Low bone mineral density and fracture risk in HIV infection

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Evaluation of: Triant VA, Brown TT, Lee H, Grinspoon SK: Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non HIV-infected patients in a large US healthcare system. *J. Clin. Endocrinol. Metab.* 93, 3499–3504 (2008).
Low bone mineral density has been strongly linked to an increased risk of fracture in HIV-uninfected older men and women. Although multiple cross-sectional studies have demonstrated that HIV-infected patients have lower bone mineral density than HIV-uninfected persons, the mechanisms for this difference and its clinical significance remain unclear. To address the clinical implications, Triant and colleagues performed a retrospective review of more than 2 million patients in the Partners Healthcare system, comparing fracture prevalence among HIV-infected and -uninfected patients. Patients with HIV had more fractures than uninfected patients and, although this analysis did not adjust for known risk factors for osteoporosis, this study is the first to demonstrate a significantly increased risk of fracture in HIV-infected patients.

Use of combination antiretroviral therapy (cART) has substantially decreased mortality in HIV-infected patients with access to such medicines. However, as this population lives longer, a greater proportion now suffers from common diseases of aging, such as diabetes, cardiovascular disease and osteoporosis [1,2].

Bone mineral density (BMD) decreases throughout life in both men and women beginning at approximately 35 years of age, and this loss accelerates in women after menopause. In HIV-negative patients, risk factors associated with low BMD include white race, older age, low body weight, smoking, sedentary lifestyle, family history and glucocorticoid use [3]. In HIV-uninfected patients, low BMD is correlated with increased risks of fracture, morbidity and mortality [3].

Over the past several years, numerous studies have demonstrated lower BMD in HIV-infected patients compared with HIV-uninfected patients [4–6], and although there now appears to be a clear relationship between HIV infection and reduced BMD, the magnitude and mechanism of this effect remains unknown. Several processes have been postulated, including: an adverse effect of antiretroviral medications; a direct, harmful effect of HIV-infection on bone metabolism; and high rates of known risk factors for low BMD in HIV-infected patients. Recent studies have therefore examined different populations (e.g., men, postmenopausal women, substance abusers) and control groups (e.g., healthy controls or controls with similar HIV-risk factors), and measured CD4 count, HIV viral load, cART exposure, and other known risk factors for low BMD (including age, smoking, weight, BMI, ethnicity, sedentary lifestyle and opiate use [7–9]) to identify factors that may worsen, attenuate or mediate the HIV-associated BMD loss that has been identified epidemiologically.

The effect of cART, or of protease inhibitors specifically, on BMD has been debated. Although early cross-sectional studies found lower BMD among men who had taken protease inhibitors [10–12], subsequent studies failed to show such an effect in men or women [13–20]. Data from longitudinal treatment cohorts and clinical trials, however, have shown that although there may be a small (2–6%) short-term decrease in BMD in patients initiated on cART, this level soon plateaus and there does not appear to be any increase in progression to osteopenia or osteoporosis associated with cART [21].

Some investigators have hypothesized that a chronic, proinflammatory state induced by HIV contributes to the lower BMD seen in HIV-infected individuals. Cytokines such as IL-1, IL-6 and TNF-α, which, in very small studies, were found to be elevated in HIV infection [22,23], have been shown in culture and mouse models to increase bone resorption by stimulating osteoclast function, inhibiting osteoclast apoptosis and stimulating osteoblast apoptosis [24–26]. These models have further shown that in ovariectomized mice, there is upregulation of IL-6 and increased osteoclastogenesis, suggesting a mechanism for accelerated bone loss after menopause [24]. However, to date, a cytokine effect has not been demonstrated in HIV-infected humans.

Keywords
■ bone loss fracture ■ bone mineral density ■ HIV ■ osteopenia ■ osteoporosis

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Given the large number of factors known to affect BMD loss among HIV-uninfected persons, it has been difficult to identify a suitable comparison group to study BMD in HIV infection, or to adequately adjust for known confounders. The heterogeneity of study populations and methodologies of the existing cross-sectional studies has resulted in the identification of several possible risk factors for low BMD in HIV-infected patients that have not been corroborated by other studies.

Markers of clinical disease serve important functions in research and can be helpful in mapping causal pathways and in early testing of novel therapeutics. Eventually, however, investigators are obligated to measure true clinical outcomes to demonstrate a relevant effect. Interventions are often demonstrated to affect laboratory values or radiological indices, but when the actual outcome of interest (e.g., myocardial infarction, survival or fracture) is measured, the effect is trivial.

It is with these concerns that we welcome the recent study by Triant and colleagues in the *Journal of Clinical Endocrinology and Metabolism* [1]. Earlier studies examining the effect of HIV infection on BMD have focused primarily on the measurement of BMD by dual x-ray absorptiometry (DXA). Recently, members of this same group (Brown *et al.*) carried out a meta-analysis of 20 observational studies and found that, compared with HIV-uninfected persons, HIV infection was associated with pooled odds ratios for osteopenia and osteoporosis of 6.4 and 3.7, respectively [4]. Although this apparent effect of HIV on BMD was impressive, the analysis was limited in its ability to adjust for covariates known to affect BMD. Studies that have attempted to adjust for known risk factors for osteoporosis, including a subsequent meta-analysis by Bolland and colleagues (which adjusted for low body weight), have shown a smaller effect size [5]. These studies found that BMD was approximately 2–5% lower in HIV-infected than HIV-uninfected persons, and that in some subgroups, such as Black women and obese men, HIV was not independently associated with low BMD, suggesting that Black race and/or high BMI may lessen the effect of HIV on BMD [7,8].

With a link between HIV and BMD epidemiologically well-established, but perhaps of modest magnitude, it remained for investigators to demonstrate its clinical significance – that is, the risk of fracture. A few earlier studies that estimated fracture risk were limited by relatively small sample sizes or insensitive methods of detection [8,9]. To assess the association between HIV infection and fracture risk, Triant and coworkers recently reviewed an extremely large database of more than 2 million patients, including 8525 with HIV-infection, to determine the prevalence of fractures. Data were obtained from a clinical care registry that captures all data from the Partners Healthcare System. The authors used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify all vertebral, wrist and hip fractures over a 12-year period (1996–2008), and stratified their analyses by race, age and gender.

Overall, the prevalence was 2.87 patients with fractures per 100 HIV-infected persons, compared with 1.77 per 100 HIV-uninfected persons. In subgroup analysis, HIV-infected women had a higher prevalence of vertebral (0.81 vs 0.45; $p = 0.01$) and wrist (1.31 vs 0.83; $p = 0.01$) fractures, but no difference in hip fractures compared with HIV-uninfected women. HIV-infected men had a higher prevalence of fractures overall (3.08 vs 1.83; $p < 0.0001$), as well as vertebral (1.03 vs 0.49; $p < 0.0001$), wrist (1.46 vs 0.99; $p = 0.001$) and hip (0.79 vs 0.45; $p = 0.001$) fractures, compared with HIV-uninfected men. Although fracture prevalence was higher among HIV-infected African–American women, Caucasian women and Caucasian men than their HIV-uninfected counterparts, there was no significant difference between African–American men with and without HIV infection.

This study is impressive in its sample size and demonstrated effect between HIV infection and fractures. However, we are troubled by the lack of adjustment for known osteoporosis risk factors. Retrospective studies are inherently dependent upon the data which has been collected, and although the authors acknowledge the potential importance of missing information, the lack of data on smoking, alcohol use, antiretroviral use, BMI, socioeconomic status, estrogen use or steroid use limits interpretation of these results. Given the degree to which adjustment for these risk factors has attenuated effect sizes in prior studies, it would have been important to see if the remaining small but persistent association between HIV and BMD is independently associated with a clinically significant increased risk of fracture among HIV-infected persons. In addition, it is unclear if both the HIV-infected and the HIV-uninfected persons in this analysis were retained by the Partners HealthCare system for similar durations during the 12-year study period. The dataset was constructed to include all patients

with at least one inpatient or outpatient encounter during the 12-year period, but it is likely that that HIV-infected and uninfected persons had different rates of retention after a single encounter. HIV-infected patients may have been more likely to be retained in the same system of care, and thus more likely to have a fracture diagnosed within the Partners HealthCare system. This may well have biased the estimate of period prevalence (defined as any fracture diagnosed within the study period), so that the fracture prevalence among HIV-uninfected persons may have been underestimated and the difference between the two groups overestimated.

Although the study by Triant and colleagues is unable to shed light on the mechanism of HIV-related BMD loss and may have underestimated the true risk of fracture, the investigators have demonstrated that HIV-infected individuals are at an increased risk of fracture compared with HIV-negative persons, and HIV providers should keep this risk in mind. Several important questions remain regarding HIV infection and the risk of fracture:

- Are HIV-associated BMD loss and fracture risk related to known osteoporosis risk factors such as BMI or smoking?
- How should HIV-infected men and women be screened for bone loss? Should pre menopausal women receive DXA scans, and should men be actively screened starting at a certain age?
- Are bone loss and fracture risk reversible through behavioral modification or pharmacologic intervention (e.g., calcium, vitamin D, bisphosphonate or selective estrogen receptor modulator therapy)?

Answering some of these questions will require large longitudinal studies with adjustment for numerous covariates, including retention in care. In the absence of such data, HIV-care providers should attempt to minimize known risk behaviors that contribute to bone loss in HIV-negative patients – namely, sedentary lifestyle, alcohol use and smoking. HIV-infected persons who present with a new fracture should be evaluated for decreased BMD. Triant and colleagues have shown, importantly, that HIV-infected patients are at increased risk of fracture. Now we must determine why and what we can do about it.

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Executive summary

- Triant and colleagues demonstrate an increase in risk of fracture in HIV-infected patients.
- The mechanism for the decrease in bone mineral density (BMD) seen in HIV-infection remains unclear but may be related to known osteoporisis risk factors such as low body weight, age, ethnicity, alcohol use, glucocorticoid use and smoking.
- Controlled, longitudinal studies with appropriate adjustment for these and other risk factors are needed to determine the independent effect of HIV-infection on BMD and fracture risk.

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