

# Longitudinal Evolution of Bone Mineral Density (BMD) and Bone Markers in HIV Infected Individuals

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## Abstract (updated)

**Background:** Osteopenia/osteoporosis has been associated both with HIV infection and its treatment. The relative contribution of each is not known. There are few longitudinal data available about the change in BMD in patients with HIV infection.

**Methods:** A longitudinal cohort study is being conducted at Washington University to evaluate the long term evolution of BMD and bone markers in a population of HIV infected individuals. All patients underwent localized DEXAs (hip and spine) and evaluation of bone markers at 24-week intervals. 128 patients have been enrolled. 72-week follow up is available. Patients with a body-mass index (BMI) >50, inability to have DEXA performed, or concurrent diagnosis of osteomalacia were subsequently excluded from all analyses. Three patients who started alendronate were excluded from the longitudinal analysis.

**Results:** Most patients were male (86%), Caucasian (84%) and taking PI based regimens (68%). Thirty-five percent were smokers, 11% were current or past heavy drinkers. Seventy percent had intakes of calcium below 1000mg/d (RDA). Nine percent were taking calcium supplements at baseline, 35% at week 48. Forty-five percent had moderate to high levels of physical activity. Median baseline BMI was 24.4 (IQR 22-28). At baseline 46% of the subjects had osteopenia/osteoporosis. Median lumbar and hip *t* scores were -0.92 (IQR -0.3 to -1.7) to and -0.95 (IQR -0.2 to -1.6) respectively. In multivariate analyses, there was no association with any specific antiretroviral class. Patients as a group had evidence of high bone turnover. There was a small, but significant, increase in lumbar and hip BMD for the whole group during the 48-week follow up (lumbar 2.3% ± 0.5% p <0.0001, hip 2.2% ± 0.5% p <0.0001). Patients that started therapy (n=4) tended to have lower improvements in lumbar BMD (-0.4% vs 2.6% p 0.11) but no differences in the hip (2.6% vs 2.2% p=0.81) when compared to patients in any or no therapy during the 48 weeks. There were no significant changes during the 48 weeks in markers of bone formation (bone-specific alkaline phosphatase, osteocalcin) and bone resorption (urine pyridinolines and deoxypyridinolines).

**Conclusions:** Osteopenia/osteoporosis is a frequent problem among HIV infected patients. During 72-week follow-up subjects receiving antiretroviral therapy had a slight improvement in BMD, suggesting either that therapy itself might not be the most significant contributing factor for the development of this problem or that the effect of treatment on bone occurs early after its initiation. Longer follow up is necessary to evaluate the long term impact of HIV infection and therapy on bone metabolism in the HIV infected population.

## Introduction

- Osteopenia/osteoporosis has been associated both with HIV infection and its treatment.
- The relative contribution of each is not known.
- There are few longitudinal data available on the change in BMD in patients with HIV infection taking different antiretroviral regimens.

## Methods

### Subjects

- A longitudinal cohort study is being conducted at Washington University AIDS Clinical Trials Unit and the Infectious Disease outpatient practice at Washington University School of Medicine.
- Patients with a body-mass index (BMI) >50, inability to have DEXA performed, or concurrent diagnosis of osteomalacia were excluded.
- All other patients were included regardless of clinical status or antiretroviral history.

### Data collection

- BMD was measured using a Hologic QDR-2000 enhanced-array whole-body DEXA scanner (Hologic, Waltham, MA), Hologic enhanced array whole body software (v5.71A) and regional array software (v4.74A:1). Each scan was acquired and processed by a certified radiology technologist.
- Socio-demographic, clinical and laboratory data were obtained on all patients:
  - \* Detailed 3-day dietary history (including vitamin D, calcium, caffeine, alcohol, and average caloric intake)
  - \* Medication history (including type and duration of all antiretrovirals and use of any medications in the past that may potentially alter bone metabolism)
  - \* Body-mass index (BMI) and DEXA. Bone mineral density (BMD) and fat mass measured by DEXA
  - \* Serum and 24-hour urine bone markers (calcium, bone-specific alkaline phosphatase, osteocalcin, urine calcium, pyridinolines, deoxypyridinolines) were obtained on all patients.

### Definitions

- Osteopenia and osteoporosis** were defined according to World Health Organization (WHO) criteria. Patients with a *t*-score between -1 and -2.5 were defined as having osteopenia and patients with a *t*-score ≤ -2.5 were defined as having osteoporosis.
- Physical activity** level was defined as moderate if the patient performed 30 minutes or more of an activity equivalent to brisk walking or jogging at least 3 times per week. A high level was defined as performing a brisk activity for more than 30 minutes at least 5 times per week and a low activity level was defined as performing minimal to no physical activity.
- Low calcium intake** was defined as ingestion of less than 1000 mg per day of calcium based on a 3-day dietary history.
- Excessive alcohol intake** was defined as having a current or past average alcohol intake of more than 2 drinks per day.
- Wasting and severe wasting:** Patients with a past documented weight loss of more than 10% of their ideal body weight were considered to have a history of wasting. Patients with a history of severe wasting were defined as having a nadir BMI below 20.
- Steroid use** was defined as any dose of steroids used daily for greater than 30 days.

### Statistical analysis

- Comparisons between categorical groups were done with Chi square and the Fisher's exact test when appropriate. The t-test was used for continuous variables. All p values were two-tailed. Partial correlations testing was performed to estimate the strength of association between various clinical and laboratory characteristics. Based on these results, potential predictors of osteopenia or changes in BMD were further evaluated for statistical significance by multiple regression analysis. Additional ordered multiple regression analyses were then performed to evaluate the contribution of HIV-related factors to BMD over and above established risk factors (i.e. steroid use, lower weight). The data set was analyzed using the SPSS software package (SPSS/Systat, Chicago).

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## Results

### BASELINE (WEEK 0) CLINICAL CHARACTERISTICS

	Osteopenia/osteoporosis n=57 (% of group)	No osteopenia n=68 (% of group)	P-values
Age (years)	42 ± 1.0	41 ± 0.9	0.43
Gender:			
Men (n=108)	50 (87.7)	58 (85.3)	0.69
Women (n=17)	7 (12.3)	10 (14.7)	
Ethnicity:			
white (n=105)	47 (82.5)	58 (85.3)	0.67
black (n=20)	10 (17.5)	10 (14.7)	
other (n=0)	0 (0.0)	0 (0.0)	
Mean duration of HIV (mos.)	86.7 ± 7.0	68.7 ± 5.8	0.05
Mean nadir CD4+ T cell count	250 ± 32	224 ± 24	0.52
Mean CD4+ T cell count	518 ± 40	514 ± 43	0.95
Mean viral load	8142 ± 3693	9704 ± 348	0.7
Mean Weight	70.0 ± 1.7	79.7 ± 1.6	<0.01
Mean BMI	23.6 ± 0.5	26.3 ± 0.5	<0.01
History of significant weight loss (wt. ≤ 90% of ideal; n=34)	21 (59.6)	13 (19.1)	0.04
History of severe wasting (BMI <20; n=17)	12 (21.1)	5 (7.4)	0.03
History of steroid use >1 month (n=8)	6 (10.5)	2 (2.9)	0.08
Current or past alcohol consumption of >2 drinks per day (n=14)	7 (12.3)	7 (10.3)	0.52
Current or past smoker (n=44)	25 (43.9)	19 (27.9)	0.06
Activity level:			
low (n=69)	29 (50.9)	40 (58.8)	
moderate (n=32)	15 (26.3)	17 (25.0)	0.58
high (n=24)	13 (22.8)	11 (16.2)	
Calcium intake ≤ RDA (n=37)	39 (68.0)	49 (72.0)	0.66
<b>TREATMENT HISTORY</b>			
Mean mos. on NRTI	1860 ± 228	2115 ± 237	0.41
Mean mos. on NNRTI	144 ± 51	128 ± 45	0.69
Mean mos. on PI	779 ± 93	736 ± 95	0.78
Ever on a PI	51 (90)	53 (78)	0.09
Ever NNRTI	25 (44)	30 (44)	1.00

Rows with p values < 0.1 highlighted

### EVOLUTION OF BMD OVER TIME

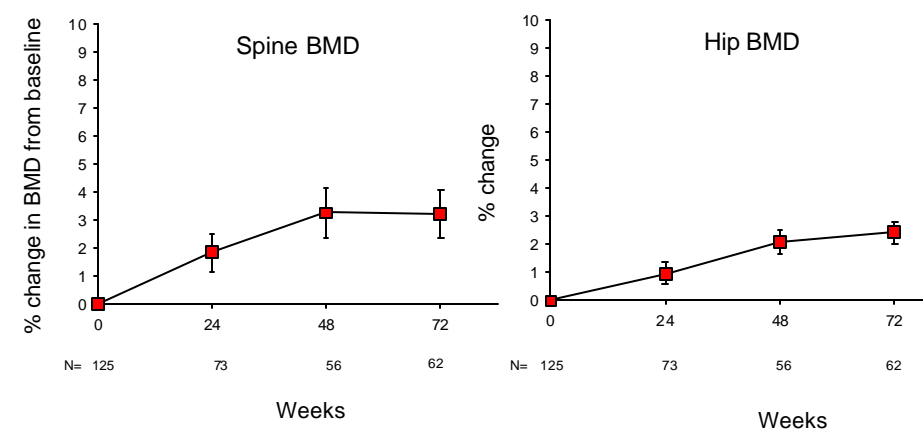


Figure 1. Evolution of BMD of the whole cohort over 72 week follow up. Patients that started alendronate (n=3) were excluded.

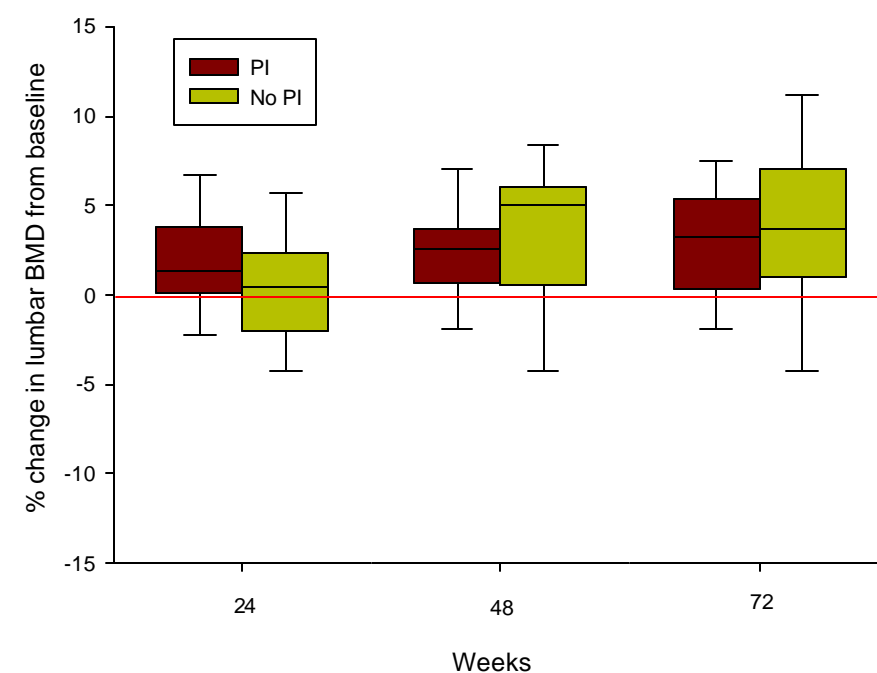


Figure 2. Evolution of BMD. Percentage of change from baseline. Patients have been classified in two groups based on the treatment they were receiving for a majority of the time of follow up: PI based regimens, non PI based regimens. There were no significant differences between the two groups. Patients on blinded medications (n=5), those who remained naive to therapy (n=5) and who started alendronate were excluded (n=3)

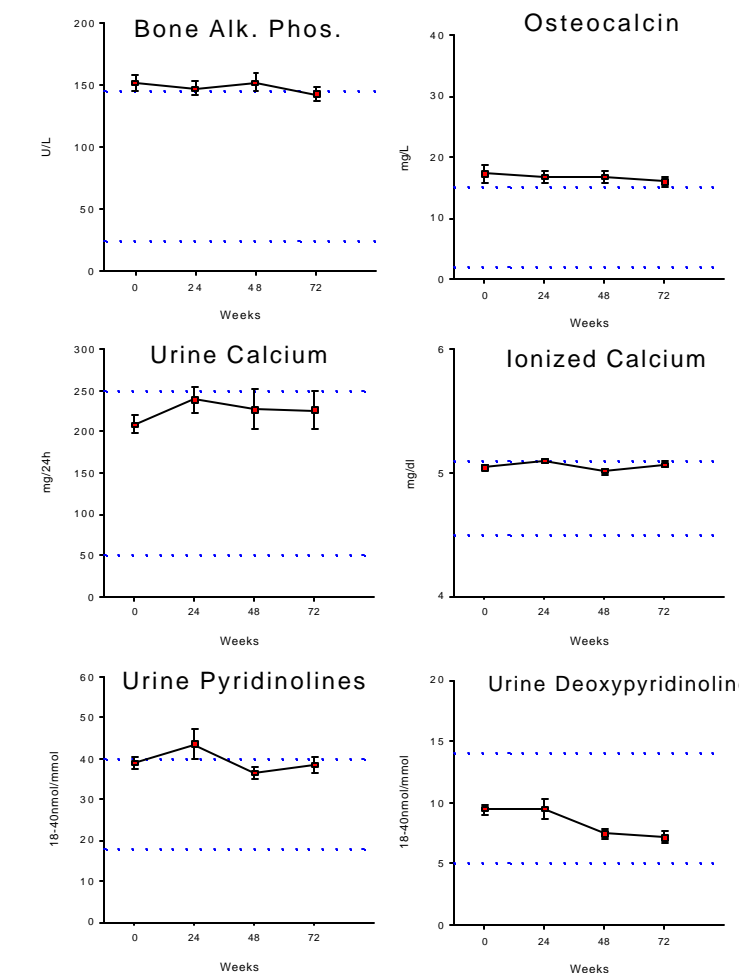


Figure 3. Evolution of bone markers of the whole cohort over 72 week follow up. Patients that started alendronate (n=3) were excluded. Bone markers were elevated indicating a high bone turnover state

## Conclusions

- The prevalence of osteopenia/osteoporosis was very high in this cohort (46%)
- In univariate and multivariate analyses, known risk factors for low BMD were also statistically significant predictors for osteopenia in our cohort.
- Although there was a trend towards a lower BMD among patients that had ever been on a PI, this was no longer evident after controlling for the other known risk factors for osteopenia.
- During longitudinal follow-up, there was an increase in the mean percent change in BMD, regardless of type of antiretroviral therapy.
- The majority of patients had high indices of bone metabolism and turnover, regardless of presence of osteopenia; no bone marker was significantly correlated with BMD.
- These results suggest that traditional risk factors, and factors associated with HIV infection are more important contributors to the pathogenesis of osteopenia/osteoporosis than treatment related factors.

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