Journal of
AIDS & Clinical Research

Cournil et al., J AIDS Clin Res 2015, 6:4
DOI: 10.4172/2155-6113.1000443

Research Article Open Access

Prevalence of Osteoporosis among HIV-1-Infected Men and Women Aged 50 years and Older in Dakar, Senegal: A Cross-Sectional Study

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Abstract

Background: Published studies reported a high prevalence of osteoporosis among HIV-1-infected subjects, but none of them were conducted in Sub-Saharan Africa. The objective was to estimate prevalence of osteoporosis based on dual energy X-absorptiometry bone mineral density in Senegalese patients above 50 years of age and to identify associated factors.

Methods: A cross-sectional study was conducted among 193 HIV patients above 50 years of age in Dakar, Senegal**.** Bone mineral density was measured by dual energy X-absorptiometry at lumbar spine, femoral neck and total hip. Osteoporosis was defined as T-score ≤ -2.5 at any site.

Results: Median age was 55 years. 99% of women were post-menopausal. Prevalence of osteoporosis at any site was 26% and 6% in women and men, respectively. One and eight subjects had osteoporosis at femoral neck and total hip, respectively, while osteoporosis was more prevalent at lumbar spine (25% in women and 4% in men). Factors independently associated with osteoporosis were female gender (OR=10.3; 95% confidence interval (CI): 3.3-32.6) body mass index (OR=0.8; CI: 0.7-1.0) and CD4 count below 350 cells/µl (OR=2.7; CI: 1.0-7.5).

Conclusions: Patients from this African setting had very low prevalence of osteoporosis at femoral neck, but osteoporosis at the lumbar spine was more prevalent especially among women. Consequences of these bone disorders in terms of fracture need to be investigated in future studies.

Keywords: Osteoporosis; Dual X-ray absorptiometry; Western Africa; HIV-1; Antiretroviral; Age ≥ 50 years

Introduction

A higher prevalence of low bone mineral density (BMD) and osteoporosis has been described in HIV-1-infected patients compared with HIV-uninfected subjects [1-3]. Recent data also suggest that HIV-1-infected people experience higher risks of osteoporosis-related fractures [4,5]. Several factors are involved in the pathogenesis of osteoporosis including traditional factors such as age, gender, low weight, current smoking, reduced physical activity, malnutrition and sex hormone deficiency; but also HIV infection specific risk factors and HIV treatment [6,7].

Most studies have been conducted in North America (among both Caucasian and Black American people) and in Europe and bone status is poorly documented in patients living in Sub-Saharan Africa. We have previously reported that quantitative ultrasound (QUS) bone mineral density was lower in HIV-positive patients compared with negative controls from a cross-sectional study conducted in Dakar, Senegal [8]. However, in accordance with International Society Clinical Densitometry (ISCD) 2013 official positions, prevalence of osteoporosis could not be derived from QUS measures [9]. To date, information on osteoporosis among African populations is lacking. Several studies among HIV-positive and negative people reported higher bone mineral density, especially at femoral neck and total hip, as well as lower risk of fracture in African-American compared to Caucasians [10-13]. If these characteristics are also applied to Africans, it could be expected that HIV-1-infected patients living in sub-Saharan Africa would experience less osteoporosis. Conversely, patients living in resource-limited settings may be more affected by nutritional deficiencies and wasting which are known to be associated with low BMD [6,14].

The aim of this cross-sectional study was to estimate the prevalence of osteoporosis based on dual energy X-absorptiometry (DXA) measurements of bone mineral density in Senegalese HIV-1-infected patients living in Dakar and to identify factors associated with osteoporosis in this population. The study focused on men and women aged over 50, for whom diagnosis of osteoporosis from DXA is fully applicable.

Methods

Study setting and patient population

From October, 2012 to February, 2013, a cross-sectional study was conducted at Fann University Hospital in Dakar. All HIV-1-infected

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Received February 19, 2015; **Accepted** March 17, 2015; **Published** March 25, 2015

Citation: Cournil A, Eymard-Duvernay S, Diouf A, Briot K, Li F, et al. (2015) Prevalence of Osteoporosis among HIV-1-Infected Men and Women Aged 50 years and Older in Dakar, Senegal: A Cross-Sectional Study. J AIDS Clin Res 6: 443. doi:10.4172/2155-6113.1000443

patients aged ≥ 50 and receiving antiretroviral treatment for at least 6 months were consecutively invited to participate until recruitment of 100 women and 100 men. Patients were not included if they were hospitalized.

Clinical evaluation

After enrolment, a standardized case report form was used to collect risk factors for osteoporosis (age, sex, weight, height, previous low-trauma fracture, parent hip fracture, current smoking, alcohol use, current glucocorticoid use and secondary osteoporosis) [15], and to assess physical activity level using the International Physical Activity Questionnaire [16]. Standard information on HIV infection (CD4 cell count and viral load in the previous six months, and CD4 cell count nadir) and antiretroviral treatment (duration, current exposure to tenofovir disoproxil fumarate (TDF) or to any protease inhibitor) were also collected from medical records review. Weight and height were assessed during the BMD measurements and body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Assessment of BMD

BMD was measured by DXA scan of the lumbar spine and hip using the DEXXUM T device (Osteosys) in all patients. BMD is determined at the lumbar spine (first to fourth vertebrae) and the upper part of the left femur (total hip and femoral neck). The results are given as BMD (g/cm^2).

All exams were performed according to the manufacturer's recommendations. Device was controlled by measuring a spine phantom at least 3 times a week throughout the study.

In accordance with the Official Positions of the International Society for Clinical Densitometry (ISCD), BMD was expressed in T-scores using female National Health and Nutrition Examination Survey (NHANES) III data as the reference standard for femoral neck and total hip [9]. The female NHANES III data were also used as the reference standard for lumbar spine T-scores.

In addition T-scores were calculated using local Senegalese reference data (referred as the local reference below). The local reference data was elaborated using the BMD measurements performed with the same DXA device in 100 subjects (50 women and 50 men), aged between 25 and 35 years, living in Dakar and in apparent good health. These subjects were recruited among Fann Hospital staff.

In accordance with ISCD guidelines and World Health Organization criteria, osteoporosis was defined as T-score ≤ -2.5 SD at any of the three anatomical sites (lumbar spine, total hip and femoral neck) examined [9].

Statistical analyses

McNemar's test was used to compare estimated prevalence of osteoporosis obtained with the two references. The exact test was used when the expected numbers were small. Characteristics of men and women were compared using $\chi 2$ or Fisher's exact tests for categorical variables and ANOVA or Wilcoxon rank-sum tests for continuous ones. Factors associated with osteoporosis (at any of the three sites and at each site and using NHANES III reference) were identified using univariable and multivariable logistic regression models. The factors considered in this analysis were age (per 10-year increase), sex, BMI, at least one risk factor for osteoporosis, high physical activity level, ART duration>3 years, current protease inhibitor use, current TDF use, nadir CD4 cell count<200 cells/µl and last CD4 cell count<350 cells/µl. Age, sex and BMI were always included in the multivariable models. Other factors were retained for multivariate analyses if the probability in univariate analyses was less than 0.25. These analyses were not stratified by sex, because the number of events was too low among male. Stata software (version 12.1, Stata Corp, College Station, TX) was used for all statistical analyses.

Ethics

The Senegalese ethics committee approved the study (protocol SEN 12/37) and all participants (HIV patients and reference population subjects) signed a written informed consent.

Results

Characteristics of the patients

A total of 206 patients met the eligibility criteria and 193 (97 men and 96 women) had a DXA measurement at the three anatomical sites. Mean age among men was 57 years and 58 years among women (Table 1). BMI was higher in women, with 45% of them being overweight or obese (BMI ≥ 25) in comparison with 9% in men. A previous low trauma fracture was reported by 12 subjects (6%). Patients were receiving antiretroviral treatment for a median duration of 6.7 years and 46 (24%) of them had a TDF-based regimen.

Characteristics	Men	Women	P-value
	n=97	n=96	
Mean age (SD), years	57.2 (5.8)	58.0 (5.9)	0.34
Mean weight (SD), kg	64.5 (11.0)	65.5 (13.5)	0.57
Mean height (SD), cm	176 (8)	163 (7)	<0.001
Mean BMI (SD), kg/m^2	20.8 (3.4)	24.5 (4.5)	<0.001
Underweight	28 (29%)	11 (11%)	<0.001
Normal	60 (62%)	42 (44%)	
Overweight	8 (8%)	30 (31%)	
Obesity	1 (1%)	13 (14%)	
At least one risk factor	29 (30%)	12 (13%)	0.003
Previous fracture	7 (7%)	5 (5%)	0.77
Parent fractured hip	4 (4%)	5 (5%)	0.75
Current smoker	17 (18%)	1 (1%)	<0.001
Alcohol (≥ 3 units/day)	3 (3%)	0	0.25
Corticosteroid use	0	1 (1%)	0.50
Rheumatoid arthritis	0	2 (2%)	0.25
Secondary osteoporosis	4 (4%)	1 (1%)	0.37
Post-menopausal (n=94)		93 (99%)	
Physical activity			
Low	26 (27%)	36 (38%)	<0.001
Moderate	38 (39%)	50 (52%)	
High	33 (34%)	10 (10%)	
Median ART duration (IQR), years	7.2 (4.0-10.4)	5.7 (3.6-8.8)	0.16
Current PI use	16 (16%)	20 (21%)	0.44
Current TDF use	22 (23%)	24 (25%)	0.71
Median CD4 count nadir (IQR), cells/µL[a]	108 (47-190)	144 (81-243)	0.029
CD4 count nadir<200 cells/µL*	72 (77%)	61 (66%)	0.12
Median current CD4 count (IQR), cells/µL[a]	422 (294-588)	470 (346-722)	0.13
CD4 cell count<350 cells/µL[a]	17 (25%)		0.13
Undetectable viral load[a]	33 (87%)		0.56

SD: Standard Deviation; BMI: Body Mass Index; ART: Antiretroviral Treatment; IQR: Interquartile Range; PI: Protease Inhibitor; TDF: Tenofovir Disoproxyl Fumarate

[a]CD cell count, CD4 nadir and viral load were available for 145, 186 and 83 subjects respectively.

Table 1: Characteristics of HIV-infected men and women.

Bone mineral density and osteoporosis

As expected, HIV-1-infected subjects had lower BMD than the young reference populations at each anatomical site (Figure 1). Comparison of data from the two references indicates that young people from the local reference population had higher BMD at the hip (femoral neck and total hip) than in NHANES reference data, whereas their BMD at the lumbar spine tend to be lower (Figure 1).

T-score was below or equal to -2.5 in at least one site in 6 men (6%) and 25 women (26%) (Table 2).

When each site was considered separately, prevalence of osteoporosis was very low at the femoral sites (one man and no woman had osteoporosis at femoral neck and two men and six women at total hip), while osteoporosis was more prevalent at lumbar spine; T-scores were below or equal to -2.5 in 25 women (25%) and four men (4%).

Compared with the NHANES III standard reference, the use of the local reference to derive T-scores led to identical values at lumbar spine, whereas proportions of T-scores below or equal to -2.5 were significantly higher at femoral neck and total hip in both men and women (Table 2).

Factors associated with osteoporosis

In multivariate analyses including age, sex, BMI and any other factor that was associated with presence of osteoporosis at a 25% level in univariate analysis; lower BMI and female gender were associated with presence of osteoporosis at the lumbar spine, total hip and with presence of osteoporosis at any anatomical site (Table 3). CD4 count

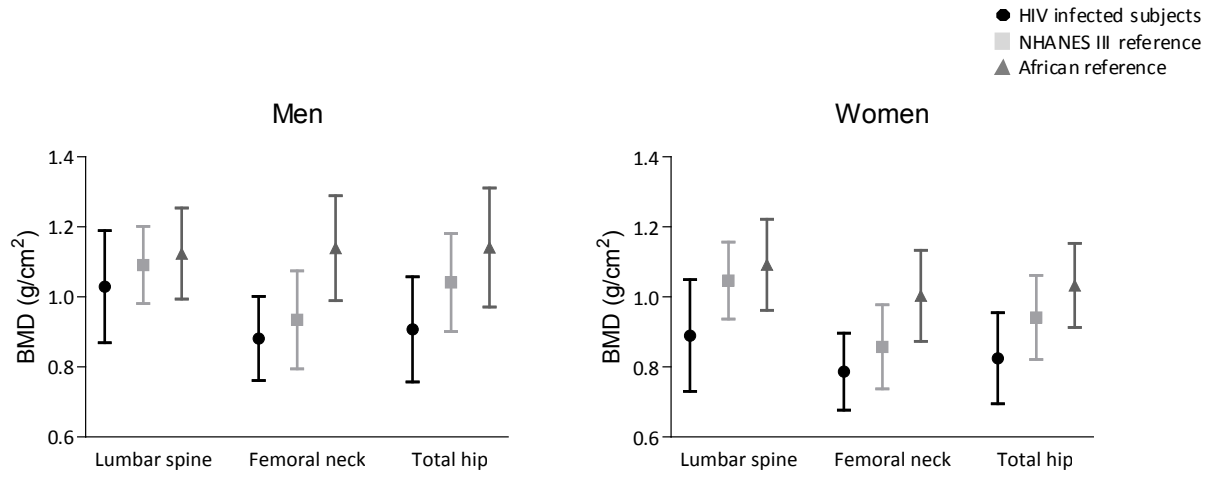

Figure 1: Crude BMD (mean ± SD) at lumbar spine, femoral neck and total hip in HIV-infected subjects and in reference populations (NHANES III and local).

	Men (n=97)			Women (n=96)			Men	Women
	Lumbar spine (L1-L4)	Femoral neck	Total hip	Lumbar spine (L1-L4)	Femoral neck	Total hip	Any site	
BMD (g/cm²), mean (SD)	1.032 (0.154)	0.881 (0.119)	0.907 (0.148)	0.892 (0.159)	0.797 (0.114)	0.825 (0.129)		
NHANES III[a] reference								
T-score, mean (SD)	-0.1 (1.4)	0.2 (1.0)	-0.3 (1.2)	-1.4 (1.4)	-0.5 (0.9)	-1.0 (1.1)		
T-score ≤ -2.5, n (%)	4 (4%)	1 (1%)	2 (2%)	24 (25%)	0	6 (6%)	6 (6%)	25 (26%)
Local reference								
T-score, mean (SD)	-0.7 (1.2)	-1.7 (0.8)	-1.3 (0.8)	-1.6 (1.3)	-1.6 (0.9)	-1.7 (1.1)		
T-score ≤ -2.5, n (%)	4 (4%)	13 (13%)	7 (7%)	24 (25%)	15 (16%)	22 (23%)	17 (18%)	38 (40%)
P[b]	NS	<0.001	NS	NS	<0.001	<0.001	0.001	<0.001

BMD: Bone Mineral Density; SD: Standard Deviation
[a]Site-specific Caucasian NHANES III female reference data were used to calculate T-score
[b]P-value for comparison of osteoporosis prevalence using the NHANES III and local references

Table 2: Bone mineral density T-scores and prevalence of osteoporosis at the different sites among HIV-infected men and women.

	Lumbar spine (n=145)		Total hip (n=193)		At least one site (n=145)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Female	15.9 (4.2-60.1)	<0.001	6.9 (1.2-40.7)	0.03	10.3 (3.3-32.6)	<0.001
Age (per 10 years)	1.3 (0.6-3.0)	0.49	1.9 (0.6-5.9)	0.25	1.3 (0.6-2.7)	0.51
BMI (per kg/m² increase)	0.8 (0.7-1.0)	0.021	0.8 (0.6-1.0)	0.028	0.8 (0.7-1.0)	0.017
Current TDF use	1.8 (0.5-5.9)	0.36	_[a]	_	1.4 (0.4-4.3)	0.56
Current PI use	1.09 (0.3-4.3)	0.90	_	_	_	_
CD4 cell count<350 cells/µL	3.0 (1.0-8.9)	0.045	_	_	2.7 (1.0-7.5)	0.048

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ART: Antiretroviral Treatment; TDF: Tenofovir Disoproxyl Fumarate; PI: Protease Inhibitor
[a]Factors were not included in multivariate models (p-value>0.25 in univariate analysis; see Methods Section).

Table 3: Factors associated with osteoporosis (T-score ≤ -2.5) at lumbar spine, total hip and at least one anatomical site.

below 350 cells/µl was associated with higher risk of osteoporosis at lumbar spine, as well as with presence of osteoporosis at any site. Although retained in multivariate analysis, neither current exposure to protease inhibitors nor current exposure to TDF was significantly associated with the presence of osteoporosis in multivariate analyses. Physical activity, ART duration and nadir CD4 were not associated with osteoporosis.

Discussion

To our knowledge, this is the first study providing an estimation of the prevalence of osteoporosis among HIV patients from a sub-Saharan setting. In this population of patients above 50 years of age, the prevalence of osteoporosis was 26% in women and 6% in men. In most cases the diagnosis of osteoporosis was the consequence of decreased BMD at lumbar spine. Low BMI, female gender and CD4 count below 350 cells/µl were associated with the presence of osteoporosis.

The prevalence of osteoporosis in HIV-positive patients varies widely ranging from 0 to 25% [1,12,17-19]. However most of these studies focused on young or middle age individuals, while we included patients above 50 years of age for whom diagnosis of osteoporosis with DXA is fully applicable. In a study conducted in the UK, the reported prevalence of osteoporosis in men and women aged over 50 were 17% and 38%, respectively [4]. A cross-sectional study among 31 post-menopausal HIV-positive women in US, reported 42% and 10% of osteoporosis at lumbar spine and total hip, respectively [20].

There is currently no available data documenting osteoporosis in the general population in Senegal; and the lack of an age-matched control group precluded any comparison with HIV-negative subjects from Senegal. Meanwhile, in a previous study we compared QUS BMD between HIV-1-infected patients and controls in Senegal and showed that HIV patients had a lower BMD, which was partly explained by lower BMI [8]. This report was consistent with several studies suggested that differences in BMI and body composition between HIV-1-infected and uninfected subjects may largely account for differences in BMD [21,22]. In contrast, a recent study conducted among 247 black South African women reported no difference in BMD DXA measurements by HIV infection status despite HIV positive women being lighter and with lower BMI [23].

Older age, low BMI and female gender are the most common traditional risk factors for increased risk of osteoporosis. And as expected, low BMI and female gender were significantly associated with the presence of osteoporosis in our study. Age was not associated and it may be explained by the skewed distribution of age in our study population; 50% of the population was concentrated between 50 and 55 years of age. Available data on the role for HIV-related factors in bone loss among HIV-1-infected patients are conflicting [6]. Some studies have suggested that the use of protease inhibitor and of TDF was associated with an increased risk of osteopenia and osteoporosis [1,12,17,24,25] while others failed to confirm this association [18,20,26,27]. In the present study, neither protease inhibitors nor TDF was associated to bone loss with statistical significance, although weak trends of association were observed at several sites for TDF. We also observed that a CD4 count below 350 cells/µl was associated with presence of osteoporosis. A previous study has reported an association between low CD4 count and increased risk of fragility fracture [28], but association between CD4 cell count and osteoporosis has not been documented so far and Hamill et al. found no difference when comparing BMD among black South African young HIV-positive women with preserved CD4 counts to women with low CD4 [23].

One of our study's strengths relies in the use of a local Senegalese reference purposely constituted for this study to derive T-score. The National Osteoporosis Foundation of South Africa (NOFSA) guideline for diagnosis and management of osteoporosis stated that "the diagnosis of osteoporosis in local black populations requires local BMD references values" [29]. Indeed, using the African Americans reference values provided by the manufacturers may not be appropriate because mean BMD values in African populations appear to be lower than those of African Americans. It is also suggested that "until validated local reference become available, reference data for Caucasian females be used for subjects of all races".

In our study, comparison of mean BMD values between the NHANES III reference values and those of our local reference population confirmed the existence of differences in BMD at least between African and Caucasian populations. Mean BMD values from the local reference population were higher than in NHANES III reference data at the hip (femoral neck and total hip), whereas mean BMD at the lumbar spine did not differed. Further comparison of our local references values with African American NHANES III values showed lower mean BMD values in the local reference at lumbar spine but not at femoral neck or total hip [30].

Thus it confirms that prospective studies assessing the fracture risk are needed in African populations to provide robust and validated local reference data.

These results suggest a low risk of hip fractures in this population, while vertebral fractures are expected to be more prevalent, but are usually asymptomatic. In our study, 6% of the patients reported low trauma fracture. This figure is consistent with prevalence reported in studies including black American like the Women's health Initiative Study, in which history of fracture at age 55 was 13.6% in white, 6.4% in black and 7.1% in Hispanic women [31].

This study had several limitations, the lack of an age-matched control group and the lack of detailed information about risk factors, like antiretroviral treatment history, to further investigate associated factors. Finally the cross-sectional design of the study precluded any interpretation of causal effect of associated factors.

In conclusion, our study provides data on osteoporosis among people living with HIV and on ART in a sub-Saharan African setting. The prevalence observed in this population of patients above 50 years of age suggested that African patients have high BMD at the hip and are at low risk of hip fracture. However osteoporosis at the spine has been diagnosed in a quarter of the women in our study, with possibly high risk of vertebral fracture. Moreover, we observed that low CD4 (below 350 cells/µl) may be associated with enhanced vertebral osteoporosis. This result, if confirmed, supports recommendation to start antiretroviral treatment early in order to preserve as much as possible CD4 count level.

Funding

The study was funded by European & Developing Countries Clinical Trials Partnership (IP.2007.31100.004).

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