Prevalence of sub-clinical vertebral fractures in HIV-infected patients

Marco Borderi[1], Leonardo Calza[1], Vincenzo Colangeli[1], Elisa Vanino[1], Pierluigi Viale[1], Davide Gibellini[2], Maria Carla Re[2]

[1]Infectious Disease Unit, Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy;
[2]Department of Haematology and Oncologic Sciences, Section of Microbiology, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy.

SUMMARY

Although the increased prevalence of low bone mineral density among HIV-infected patients has raised concern for increased fracture risk, few investigations have evaluated fracture rates. Increasing evidence indicates that HIV patients are at higher risk of osteoporotic fractures compared to the general population. This is a very important issue, because fragility fractures are complications with a significant prognostic value.

Our study performed lateral spine X-ray to assess the prevalence of sub-clinical vertebral fractures in 202 HIV patients. Factors associated with vertebral fractures were also investigated.

The prevalence of vertebral fractures was significantly high (23.3%): 14 subjects had SDI (spine deformity index)=1, 22 SDI=2-3 and 11 SDI >4. Differences in the prevalence of vertebral fractures between naïve and ART-experienced patients was 18% vs. 24%, respectively. Furthermore, patients had a high prevalence of severe and multiple fractures; in 19 patients (40%) fractures involved multiple vertebrae.

Patients with vertebral fractures were significantly older, with renal insufficiency and steroid use more frequently than subjects with no fractures.

Our data suggest that the prevalence of vertebral fractures in HIV infection may be higher than expected, and lateral spine X-ray has a role in the screening of bone disease, at least in patients with a significant risk of fragility fractures.

KEY WORDS: HIV infection, Spine X-ray, Vertebral fractures.

INTRODUCTION

An increased prevalence of low bone mineral density (BMD), osteopenia and osteoporosis has recently been reported in both men and women with HIV infection and, compared to uninfected individuals, low BMD is more common among HIV-infected subjects (Arnsten *et al.*, 2006; Amiel *et al.*, 2004; Tebas *et al.*, 2000; Bruera *et al.*, 2003; Carr *et al.*, 2001; Moore *et al.*, 2001).

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Corresponding author
Marco Borderi
Infectious Diseases Section
Department of Medical and Surgical Sciences
University of Bologna, Italy
E-mail: marco.borderi@aosp.bo.it

Many recent studies have investigated BMD among patients with HIV infection (Gold *et al.*, 2002; Mondy *et al.*, 2003; Bongiovanni *et al.*, 2005; Cazanave *et al.*, 2008; Rivas *et al.*, 2008), finding have a high prevalence of osteopenia and osteoporosis in HIV-infected compared with control groups (Brown *et al.*, 2004; Dolan *et al.*, 2004; Yin *et al.*, 2005; Dolan *et al.*, 2007; Jones *et al.*, 2007, Brown *et al.*, 2006a).

A meta-analysis of studies comparing BMD in HIV-infected with non-HIV-infected patients estimated that 67% of HIV-infected persons had reduced BMD, and 15% had osteoporosis, demonstrating a pooled odds ratio of 3.7 for osteoporosis (Brown *et al.*, 2006b).

Although the increased prevalence of low BMD among HIV-infected patients has raised concern for increased fracture risk, few investi-

gations have evaluated fracture rates among HIV-infected patients (Triant *et al.*, 2008; Collin *et al.*, 2009; Arnsten *et al.*, 2007). Nonetheless, increasing evidence indicates that HIV patients are at higher risk of osteoporosis-related bone fractures compared to the general population. This is a very important issue, because fragility fractures are complications with a significant prognostic value (Ensrud *et al.*, 2011).

A US population-based report in a large health-care system found that fracture prevalence was significantly increased in HIV-infected subjects (N=5555), with a 60% higher period prevalence of spine, hip, and wrist fracture in HIV-infected patients compared to persons whose HIV status was negative or unknown (N=975158), after controlling for age and race (2.87 per 100 persons vs. 1.77; P,0.0001). This study did not include other recognized risk factors for fragility fracture.

The Veterans Aging Cohort Study found that HIV infection was associated with a 24% increased risk of fragility fracture after adjusting for demographics, co-morbid disease, smoking, and alcohol (HR 1.4, 95% CI 1.11-1.39). Current protease inhibitor (PI) use increased the risk of fracture (HR 1.41, 95% CI 1.16-1.70) (Womack *et al.*, 2001).

In the HIV Outpatient Study (HOPS), age-adjusted fracture rates for HIV-infected adults were higher than rates in the general population: fracture rate per 10000 population, HOPS 83.2 (95% CI 65.2-146.3) and general population 35.9 (95% CI 24.1-53.5) (Young *et al.*, 2001). In addition, both HIV-infected men and women were at an increased risk of fracture, IRR (incidence rate ratio) 1.5, compared to population controls in a population-based nationwide cohort study. The fracture rate was increased in both ART-naïve (IRR 1.4) and ART-exposed (IRR 1.6) subjects (Hansen *et al.*, 2011).

In a Canadian case-control study of bone health in women, HIV-infected women were more likely to have a fragility fracture than HIV-uninfected women (26.1 vs. 17.3%, OR 1.7). Risk factors for fracture among the HIV-infected women included systemic steroid therapy, oligomenorrhea, weight cycling, and tobacco use (Prior *et al.*, 2007).

By contrast, some data suggest a similar risk of fracture in HIV-infected and HIV-uninfected persons: among premenopausal women in the WIHS, there was no difference in the incidence of fracture by HIV status (1.8 vs. 1.4/100 person years, p = 0.18) (Yin *et al.*, 2010). In addition, there was no difference in the rate of incident fracture between aging men with HIV (N=328) and those at-risk without HIV (N=231) during 1140 person years (py) of follow-up (3.1/100 py vs. 2.6/100 py, p=0.69); the 38% increased fracture incidence among HIV-infected men was not statistically significant, likely due to small sample size. In both studies, the HIV-uninfected control groups reported drug use and other lifestyle behaviours similar to the HIV-infected groups. The differences in these control groups compared to general population-based controls used in other studies, as well as the low rates of fractures, may account for the contrasting results.

Other fracture studies have focused on HIV cohorts, allowing identification of fracture risk factors specific to HIV-infected persons. A study of a cohort of 1281 antiretroviral–treated HIV-infected persons (77% male) in France from 1997 through 2007 found an increasing incidence of fractures: 3.3 per 1000 patient years (95% CI 2.0-4.6), associated with excessive alcohol consumption and hepatitis C co-infection, but this study did not include a general population comparison group.

The Swiss HIV Cohort Study, in which the median duration of HIV infection was 15.4 years, reported a fracture incidence rate of 1.64 per 1000 person years (95% CI 1.19-2.26). The risk of fracture was particularly elevated in persons aged 65 years and older (HR 10.5, 95% CI 3.58-30.5) (Hasse *et al.*, 2011).

A large Australian case–control study of HIV-infected persons predominantly male found an overall fracture incidence rate of 0.53 per 100 person years, and period prevalence of 3.34 per 100 patients (95% CI 2.66-4.13). Fracture risk was associated with low CD4 cell count, corticosteroid use, and anti-epileptic medication use (Yong *et al.*, 2011).

Many of the risk factors associated with reduced BMD in cross-sectional studies are also implicated in the increased fracture risk among HIV-infected persons, as expected. Indeed, the risk for fragility fracture is multifactorial, as highlighted in the World Health Organization's Fracture Risk Assessment Tool (FRAX).

FRAX® was developed to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (defined as clinical vertebral, hip, forearm or proximal humerus fracture) taking into account femoral neck BMD and the clinical risk factors. The FRAX® algorithm is available at www.nof. org and at www.shef.ac.uk/FRAX. FRAX® is most useful in patients with low hip BMD. Utilizing FRAX® in patients with low BMD at the spine but a relatively normal BMD at the hip requires special consideration. Specifically, the WHO algorithm has not been validated for the use of spine BMD. As such, clinicians will need to use clinical judgment in this situation, since FRAX® may underestimate fracture risk in these individuals based on the exclusive use of femoral neck BMD. FRAX® is intended for post-menopausal women and men age 40 and older; it is not intended for use in younger adults or children. In the absence of femoral neck BMD, total hip BMD may be substituted. However, use of BMD from non-hip sites in the algorithm is not recommended because such use has not been validated.

The WHO determined that for many secondary causes of osteoporosis, fracture risk was mediated primarily through impact on BMD: for this reason, when T-scores are inserted into FRAX®, the secondary osteoporosis button is automatically inactivated.

Among HIV-infected individuals, fragility fractures may be related to HIV-specific as well as traditional risk factors: increasing age, female gender, white race, low BMI, previous fracture, parental history of hip fracture, current smoking, glucocorticoid use, three or more units of alcohol per day, rheumatoid arthritis, secondary osteoporosis, and decreased femoral neck BMD. Many FRAX risk factors have not been explored in the context of HIV infection, and there are also fragility fracture risk factors not included in the FRAX but that are also associated with HIV infection. These include: chronic hepatitis B or C infection (Steikne *et al.*, 2002), chronic obstructive pulmonary disease, (Crothers *et al.*, 2006), coronary artery disease, (Weber *et al.*, 2006), cerebrovascular disease, (Hoffman *et al.*, 2000), and proton pump inhibitor use (Targownik *et al.*, 2008). The nature of these associations likely differs by disease, thus the role that these conditions play in the relation between HIV infection and fragility fractures may vary.

Data on fragility fractures in HIV-infected patients are usually based on retrospective historical assessment of clinical fractures, but this approach underestimates these events because the majority of vertebral osteoporotic fractures are asymptomatic (Angeli *et al.*, 2006). Current knowledge supports the clinical relevance of radiologically diagnosed vertebral fractures (Grigoryan *et al.*, 2003).

MATERIALS AND METHODS

A cross-sectional study of 202 unselected progressive HIV+ patients (median age: 51 years old, range: 31-67, 68% males) was performed. Twenty-eight patients were drug-naïve whereas 174 patients were ART-experienced. The database of these patients was created using data from electronic charts of HIV-infected patients at the Infectious Diseases Unit of Bologna from 2011 (October) to 2012 (October). We considered the principal epidemiological, immunological, virological and clinical risk factors for osteoporosis: sex, age, race, weight, CD4+ cell count, nadir CD4+ cell count, HIV viral load, AIDS diagnosis, duration of cART exposure, boosted protease inhibitors exposure, NNRTI exposure, opiate use, low body mass index, tobacco use, alcohol use, Hepatitis C coinfection, diabetes mellitus, chronic renal insufficiency, current corticosteroid use, hypogonadism, vitamin D deficiency, malabsorption, menopause, personal history of fracture, parental history of hip fracture, rheumatoid arthritis, low calcium intake with diet.

To admit these patients to this study, several exclusion criteria were chosen: treatment with anti-osteoporotic drugs and/or with drugs causing osteoporosis and fractures (Mazziotti *et al.*, 2010), chronic diseases known to be associated with osteoporosis, menopause and a clinical history of recent significant traumas or prolonged immobilization. Vertebral deformities were detected on lateral spine X-ray using a semi-quantitative evaluation of vertebral heights and quantitative morphometric analysis of centrally digitized images: anterior

(Ha), middle (Hm) and posterior (Hp) vertebral heights were measured, and height ratios calculated. For each vertebral body the fractures were defined as mild, moderate and severe on the basis of height ratio decreases of 20-25% (grade 1), 26-40% (grade 2) and >40% (grade 3) (Genant *et al.*, 1996). For each patient, the "spine deformity index" (SDI) was calculated by summing the grade of vertebral deformities, according to the semiquantitative method by Genant: SDI>1 is indicative of vertebral fracture according to its definition (reduction in vertebral high of 4 mm or of 15%).

Data were expressed as the median and range. Frequencies were compared using Chi-square test, with Fisher correction when appropriate. Unpaired data were compared using the Mann-Whitney test. Logistic regression models were used in the statistical analysis of factors associated with any, severe and multiple vertebral fractures. Characteristics of HIV-infected patients and risk factors associated with vertebral fractures were evaluated in univariate and multivariable models. Statistical significance was assumed when P values were equal to or less than 0.05.

RESULTS

The median age of HIV-infected patients was 51 years (range: 31-67) and median duration of HIV infection was 8.7 years (range: 1.9-22); 14% of patients (28) were naïve to ART and 86% (174) were experienced (Table 1).

The prevalence of vertebral fractures was significantly high (23.3%): 14 subjects had a single grade 1 fracture (SDI=1), 22 had SDI=2-3, and 11 SDI >4. Differences in the prevalence of vertebral fractures between patients who were naïve or ART-experienced was 18% (5 subjects) vs. 24% (42 subjects), respectively. Furthermore, patients had a high prevalence of severe and multiple fractures; in 19 patients (40%) fractures involved multiple vertebrae (Table 2).

Patients with vertebral fractures were significantly older (p=0.012), and presented with renal insufficiency (eGFR<60 mL/min) (p=0.02) more frequently than HIV-positive patients with no fractures.

Logistic regression analyses were performed

TABLE 1 - *Baseline characteristics of HIV-1 infected subjects.*

	Naïve	*Experienced*
Male	18	114
Female	10	60
Age (years)	49	52
Caucasian	28	174
Opiate use	3	78
AIDS diagnosis	0	6
Viral load (copies) (mL)	38200	1258
CD4+ cell count (cell/mm³)	468	542
Nadir CD4+ (cell/mm³)	362	285
BMI (kg/m²)	22.5	23.7
Tobacco use	17	128
Alcohol use (3 units/day)	8	65
HCV coinfection	19	102
Diabetes mellitus	0	21
Chronic renal insufficiency	0	8
PI/r exposure	-	104
NNRTI exposure	-	70
Duration cART exposure (days)	-	2724
Current corticosteroid use	0	0
Hypogonadism	0	0
Malabsorption	0	0
Menopause	0	0
Personal history of fracture	0	5
Parental history of hip fracture	0	8
Weight (kg)	64	71
Rheumatoid arthritis	0	0
Calcium intake with diet (mg/day)	568	712
Vitamin D deficiency	6	36
Duration of HIV infection (years)	6.7	9.8

TABLE 2 - *Characteristics of fractures.*

Prevalence of vertebral fractures	23.3%
Subjects with SDI=1	14
Subjects with SDI=2-3	22
Subjects with SDI>4	11
Vertebral fractures in naïve patients	5 (18%)
Vertebral fractures in experienced patients	42 (24%)
Subjects with multiple fractures	19 (40%)

TABLE 3 - *Factors associated with vertebral fractures.*

Factors associated with vertebral fractures	OR	p
Age (for each increased year)	1.18 [95% CI 1.03-1.25]	0.01
eGFR<60 mL/min	3.9 [95% CI 1.18-11.12]	0.04
Steroid use	2.65 [95% CI 1.11-7.12]	0.02

Other variables were not associated with any outcomes: sex, race, weight, CD4+ cell count, nadir CD4+ cell count, HIV viral load, AIDS diagnosis, duration of cART exposure, boosted protease inhibitors exposure, NNRTI exposure, opiate use, low body mass index, tobacco use, alcohol use, Hepatitis C coinfection, diabetes mellitus, hypogonadism, vitamin D deficiency, malabsorption, menopause, personal history of fracture, parental history of hip fracture, rheumatoid arthritis, low calcium intake with diet.

using any vertebral fractures, severe vertebral fractures and multiple vertebral fractures as dependent variables.

In univariate analysis, age was significantly associated with any fractures (for each increased year: OR=1.18, 95% CI 1.03-1.25, p=0.01). Patients aged 50-67 years old showed a higher prevalence of vertebral fracture (32%) than those aged 31-50 years (13%, p=.008). Again in univariate analysis, chronic renal insufficiency (eGFR<60 mL/min) was associated with any fractures (OR=3.9, 95%CI 1.18-11.12, p=0.04). In multivariate analysis previous steroid use (OR 2.65 [95%CI 1.11-7.12]; p=0.02) were associated with vertebral fractures (Table 3).

Other variables were not associated with any outcomes: sex, race, weight, CD4+ cell count, nadir CD4+ cell count, HIV viral load, AIDS diagnosis, duration of cART exposure, boosted protease inhibitors exposure, NNRTI exposure, opiate use, low body mass index, tobacco use, alcohol use, Hepatitis C coinfection, diabetes mellitus, hypogonadism, vitamin D deficiency, malabsorption, menopause, personal history of fracture, parental history of hip fracture, rheumatoid arthritis, or low calcium intake with diet.

DISCUSSION

Vertebral Fracture Assessment (VFA) is the correct term to denote densitometric spine imaging performed for the purpose of detecting vertebral fractures. Independent of BMD, age and other clinical risk factors, radiographically confirmed vertebral fractures are a strong predictor of new vertebral fractures, and they also predict other fractures. VFA imaging of the thoracic and lumbar spine using central DXA scanners should be considered at the time of BMD assessment when the presence of a vertebral fracture not previously identified may influence the clinical management of the patient. Usually VFA finds an indication when the results may influence clinical management.

1) Postmenopausal women with low bone mass (osteopenia) by BMD criteria, plus any one of the following: age greater than or equal to 70 years, historical height loss greater than 4 cm, prospective height loss greater than 2 cm, and self-reported vertebral fracture (not previously documented); or two or more of the following: age 60 to 69 years, self-reported prior non-vertebral fracture, historical height loss of 2 to 4 cm, and chronic systemic diseases associated with increased risk of vertebral fractures (for example, moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease);

2) Men with low bone mass (osteopenia) by BMD criteria, plus any one of the following: age 80 years or older, historical height loss greater than 6 cm, prospective height loss greater than 3 cm, and self-reported vertebral fracture (not previously documented); or two or more of the following: age 70 to 79 years, self-reported prior non-vertebral fracture, historical height loss of 3 to 6 cm, on pharmacologic androgen deprivation ther-

apy or following orchiectomy, and chronic systemic diseases associated with increased risk of vertebral fractures (for example, moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease);

3) Women or men on chronic glucocorticoid therapy (equivalent to 5 mg or more of prednisone daily for three months or longer);

4) Postmenopausal women or men with osteoporosis by BMD criteria, if documentation of one or more vertebral fractures will alter clinical management.

Our study investigated the use of VFA in a different setting of subjects, patients with HIV infection, and showed that the prevalence of vertebral fractures in HIV-infected patients was very high. We observed a difference between drug- naïve patients and ART-experienced patients.

Age, chronic renal insufficiency (Calmy *et al.*, 2009) and previous steroid use (Gallant *et al.*, 1998) are associated with increased risk of fractures in HIV-infected subjects. Our data suggest that prevalence of vertebral fractures in the HIV population may be higher than expected. The finding of almost one out of four HIV-infected patients bearing a vertebral fracture is of potential clinical relevance, because it suggests that bone damage is much more frequent than that assessed in previous studies by DXA measurement, and lateral spine X-ray has a role in the screening algorithms of osteoporosis even before DXA scanning, at least in patients with a significant risk of fragility fractures. In addition, X-rays are simple to carry out, readily available and cheaper than DXA scan.

Based on this evidence, we recommend considering the introduction of lateral spine X-ray in the screening program of bone-metabolism disorders, especially in older patients and/or patients with chronic renal insufficiency or steroid use.

Our study has several limitations: BMD was not assessed, potential selection bias in our study population may have occurred, and the cross-sectional design could not properly assess the predictors of vertebral fractures.

In conclusion, a high prevalence of sub-clinical vertebral fractures was observed in HIV-positive patients; therefore, these patients should be targeted with screening and preventative

strategies. Age, chronic renal insufficiency and previous steroid use are associated with an increased risk of fractures.

As yet, the association between combined antiretroviral therapy (cART) and fragility fracture remains uncertain, and a clear association between specific antiretrovirals and fragility fractures has yet to be determined (Grund *et al.*, 2009). The impact of certain antiretroviral drugs (TDF and specific boosted PI) (Gallant *et al.*, 2004; McComsey *et al.*, 2011, Duvivier 2009, Piliero *et al.*, 2002, Gibellini *et al.*, 2010) will be assessed in further studies. The proximal causes of fragility fractures in the population require further exploration. A combination of decreased BMD and other factors may cause fragility fractures: while the role of decreased BMD has been investigated, that of other factors remains partially unexplored and requires elucidation.

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