2% / 28% | 2% / 38% |
| Vit D deficiency / insufficiency | 8% / 79% | 11% / 72% |
| Type II diabetes % | 7 | 5 |
| HCV seropositive %* | 12 | 3 |
| AIDS % | 44 | 44 |
| Baseline CD4 (cells/uL) / Nadir CD4 | 433 \pm 238 / 254 \pm 167 | |
| ART naive % | 15 | 15 |
| ART at baseline / duration (yrs) | 52% / 2.6 \pm 2 | |
| PI-HAART at baseline | 19/52 (37%) | |
| Non-PI HAART at baseline | 29/52 (56%) | |

*P value \leq 0.05 in comparison between groups

RESULTS

Table 2. Baseline biochemical indices in premenopausal women (mean \pm SD)

| | HIV- (N=68) | HIV+ (N=100) | P value |
|---|-----------------|-----------------|---------|
| Osteocalcin (ng/ml) [17.9 \pm 6.5 ng/mL] | 12.0 \pm 5.8 | 11.8 \pm 7.0 | 0.81 |
| BAP (U/L) [11.6-29.6U/L] | 27.4 \pm 10.0 | 29.3 \pm 12.2 | 0.31 |
| NTX (nmol/BCE/L) [6.2-19.0 nmol BCE/L] | 10.4 \pm 3.2 | 11.3 \pm 4.3 | 0.17 |
| IL-6 (ng/ml) [0.4-10.0 pg/mL, mean 1.77] | 3.0 \pm 2.2 | 2.9 \pm 2.5 | 0.77 |
| TNF- α (pg/ml) [0.6-2.8 pg/mL, mean 1.2] | 2.8 \pm 4.0 | 3.7 \pm 6.5 | 0.36 |
| RANKL (nmol/L) [mean 3.8 \pm 1.8] | 1.5 \pm 1.6 | 1.3 \pm 1.6 | 0.55 |
| Intact PTH (pg/ml) [14-66 pg/mL] | 26.4 \pm 9.0 | 28.7 \pm 10.3 | 0.11 |
| 25 OH (ng/ml) [3-32ng/ml] | 20.8 \pm 7.8 | 20.1 \pm 8.7 | 0.62 |

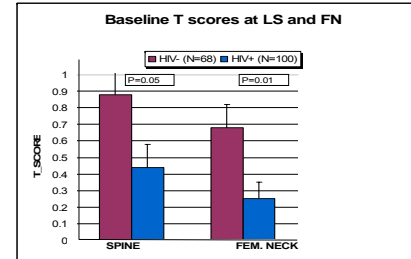


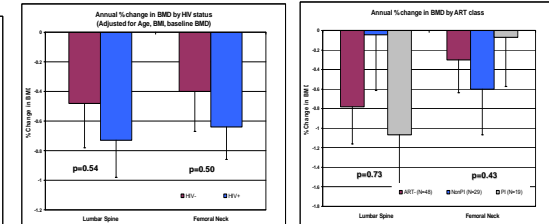
Table 3. Baseline biochemical indices in premenopausal HIV+ women (mean \pm SD)

| | No current ART (N=40) | Non-PI HAART (N=29) | PI-based HAART (N=19) | P value |
|-----------------------|-----------------------|---------------------|-----------------------|---------|
| Osteocalcin (ng/ml) | 10.1 \pm 3.9 | 11.2 \pm 6.0 | 14.0 \pm 6.9 | 0.43 |
| BAP (U/L) | 25.6 \pm 10.6 | 36.2 \pm 14.1 | 28.8 \pm 10.8 | 0.003 |
| NTX (nmol/BCE/L) | 11.4 \pm 3.5 | 11.0 \pm 3.8 | 14.9 \pm 8.9 | 0.03 |
| IL-6 (ng/ml) | 3.2 \pm 2.3 | 3.5 \pm 3.1 | 2.4 \pm 1.6 | 0.32 |
| TNF- α (pg/ml) | 2.9 \pm 2.9 | 3.2 \pm 7.8 | 5.1 \pm 8.5 | 0.74 |
| RANKL (nmol/L) | 1.1 \pm 1.6 | 1.1 \pm 1.5 | 2.0 \pm 1.9 | 0.43 |
| Intact PTH (pg/ml) | 32.0 \pm 10.8 | 28.8 \pm 11.2 | 23.9 \pm 8.2 | 0.09 |

*P value \leq 0.05 in comparison between groups

Table 4. Linear regression of baseline variables associated with LS or FN BMD

| Variables | Lumbar Spine | | Femoral Neck | |
|---------------------------|--------------|---------|--------------|---------|
| | Estimate | P value | Estimate | P value |
| Weight | | | 0.0022 | <0.01 |
| Current alcohol use | 0.0821 | 0.01 | 0.0962 | <0.01 |
| Osteocalcin | -0.0088 | 0.01 | -0.0032 | 0.06 |
| RANKL | | | 0.0161 | 0.02 |
| TNF- α | -0.0047 | 0.06 | | |
| Bone alkaline phosphatase | -0.0025 | 0.06 | | |
| HIV status | -0.0567 | 0.05 | | |



- Among HIV+, higher baseline BMI was associated with less bone loss (r=-0.22, p=0.03) and opiate use (p=0.003), diabetes (p=0.002), and vitamin D deficiency (p=0.004) were associated with more bone loss at the FN
- Among HIV+, higher baseline BAP (r=-0.30, p=0.01) and osteocalcin levels (r=-0.20, p=0.07) were associated with less bone loss at the LS
- HIV (AIDS, CD4) and ART specific variables did not reach significance

SUMMARY AND CONCLUSION

- In this cohort of premenopausal, predominantly African American women, baseline BMD was significantly lower in HIV+ subjects, while baseline vitamin D status and bone turnover markers were similar between HIV+ and HIV- women.
- Rates of bone loss over 2 years were similar between HIV+ and HIV- women.
- Despite higher baseline bone resorption markers and lower formation markers, HIV+ women on PI-based HAART did not have increased bone loss.
- We conclude that premenopausal HIV+ women do not lose bone more rapidly than matched controls.