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Abstract

Objective: High prevalence of osteopenia and osteoporosis has been described in HIV+ patients. A possible association with HAART remains controversial. We conducted a prospective study to identify factors associated with reduced bone mineral density (BMD) among HIV+ individuals.

Methods: Consenting ambulatory HIV+ adults were enrolled. All participants completed a detailed questionnaire and a dual-energy X-ray absorptiometry (DEXA) scan of lumbar spine and femoral neck. Full laboratory and HAART-related information were also obtained. Osteopenia and osteoporosis were diagnosed according to the WHO criteria. Logistic regression analysis was performed in both univariate and multivariate setting to investigate factors associated with abnormal BMD.

Results: 285 patients completed the study from Jan 2005 to Jul 2007; 79% were Caucasian and 89% male. Median age was 48 years [IQR: 43 - 55]. A full 67% of patients had abnormal DEXA scans with osteopenia in 54% and osteoporosis in 13%. Using an Akaike's information criterion (AIC) model selection approach, the multivariate analysis confirms that low BMI, Caucasian ethnicity, and current low CD4's count were risk factors related to low BMD. Low physical activity, alcohol consumption and current high pVL were also significantly associated with low BMD among men. There was no correlation between abnormal BMD and any metabolic or laboratory parameters evaluated. When ART drugs were explored, Tenofovir (TDF) exposure (but not PI exposure or total ART exposure) was associated with low BMD (OR 1.56, p < 0.08). The mechanism behind this association could not be elucidated within this analysis.

Conclusions: We found a 67% prevalence of abnormal BMD by DEXA scan in an unselected group of HIV+ individuals. Risk factors for low BMD included those observed in the normal populations (low BMI, Caucasian ethnicity and lower physical activity) and others related to advanced HIV illness (low CD4 count). An association was also uncovered with longer exposure to Tenofovir; this merits further study.

Background

Reduced bone mineral density (BMD) has been frequently reported among HIV infected individuals receiving antiretroviral therapy (ART). Brown et al. (AIDS 2006,20:2165-2174) reported a three-fold increased prevalence of osteoporosis and a 2.5-fold higher prevalence of reduced BMD among ART treated vs. naïve HIV-infected individuals.

Multiple factors have been postulated to increase the risk for osteoporosis and reduced BMD, including HIV infection and use of ART.

Objective

We conducted a prospective cross-sectional study to evaluate the frequency and factors associated with decreased BMD, osteopenia and osteoporosis among HIV infected individuals.

Methods

Consenting HIV positive adults attending the Immunodeficiency Clinic (IDC) at St. Paul's Hospital (Vancouver, BC, Canada) were enrolled. The following parameters were obtained in all patients:

- Detailed life style and medical history questionnaire.
- Dual-energy X-ray absorptiometry (DEXA) scan of lumbar spine and femoral neck. Osteopenia and osteoporosis were diagnosed according to the WHO criteria .
- Full laboratory, including: 24-hour urinary calcium, and urinary N-telopeptide, Alkaline Phosphatase, Ionized calcium, phosphorus, serum testosterone (total and bioavailable), TSH, PTH, CD4 count, plasma HIV RNA level.
- Complete ART exposure history was obtained through a linkage with the British Columbia Centre for Excellence in HIV-AIDS (BC-CfE) database. The BC-CfE Drug Treatment Program is responsible for the distribution of free antiretrovirals to all BC residents

Logistic regression analysis was performed in both univariate and multivariate settings to investigate factors associated with decreased BMD, osteopenia and osteoporosis.

Results

As shown in Table 1, a total of 299 patients were enrolled and 285 completed the study between Jan 2005 and Jul 2007; 80% were Caucasian and 89% male. Median age was 48 years [IQR: 43 – 55 years]. A total of 67% of patients had an abnormal BMD. Patients with an abnormal BMD had a statistically lower body mass index (BMI) (p<0.01), and had higher rates of alcohol use (p = 0.01).

Table 1. Patients characteristics associated with BMD results

Whole patients	BMD Normal N=95(33%)	BMD Abnormal N=190(67%)	P-value
Gender			0.60
Female	12(13%)	20(11%)	
Male	83(87%)	170(89%)	
Ethnicity			0.20
White	79(86%)	148(80%)	
Not white	13(14%)	38(20%)	
Age	47(42-53)	49(44-56)	0.18
BMI	25(24-28)	23(21-26)	<0. 01
Physical Activity			0.26
High	39(41%)	65(635%)	
Low/mod	55(59%)	123(65%)	
Smoking			0.69
No	57(61%)	116(64%)	
Yes	36(39%)	66(36%)	
Alcohol			0.01
No	70(75%)	108(59%)	
Yes	23(25%)	74(41%)	
Family History of Osteoporosis			0.86
No	61(69%)	127(68%)	
Yes	27(31%)	59(32%)	
Intravenous drug use			0.99
No	76(87%)	151(87%)	
Yes	11(13%)	22(13%)	

Table 2. Patient's HIV-related characteristics associated with BMD results

	BMD Normal N=95 (33%) n(%) or Median (IQR)	BMD Abnormal N=190 (67%) n(%) or median (IQR)	P-value
Prior ADI			0.30
No	40 (49%)	66 (42%)	
Yes	41 (51%)	90 (58%)	
Current CD4 (x 100 cells/mm3 increase)	4.0 (2.9-6.1)	3.9 (2.7-5.5)	0.03
CD4 nadir (x 100 cells/mm3 increase)	1.5 (0.7-2.3)	1.2 (0.4-1.9)	0.10
Current viral load (copies/mL)			0.41
≤10000	76 (81%)	160 (87%)	
10000 to 100000	10 (11%)	13 (7%)	
>100000	8 (8%)	11 (6%)	
Cumulative time on ART			1. 00
< 6 month s	11 (12%)	22 (12%)	
≥ 6 months	84 (88%)	168 (88%)	
Cumulative time on PI's			0. 47
< 6 month s	22 (23%)	37 (19%)	
≥ 6 months	73 (77%)	153 (81%)	
Cumulative time on TDF			0. 08
< 6 month s	53 (56%)	85 (44%)	
≥ 6 months	84 (88%)	105 (56%)	

ADI= AIDS Defining Illness, ART = Antiretrovirals, PI's= Protease Inhibitors, TDF= Tenofovir

As shown in Table 3, 67% (n= 190) of patients had abnormal DEXA scans. Of those, 54% (n=152) had osteopenia and 13 % (n= 38) had osteoporosis according to the WHO criteria.

Table 3. Median T-score [IQR] according to gender, site and patients diagnosis category

		Normal T-score > -1 (n=95)	Osteopenia or Osteoporosis T-scores≤-1(n=190)
Left hip	men	0.0 [-0.4, 0.6]	-1.1 [-1.6, -0.7]
	women	0.2 [-0.3, 1.1]	-1.3 [-2.1, -1.0]
Right hip	men	0.0 [-0.5, 0.4]	-1.1 [-1.5, -0.7]
	women	0.6 [-0.1, 1.3]	-1.5 [-1.9, -1.0]
Lumbar Spine	men	0.1 [-0.4, 0.7]	-1.7 [-2.4, -1.2]
	women	0.3 [-0.3, 1.3]	-2.0 [-2.8, -1.4]

Multivariate Analyses

The multivariate analysis confirms that low BMI, ethnicity (Caucasian), and current low CD4's count were associated with lower BMD (p <0.03) (Table 4)

Low physical activity, alcohol use, and current high plasma viral load (pVL) were also significantly associated with low BMD among men only (p<0.03)(Table 5).

When we analyzed time of exposure to total ART, by drug class (PI's only), or to Tenofovir (TDF)specifically; we observed that only TDF exposure of more than 6 months was associated with lower BMD (p< 0.02).

There was no correlation between low BMD and any metabolic or laboratory parameters, concomitant medications (including corticosteroids or anabolic steroids), family history, or duration of HIV infection.

Table 4. Multivariate analysis of factors associated with BMD abnormalities in 285 patients

Factors associated with abnormality (all patients)	Odds Ratio [95% CI]	P-value
BMI	0.85 [0.78, 0.91]	<0. 01
Ethnicity (non-white vs. white)	2.52 [1.09, 5.84]	0.03
Alcohol (yes vs. no)	1.73 [0.93, 3.20]	0.08
Current CD4 (per 100 cells/mm3 increase)	0.87 [0.77, 0.98]	0.03
Cumulative time on Tenofovir (<6 mos vs. ≥6 mos)	2.01 [1.11, 3.62]	0.02

Table 5. Multivariate analysis of factors associated with BMD abnormalities in 253 male patients

Factors associated with abnormality (male patients)	Odds Ratio [95% CI]	P-value
BMI	0.81 [0.74, 0.89]	< 0.01
Physical activity (low/mod vs. high)	2.16 [1.09, 4.27]	0.03
Alcohol use (yes vs. no)	2.08 [1.01, 4.29]	0.04
Prior ADI (yes vs. no)	1.87 [0.95, 3.68]	0.07
Current CD4 (per 100 cells/mm3 increase)	0.80 [0.69, 0.94]	0.01
Current viral load (> or ≥10, 000 copies/mL)	0.24 [0.06, 0.86]	0.02

Discussion

We found a 67% prevalence of abnormal BMD by DEXA scan in an unselected group of HIV+ individuals who attended an ambulatory HIV clinic between January 2005 and July 2007. Of those 54% had osteopenia and 13% osteoporosis. Risk factors associated with decreased BMD included low BMI, caucasian ethnicity and low CD4 cell count. Among men, additional risk factors included low physical activity, alcohol consumption and high pVL.

The results of our analyses did not confirm previously reported associations between low BMD and duration of exposure to ART or exposure to PI's. In contrast, we found a statistically significant association between low BMD and duration of exposure to tenofovir. The mechanism behind this association could not be uncovered in these analyses. Of note, adherence to ART, an important potential confounder, was not adjusted for in these analyses.

Conclusion

Our results support the recommendation that HIV infected individuals be closely monitored for bone density abnormalities. Further prospective evaluation of the possible contribution of tenofovir-containing ART to the development of low BMD is warranted based on our findings.

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