



Duration of Anti-retroviral Therapy and Change in Bone Mineral Density Over Time

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ABSTRACT

Background: The etiology of bone loss in HIV disease is unclear. Osteopenia has been frequently observed in the era of highly active antiretroviral (HAART) use. We evaluated the association between time on specific anti-retroviral therapies and change in total bone mineral density (BMD) over time in HIV-infected men and women.

Methods: Total bone mineral density (BMD) was measured at annual clinic visits, in 283 men and 98 women in the Nutrition for Healthy Living Cohort (NFHL) using dual energy absorptiometry (DXA) on the Hologic QDR 2000. Concurrent data was collected on medical and behavior history, CD4 count, HIV viral load, time known HIV+, liver function, weight change and duration of specific anti-retroviral therapies (ART). The median time of follow-up from first to last DXA was 2.9 years (25th 1.5, 75th 4.1). For each person, the percent change in Total BMD from first to last visit was divided by the total follow-up time to obtain the annualized percent change in Total BMD per year of follow-up. Using a repeated measures regression model, we evaluated the relationship between duration of anti-retroviral therapies and the percent change in BMD between consecutive DXA exams (n=717 intervals), adjusted for age, gender, race, albumin, menopause, smoking, changes in viral load and weight and time between visits.

Results: At baseline, the median age was 42 years old, median CD4 was 364 cells/mm³ and median log₁₀ viral load was 2.7 copies/ml. The median annualized change in Total BMD was -0.17% (25th -0.83%, 75th 0.43%) per year (P=0.0004), and a loss of 0.51% over three years (25th -2.5%, 75th 1.3%). Longer durations of ddI use (P=0.001), tenofovir use (P=0.0002) and occurrence of bilirubin > 2 (P=0.0003) were independently associated with greater loss of Total BMD over time. Longer duration of d4T (P=0.003) and increase in viral load were independently associated with less loss of Total BMD over time.

Conclusion: Specific anti-retrovirals may accelerate bone loss (ddI, tenofovir), be protective (d4T) or be markers for other factors. Elevated bilirubin was associated with more bone loss.

BACKGROUND

• Low bone mineral density (BMD) is an important metabolic abnormality noted recently in HIV.

• Prevalence of low BMD higher than expected for age groups observed.

• Epidemiologic and laboratory studies in HIV suggest numerous factors may alter bone mineral metabolism including:
host factors, the virus, chronic immune activation, nutrition, antiretrovirals (ART) and low levels of 1,25 dihydroxyvitamin D₃.

• Several studies noted elevated levels of bone formation and resorption markers, suggesting high rates of bone turnover.

RESULTS

TABLE 2. INDEPENDENT PREDICTORS OF PERCENT CHANGE IN TOTAL BODY BMD –MULTIVARIATE REPEATED MEASURES ANALYSIS

Table 2. Independent predictors of percent change in total BMD - Multivariate *			
Repeated measures analysis			
	Estimate	(SE)	P value
Demographics			
Age (yrs)	-0.01	0.01	0.22
African American	-0.23	0.14	0.1
White/Hispanic/Other	Ref.		
Current smoker (yes vs. no)	0.3	0.15	0.05
Clinical			
Non-menopausal females vs. males	0.17	0.15	0.26
Menopausal females vs. males	-1.4	0.48	0.004
Albumin (gm/dL)	0.31	0.18	0.09
Abnormal Bilirubin ever (> 2 mg/dL)	-1.1	0.3	0.0003
Change in viral load (copies/ml)	0.26	0.12	0.036
%change in weight over interval (per 1%)	-0.04	0.01	0.007
Anti-retroviral therapy			
DDI - continuous use through interval (months)	-0.02	0.01	0.001
d4T - continuous use through interval (months)	0.01	0	0.003
Tenofovir - use in interval (months)	-0.14	0.04	0.0002

* Adjusted for days in interval

The following variables were not significant independent predictors or confounders and were not included in the multivariate model. The p values from univariate analyses are shown below.

Absolute CD4 (P=0.24), change in CD4 (P=0.06), absolute viral load (P=0.39), dietary vitamin D (P=0.20), dietary calcium (0.42)

Known years HIV+ (P=0.13), Durations of HAART (P=0.24), PI-HAART (P=0.99), NRTI HAART (P=0.48), NNRTI HAART (P=0.06), indinavir (P=0.56), nevirapine (P=0.97), nelfinavir (P=0.59), ritonavir (P=0.60)

METHODS

LONGITUDINAL STUDY

Study Population:

- Nutrition for Healthy Living Study (NFHL) in Boston MA and Providence, RI, 1996-2003
- HIV-infected adults (men=283, women=98) 25 to 64 years old

Semi-annual data collection

- Interview –demographics, medical history, reproductive history, current and past medication use, years known HIV+ (years HIV+), substance use, dietary intake (3-day food record)
- Physical exam – height, weight, waist circumference, triceps skinfold
- Laboratory (after a 5 hour fast) –CD4 lymphocytes, HIV viral load, bilirubin, ALT, alkaline phosphatase

Performed at approximately yearly intervals

Total BMD – Total body bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) on Hologic QDR 2000

Analysis:

- #1: Baseline characteristics of cohort**
 - #2: Percent change in total BMD over total follow-up time**
% change BMD = (Last DXA minus first DXA/First DXA) * 100
% change BMD per year = % change BMD/ years of follow-up
 - #3: Predictors of % change in BMD**
Interval analysis, Multiple intervals per person (e.g. Baseline to year 1, year 1 to 2, etc.)
- Outcome :** % change in BMD across each interval = (BMD at end of interval minus BMD at start of interval/ BMD at start of interval) * 100

Predictors/confounders:

age, race, gender, menopause, hormonal contraception, smoking, weight change, dietary intake, antiretroviral therapy (duration of continuous use through interval, duration in interval), viral load, CD4, bilirubin, albumin, ALT, alkaline phosphatase, wasting (BMI < 20, weight loss 10% or > 5% maintained > 6 months)

Generalized estimating equations (GEE) for continuous measure of change using robust variance and TOEP(2) covariance structure (SAS 9.2), adjusted for time in interval (range 9-24 months)

Table 1a. Baseline characteristics of HIV-infected men and women				
	Men (n=283)		Women (n=98)	
	Median (25th, 75th)	%	Median (25th, 75th)	%
Demographics				
Age (years)	42.7 (37.9, 47.6)		39.6 (35.4, 44.1)	
Race				
White		59.4		34.7
African American		25.4		51.0
Other		15.2		14.3
Ever smoker		76.0		86.6
Ever injected drugs		32.2		45.4
Clinical				
Menopause				17.3
Hysterectomy				12.2
Body composition				
BMI (kg/m ²)	24.5 (22.6, 27.1)		26.2 (22.9, 31.1)	
Total BMD (gm/cm ²)	1.13 (1.07, 1.2)		1.09 (1.04, 1.2)	
Wasted		15.7		21.9
Dietary intake				
Calories (kcal/kg/day)	36.2 (26.9, 44.3)		28.6 (23.8, 39.5)	
Protein (gm/kg/day)	1.3 (1.05, 1.8)		1.1 (0.9, 1.4)	
Calcium (mg/day)	1063 (682, 1534)		778 (495, 1017)	
Vitamin D (mcg/day)	11.8 (535, 17.4)		6.9 (4.0, 12.9)	
HIV disease severity				
CD4 count (cells/mm ³)	334 (207, 552)		439 (271, 662)	
HIV viral load (log ₁₀ copies/ml)	2.8 (2.3, 4.0)		2.3 (2.3, 3.8)	
Liver function				
Albumin (gm/dL)	4.1 (3.9, 4.4)		4.0 (3.7, 4.2)	
Abnormal ALT GPT (> 80 IU/L)		19.5		7.7
Abnormal Bilirubin (> 2 mg/dL)		1.2		0.0
Abnormal Alk. phos (> 140 IU/L)		4.1		4.5

Table 1b. Frequency of anti-retroviral use at baseline				
	Men (n=283)		Women (n=98)	
	Users	Continuous use (mos)	Users	Continuous use (mos)
	%	median (25th, 75th)	%	median (25th, 75th)
HAART	72.4	15 (8, 28)	67.1	12 (6, 24)
PI-based HAART	40.3	17 (8, 26)	34.4	12 (6, 24)
NRTI-based HAART	2.5	2 (1, 19)	4.2	4 (2, 8)
NNRTI-based HAART	13.1	12 (6, 24)	12.5	9 (7, 16)
MIXED HAART	9.5	6 (5, 16)	4.2	8 (6, 13)
DDI	10.9	12 (6, 23)	13.5	12 (6, 24)
Tenofovir	1.8	2 (1.2)	2.1	2 (1, 3)
Ritonavir	14.1	11 (5, 21)	4.2	13 (10, 14)
Indinavir	17.7	13 (7, 24)	19.8	12 (5, 24)
Nevirapine	10.9	10 (6, 16)	9.4	9 (7, 14)
d4T	37.1	17 (8, 30)	30.2	16 (9, 24)
Nelfinavir	20.1	12 (6, 24)	12.5	15 (7, 24)

Median percent change in BMD per year of follow-up

-0.17% per year (25th -0.83%, 75th 0.43%)
(range -8.6% to 11.6%)

SUMMARY

- Median annualized change in Total BMD was -0.17% per year.
- Longer duration of DDI and tenofovir predicted a greater loss of Total BMD
- Longer duration of d4T predicted less loss of Total BMD
- Hyperbilirubinemia associated with greater loss of Total BMD

CONCLUSIONS

- Our data on tenofovir and bone loss is supported by other studies and observations:
 - Defective bone mineralization of newly formed cortical bone in macaques treated with high doses of tenofovir (J Orthopaedic Res 2002;20:1185-1189)
 - Efficacy study of tenofovir versus stavudine in antiretroviral naïve patients. Patients treated with tenofovir had lower bone density in the spine after 144 weeks than those treated with stavudine (JAMA 2004;292:191-201).
 - Fanconi's syndrome associated with tenofovir use, could potentially affect 1,25 dihydroxyvitamin D₃ metabolism.
- Further studies needed to understand mechanisms of bone loss in HIV and to examine associations at specific bone sites (including lumbar spine and hip)
- This level of bone loss we observed was small but could be clinically significant over time.