High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study

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Background: Low bone mineral density (BMD) is an emerging metabolic condition in HIV-infected patients; however, data on progression of this disease are scarce.

Methods: We studied 671 patients with at least one dual-energy X-ray absorptiometry scan (391 of them ≥2 scans) to determine the prevalence and progression of BMD and establish related factors. Linear regression and logistic polytomic regression were used for the cross-sectional study and mixed effects and generalized estimating equations were used for the longitudinal study.

Results: Osteopenia and osteoporosis were diagnosed in 47.5 and 23%, respectively. Progression to bone demineralization was observed in 28% of the patients over a median of 2.5 years (12.5% progressed to osteopenia and 15.6% to osteoporosis). In the 105 patients with at least 5 years of follow-up, progression was 47% (18% to osteopenia; 29% to osteoporosis). Factors associated with bone loss and progression were age [odds ratio (OR) 1.07; 95% confidence interval (CI) 1.05–1.08; \( P < 0.0001 \)], male sex (OR 2.23; 95% CI 1.77–2.8; \( P < 0.0001 \)), low body mass index (OR 1.14; 95% CI 1.11–1.17; \( P < 0.0001 \)), time on protease inhibitor (OR 1.18; 95% CI 1.12–1.24; \( P < 0.0001 \)), time on tenofovir (OR 1.08; 95% CI 1.03–1.14; \( P < 0.0019 \)), and current use of protease inhibitors (OR 1.64; 95% CI 1.35–2.04; \( P < 0.0001 \)).

Conclusions: Our results show a high prevalence of and considerable progression to osteopenia/osteoporosis in our cohort. Our findings support the importance of applying adequate strategies to prevent bone demineralization and of close monitoring of BMD in HIV-infected patients, specifically in at-risk patients who are taking antiretrovirals that affect bone mineralization.

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Introduction

Low bone mineral density (BMD) is an emerging metabolic condition in HIV-infected patients, with an estimated incidence that is three-fold greater than in the general population [1–3]. This disorder is caused mainly by lifestyle factors such as smoking, alcohol intake, decreased physical activity, opiate use, or malnutrition. However, the presence of comorbid conditions (e.g. gonadal hormone deficiency, vitamin D deficiency, or...
HIV infection itself is involved in bone demineralization through activation of HIV viral proteins and inflammatory cytokines [2]. Additionally, the relationship between prolonged antiretroviral therapy and bone loss is patent, although there are few data on the specific role of individual agents [4,6–8]. Tenofovir (TDF) has proven to be the most widely involved antiretroviral agent in bone demineralization [9–12]. Renal phosphate and calcium losses caused by TDF could be related to compensatory resorption of bone (osteoporosis) and mineralization defects in regenerating bone (osteomalacia) [7]. However, some studies have also found an association between protease inhibitors and loss of BMD [13,14], although results are contradictory [6] and the effect varies with the protease inhibitor analyzed [8]. Overall, it seems that protease inhibitors affect bone metabolism by increasing osteoclast differentiation, inhibiting osteoblastic differentiation secondary to lipid abnormalities, and altering vitamin D metabolism [14–16]. The non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) has recently been associated with a decrease in vitamin D levels that could lead to bone loss [17]. Finally, in-vitro studies with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine have linked this agent to osteoclastogenesis [18,19], and a recent clinical study associates zidovudine and lamivudine with bone loss [20].

Although many factors contribute to loss of BMD in HIV-infected patients, the exact role and mechanisms of some of these remain unclear.

Despite the number of trials assessing the incidence of bone demineralization in HIV-infected patients, few longitudinal studies have analyzed progression of this condition [21,22], with the exception of clinical trials assessing specific antiretroviral drugs [9,10,12,23]. Although follow-up in these trials is usually short, it is sufficiently long to show the rapid progression of loss of BMD in HIV-infected patients, with the consequent increase in the incidence of fractures [19–21]. The objectives of this study were to determine the prevalence and predictive factors of bone demineralization and to evaluate the progression of low BMD in a large cohort of HIV-infected patients over a long follow-up period.

Material and methods

Study design, patients, and study objectives

The retrospective observational cohort study included all those patients with at least one dual-energy X-ray absorptiometry (DXA) scan from among the 2300 patients who attended our HIV Unit between 2000 and 2009.

The mean BMD and T score (comparison with young normal reference value expressed as standard deviation units) of the total body, lumbar spine, and femoral neck were measured using the same DXA device (Lunar Prodigy; GE Healthcare, Belgium) at an external center (CETIR Grup Médic, Barcelona, Spain).

A first analysis including the most recent DXA measurements of all participants was performed to determine the prevalence of bone demineralization and to define factors related to low BMD. A second longitudinal analysis including those patients with at least two DXA scan results during the study period was performed to evaluate the rate of loss of BMD and related factors.

Assessments and definitions

The data included in the analysis were as follows: demographic data (age, ethnicity, and sex), menopause, smoking habit, physical exercise, body mass index (BMI), serum creatinine and estimated glomerular filtration rate by the Modification of Diet in Renal Disease equation, comorbid conditions (including kidney disease or coinfection with hepatitis), and concomitant medication (including hormone treatments, bisphosphonates, and calcium) at the time of the most recent DXA scan.

Data associated with HIV infection at the time of the most recent DXA scan were also collected from the patient’s records. Time on antiretroviral therapy and time with suppressed viral load were considered as categorical variables (≤25%, 26–50%, 51–75% and >75% of time with infection in the first case and less or more than 75% of the time on treatment in the second) and continuous variables. Other studied variables were time with HIV-1 infection, current and previous antiretroviral regimens, current CD4⁺ T-cell count, nadir CD4⁺ T-cell count, and current and peak HIV-1 viral load. Time on antiretroviral therapy was assessed as follows: time on antiretroviral therapy/time with HIV infection × 100. Time with suppressed viral load was assessed as follows: time on suppressed viral load/time with HIV infection × 100.

The prevalence of bone abnormalities was based on the first DXA scan available. In the multivariate analysis, the predictors of loss of BMD were based on the most recent DXA scan. The longitudinal assessment was based on all the DXA scans available for each patient.

Variables from the DXA scan were considered as categorical (normal values, osteopenia or osteoporosis) or continuous (T score). In cases with at least two DXA scans, progression of low BMD was defined as a normal...
lumbar and femoral T score in the first scan that progressed to osteopenia or osteoporosis, or osteopenia that progressed to osteoporosis.

The World Health Organization (WHO) classification was used for diagnostic purposes [18]. Osteopenia was defined as a T score of between −1 and −2.5 SD, and osteoporosis was defined as a T score of less than −2.5 SD. The T score at the femoral neck makes it possible to quantitatively evaluate cortical bone tissue; the T score at the lumbar spine (L2–L4) makes it possible to quantitatively evaluate trabecular bone tissue.

Statistical analyses
Statistical summaries were prepared for the main variables; DXA scan results and clinical and demographic characteristics were represented as graphs and tables. In the cross-sectional study, multivariate linear regression and polytomous logistic regression models were applied to correlate the effect of the independent variables (clinical and demographic characteristics) with the most recent DXA results [considered as continuous or classified as normal, osteopenia, or osteoporosis (WHO criteria)]. Repeated DXA measurements over time were modeled using the linear mixed-effects model (LMM) for the continuous outcome and generalized estimating equations (GEEs) for the polytomous one. These techniques can accommodate correlated outcome variables. In addition, the LMM makes it possible to incorporate random effects to show how a specific patient differs from the average individual with respect to progression of BMD.

The regression models were built using a forward stepwise procedure. The P value for inclusion of a covariate in the model was set at 0.15, and the P value for removal of the covariate was set at 0.20. The confidence level (CI) was set at 95%.

Wald and F statistics were used to test the hypothesis for the effect of the independent variables. The model specification, including the correlation matrix structure in the longitudinal context, was assessed using the Akaike Information Criterion (AIC), or pseudo-AIC for GEE.

The analysis was conducted using the statistical package SAS 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics at the most recent DXA scan
The analysis was based on 1982 DXA measurements corresponding to 671 patients: of these, 391 patients had at least two DXA scan results (1656 DXA scans) and were included in the longitudinal analysis.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics.</th>
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<tbody>
<tr>
<td>Sex (male, %)</td>
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<tr>
<td>Menopause, n (%)</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>&gt;65 years old (male), n (%)</td>
</tr>
<tr>
<td>&gt;55 years old (female), n (%)</td>
</tr>
<tr>
<td>Smoking habit, n (%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>BMI from 18.6 to 25 kg/m², n (%)</td>
</tr>
<tr>
<td>Calcium intake (g/day)</td>
</tr>
<tr>
<td>Adequate calcium intake (&gt;800 mg/day), n (%)</td>
</tr>
<tr>
<td>Hepatitis B/C co-infection, n (%)</td>
</tr>
<tr>
<td>Concomitant therapy*, n (%)</td>
</tr>
<tr>
<td>Hormone treatment, n (%)</td>
</tr>
<tr>
<td>Alendronate, n (%)</td>
</tr>
<tr>
<td>Calcium, n (%)</td>
</tr>
<tr>
<td>Time since HIV+ diagnosis (years)</td>
</tr>
<tr>
<td>Current CD4⁺ T, absolute value (cells/µl)</td>
</tr>
<tr>
<td>Current CD4⁺ T, % (cells/µl)</td>
</tr>
<tr>
<td>Suppressed viral load, n (%)</td>
</tr>
<tr>
<td>Proportion of time with suppressed viral load, n (%)</td>
</tr>
<tr>
<td>Naïve, n (%)</td>
</tr>
<tr>
<td>Time on ART (years)</td>
</tr>
<tr>
<td>Proportion of time with infection</td>
</tr>
<tr>
<td>≥25–50%: 97 (15.77%)</td>
</tr>
<tr>
<td>&gt;50–75%: 151 (24.55%)</td>
</tr>
<tr>
<td>&gt;75%: 332 (53.98%)</td>
</tr>
<tr>
<td>Current use of protease inhibitors, n (%)</td>
</tr>
<tr>
<td>Time on protease inhibitors (years)</td>
</tr>
<tr>
<td>Current use of tenofovir, n (%)</td>
</tr>
<tr>
<td>Time on tenofovir (years)</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, n (%)</td>
</tr>
<tr>
<td>&gt;60: 21 (95.45%)</td>
</tr>
</tbody>
</table>

Values are expressed as median (IQR) or number (%). ART, antiretroviral therapy; BMI, body mass index.

*Agents that potentially affect bone mineralization (corticosteroids, antiepileptic agents, anticoagulant agents, and chemotherapy).

Most of the 671 patients were male, with long-term HIV infection and prolonged antiretroviral therapy. The most frequent comorbid condition was hepatitis B or C infection. This information is summarized in Table 1.

Prevalence of low bone mineral density and related factors
On the basis of WHO criteria, osteopenia was diagnosed in 47.5% of patients (319 patients) and osteoporosis in 23% (155 patients). The median T score was −1.7 [interquartile range (IQR) −2.40 to −0.9] (Table 2).

With regard to the subgroups of patients analyzed, the rate of osteoporosis increased for duration of infection (16% in patients with <2 years versus 31% in patients with >11 years) and time on antiretroviral treatment (17% in patients with <2 years and 36% in patients with >10). The antiretroviral agents associated with an increased rate of osteoporosis over time were TDF (20% in patients with ≤1 year and 37% in patients with >5 years) and PIs.
Taking the DXA value as a numeric variable, the following factors were significantly associated with loss of bone mass in the logistic regression analysis (estimate; standard error; \( P \) value): age (estimate: \(-0.0526; 0.0062; P < 0.001\), low BMI (estimate: \(-0.971; -0.0155; P < 0.001\), male sex (estimate: \(-0.3343; 0.125; P = 0.0078\), high level of creatinine (estimate: \(-0.0101; 0.0036; P = 0.0047\), antiretroviral treatment at the most recent DXA evaluation (estimate: \(-0.5944; 0.1752; P = 0.0007\)), time on a protease inhibitor-containing regimen (estimate: \(-0.0837; 0.0192; P < 0.0001\), and categorized time on antiretroviral treatment (<25% compared with >75%: 0.702; 0.2432; \( P = 0.0040\)).

When we analyzed DXA values as a categorical variable (classifying the results as normal, osteopenia, or osteoporosis), the significant factors related to loss of BMD were age, low BMI, male sex, hepatitis coinfection, time on protease inhibitors, and use of a protease inhibitor or TDF at the most recent DXA evaluation (Table 3).

Progression of bone mineral density loss and related factors

The longitudinal analysis included 391 patients with at least two DXA scans available (a total of 1656 DXA evaluations). The median number of DXA scans per patient was 3 (IQR 2–5). The median time between the first and the last DXA scan was 2.5 years (IQR 1.2–5.3); in 105 patients (27%), this was more than 5 years.

Table 3. Estimation of the parameters for the logistic model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant osteoporosis</td>
<td>0.4450</td>
<td>(0.1142–1.7346)</td>
<td>0.2435</td>
</tr>
<tr>
<td>Constant osteopenia</td>
<td>6.0345</td>
<td>(1.5423–23.6107)</td>
<td>0.0098</td>
</tr>
<tr>
<td>Age</td>
<td>1.0736</td>
<td>(1.0512–1.0965)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.8513</td>
<td>(0.8084–0.8965)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time with PI</td>
<td>1.0814</td>
<td>(1.0098–1.1581)</td>
<td>0.0251</td>
</tr>
<tr>
<td>Male sex</td>
<td>3.1078</td>
<td>(2.0953–4.6094)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1.5701</td>
<td>(1.0943–2.2523)</td>
<td>0.0143</td>
</tr>
<tr>
<td>Taking PI at the last DXA</td>
<td>2.1088</td>
<td>(1.4213–3.1289)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Taking TDF at the last DXA</td>
<td>1.4426</td>
<td>(1.0295–2.0214)</td>
<td>0.0332</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; PI, protease inhibitors; TDF, tenofovir.

At the first scan, 49% of patients were affected by osteopenia and 22% by osteoporosis; at the second, 50% were affected by osteopenia and 27% by osteoporosis.

The median \( T \) score remained stable in patients with at least two DXA scans available: in the first scan, the median \( T \) score was \(-1.70\) (IQR \(-2.4\) to \(-0.90\)); in the most recent it was \(-1.90\) (\(-2.5\) to \(-1.1\)). Nevertheless, when progression from normality to osteopenia or from osteopenia to osteoporosis was assessed, 72% of the patients remained stable, although 28% suffered progression of low BMD during follow-up: 12.5% progressed from normal criteria to osteopenia and 15.6% from osteopenia to osteoporosis. When the subgroup of patients with 5 or more years of follow-up was assessed (\( n = 105, 27\%\)), 47% experienced loss of BMD: 18% progressed to osteopenia and 29% to osteoporosis (Table 4).

When DXA was evaluated as a categorical variable, the factors associated with low BMD in the longitudinal analysis were as follows: age (estimate: \(-0.044; \text{standard error (SE)} = 0.011; P < 0.001\), low BMI (estimate: 0.0962; SE 0.033; \( P = 0.0037\)), male sex (estimate: female versus male: \(-0.6955; \text{SE} = 0.22; P = 0.0019\), and high viral load (estimate: \(-0.079; \text{SE} = 0.036; P = 0.033\)).

When DXA was evaluated as a categorical variable, the results from the longitudinal follow-up showed that the factors related to bone abnormalities were age (odds ratio (OR) 1.07; 95% CI 1.05–1.08; \( P < 0.0001\), male sex (OR 2.23; 95% CI 1.77–2.8; \( P < 0.0001\)), low BMI (OR 1.14; 95% CI 1.11–1.17; \( P < 0.0001\), time on protease inhibitor (OR 1.18; 95% CI 1.12–1.24; \( P < 0.0001\), time with TDF (OR 1.08; 95% CI 1.03–1.14; \( P < 0.0019\), and treatment including protease inhibitor when DXA was performed (OR 1.64; 95% CI 1.35–2.04; \( P < 0.0001\)).

Discussion

Our observational study revealed a marked incidence of low BMD in a large number of patients with long-term HIV infection and prolonged antiretroviral therapy. Furthermore, the number of patients suffering from...
progression of low BMD increased with follow-up. Rate of progression has not been described elsewhere with such a long follow-up. The risk factors associated with bone loss in our population are consistent with those described elsewhere [4,5].

The proportion of patients with low BMD in our cohort was very high. Almost 75% presented some grade of low bone mass, and around a third already had osteoporosis. These rates are slightly higher than those reported by other authors [24,25] and could be related to long-term HIV infection and prolonged exposure to antiretroviral drugs. Previous studies have evaluated other populations, which differ in terms of sex or age, both of which factors show a strong association with bone abnormalities [22,26,27]. In contrast, the incidence in our group was comparable with that of other authors who evaluated patients with similar characteristics [21,28–30].

Our results confirm a marked progression towards bone demineralization. More than a quarter of the study patients (28%) experienced some type of bone mineral abnormality during follow-up: 15.5% developed osteopenia after a median of 2.5 years, and this figure increased to almost one-third after more than 5 years. Other longitudinal studies evaluating progression to osteopenia or osteoporosis show that 12% of the study population progressed to osteoporosis [21,22]. This slightly lower rate of progression can probably be explained by the shorter follow-up in those studies.

The clinical impact of low bone density is seen as an increased risk of fractures, which was recently reported to be higher in HIV-infected patients than in the general population [19,20,31]. The higher incidence of osteoporosis and more rapid progression described in HIV-infected patients due to viral infection itself, as well as prolonged therapy with antiretroviral drugs, may explain the higher proportion of HIV-infected patients with fractures.

Therefore, clinical monitoring of BMD by DXA scan should be a priority in HIV-infected patients, specifically in those at risk of fracture. Prevention strategies such as lifestyle modifications and management of abnormal scans according to general guidelines should also be pursued.

Our results confirm data from other studies on the role of traditional risk factors for low BMD in HIV-infected patients [13,32,33]. Low BMI and inadequate nutrition, which are often associated with profound immunosuppression, were already related to bone demineralization in the pre-highly active antiretroviral therapy (HAART) era. Today, improved control of viral replication preserves the immune system and helps normalize body composition. The role of low BMI as a predictive factor for osteoporosis led us to recommend nutritional counseling for HIV-infected patients, including adequate calcium and vitamin D intake. Of note, a considerable proportion of patients in our cohort exhibited a low level of calcium intake.

Other epidemiological and clinical conditions that have already been reported as traditional risk factors for low BMD were also identified in our cohort. The most relevant were age, male sex, and hepatitis coinfection.

With respect to specific HIV-related factors, time since diagnosis, nadir CD4 T-cell count, and CD4 T-cell counts were not correlated with bone abnormalities in our analysis. A previously reported association between CD4 T-cell count and bone demineralization was mainly related to severe immunosuppression [6]. However, our cohort presented a preserved immune status (median of CD4+ cell counts of 496 cell/μl). This could explain the lack of association between low BMD and CD4 T-cell count in our patients. Other HIV-related factors such as high viral load, current use of antiretroviral treatment (especially protease inhibitors and TDF), and cumulative time on these treatments strongly correlated with bone demineralization in our study.

Data on the role of specific antiretroviral drugs in bone demineralization remain controversial [3,4,6,13,27]. The long follow-up and resulting prolonged exposure to antiretroviral drugs in our study sustain the negative impact of therapy, specifically protease inhibitors [8,15,24,30,34] and TDF [9–12].

We found an association between low BMD and TDF. The cause of TDF-related bone demineralization seems to be associated with tubular dysfunction, which may in turn lead to loss of renal calcium and phosphorus and onset of hypophosphatemia followed by compensatory bone resorption [7]. Some studies found an association between TDF, osteomalacia, and bone fractures [10,32,35,36]. In contrast, others did not establish this association [9,37–39]. Such controversial results could be
due to differences in duration of follow-up, pre-existing renal damage, or combination of TDF with potentially toxic antiretroviral drugs. Although most of our patients had normal renal function, our results showed a strong correlation between TDF and low BMD in patients with a median of 2.2 years on TDF-containing regimens.

Our results also confirm that protease inhibitors are associated with low BMD, as reported elsewhere [8,15,24,30,34]. In-vitro studies suggest that the cause of this abnormality is linked to an increase in osteoclast resorption and inhibition of osteoblast function [34]. Protease inhibitor-associated loss of BMD could also be associated with altered 1,25-dihydroxyvitamin D3 production [40].

Despite these associations, continuous antiretroviral therapy is essential to prevent clinical progression to AIDS and non-AIDS-related diseases [41]. Knowledge of the safety profile of individual drugs is crucial to determine the best combination and to establish adequate monitoring. Our results have important implications for monitoring and point to the need for less aggressive alternatives. DXA should be routinely applied in the presence of risk factors for bone loss.

A possible limitation of our study is the representativeness of the cohort. Given that a DXA scan could be repeated in patients with worse bone mineralization, the results may overestimate the incidence of bone loss in the HIV-infected population. However, routine monitoring of HIV-infected patients in our unit included DXA, and the incidence of osteopenia/osteoporosis was similar when we evaluated the first and the most recent DXA scan in cases with more than two DXA evaluations. Another limitation is the retrospective design, which means that the intervals between consecutive DXA scans are heterogeneous, with a different number of evaluations for each patient. Nevertheless, the results are consistent in the cross-sectional and longitudinal analyses and agree with those of other authors on the role of HIV-related factors in low BMD.

In conclusion, we reveal a high prevalence of low BMD in our cohort. The longitudinal analysis – more than 5 years of follow-up in some cases – revealed rapid progression of demineralization. Specific HIV-related factors, mainly use of and time on protease inhibitors and TDF and high viral load, play an important role in low BMD, as do traditional factors such as old age and male sex.

We show the importance of an adequate diet and lifestyle and of maintained virological suppression to prevent bone demineralization in HIV-infected patients. We confirm the need for close monitoring of BMD, specifically in at-risk patients who are taking antiretrovirals that affect bone demineralization.

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Contributors: A.B., C.E., E.N., L.G. and B.C. participated in the design of the study. A.B., C.E., E.N., J.P. and B.C. participated in the recruitment of patients and reporting of data. C.E. constructed the database and monitored patients’ diet. J.R., L.d.R. and S.d.G. performed the DXA scans of the patients included. M.F. and N.P.-A. performed the statistical analysis. G.G. provided advice on the statistical analysis. All the authors revised and approved the final version of the manuscript.

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