Bone health in HIV infection

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Introduction: Osteoporosis is among the chronic problems emerging as the human immunodeficiency virus (HIV)-positive population ages.

Sources of data: We reviewed the English language bibliography using Pubmed 2.0, Web of Science and Embase for relevant abstracts and articles.

Areas of agreement: The prevalence of low bone mineral density (BMD) and fracture is increased in the HIV-positive population.

Areas of controversy: The pathogenesis is multifactorial; there is some evidence that HIV infection is an independent risk factor and that highly active antiretroviral therapy has adverse skeletal effects.

Growing points: Physicians should routinely review the bone health of all HIV patients.

Areas timely for developing research: More studies of the mechanisms of bone loss, the skeletal effects of antiretroviral therapy and the therapeutic outcome of bone-protective therapy in HIV-positive individuals are needed.

Keywords: HIV/AIDS/osteoporosis/fracture/vitamin D/bisphosphonates/bone mineral density/antiretroviral

Introduction

The success of highly active antiretroviral therapy (HAART) has dramatically increased life expectancy for human immunodeficiency virus (HIV)-positive patients in the developed world, revealing a range of chronic problems associated with HIV. As people with HIV live longer, bone disease is among the metabolic complications presenting physicians with new challenges in the management of the HIV-positive patient.¹ The most common bone disease described in HIV is osteoporosis, but osteomalacia, usually in association with Fanconi’s syndrome and most commonly described in patients treated with
tenofovir, can also occur. The rest of this review focuses on osteoporosis.

Osteoporosis is characterized by a reduction in bone mass and disruption of bone architecture, resulting in increased bone fragility and an increase in fracture risk. These fractures are a major health problem in the elderly population, leading to significant morbidity and mortality and resulting in an estimated annual cost to health services of £1.8 billion in the UK and €30 billion in Europe. One in two women and one in five men over the age of 50 years will suffer a fracture due to osteoporosis during their remaining lifetime.\(^2\)

The exact number of HIV-infected men and women in the UK is unknown. According to the Health Protection Agency, an estimated number of 77,400 people were living with HIV in the UK, 28% of them being unaware of their diagnosis.\(^3\) Accordingly, the exact number of HIV-positive men and women at risk for bone disease is unknown. Among the people with HIV in the UK accessing care, 8% of women and 19% of men were aged \(\geq 50\) in 2006.

A number of studies have documented increased rates of osteoporosis in HIV-positive populations,\(^4\) but the mechanisms behind this link have been less clear: both HIV itself and HAART toxicity have been implicated.\(^5\) There are concerns that as the HIV-positive population ages, increased rates of bone loss may give rise to an ‘epidemic’ of fragility fractures.\(^6\) Evidence is needed to inform judicious use of bone-protective agents so that this situation can be avoided. Here, we bring together the results of some of the most recent studies in these areas and review their implications.

**Sources of data**

We searched the available literature between January 2006 and August 2009 using Pubmed 2.0, Web of Science and Embase, with the terms ‘HIV’, ‘AIDS’, ‘antiretroviral’, ‘bone mineral density’, ‘osteopenia’ and ‘osteoporosis’ and looking for articles in English relating to adults.

**Areas of controversy**

*Does HIV cause low bone mineral density?*

HIV has a number of effects that are themselves risk factors for reduced bone mineral density (BMD), including low body mass index (BMI), physical inactivity, hypogonadism and malabsorption. The HIV-positive population also has high rates of vitamin D insufficiency,
smoking, alcohol abuse and injection drug use, which are risk factors for osteoporosis. A recent meta-analysis of 20 studies found an odds ratio (OR) for osteoporosis, defined as a BMD T-score ≤ –2.5, within HIV-positive groups of 3.68 (95% CI 2.31, 5.84) compared with HIV-uninfected controls. The clinical significance of this reduction in BMD has recently been demonstrated by Triant et al., in a population-based study of 8525 HIV-positive individuals and 2,208,792 uninfected controls. Fracture prevalence at all sites including the wrist, hip and spine was significantly increased in HIV-positive men and women compared with controls; this increase was seen for all age groups from 20–69 years in men and 20–79 years in women (Table 1).

The contribution of HIV infection per se to osteoporosis has been investigated in several recent cross-sectional studies. Arnsten et al. found that the prevalence of reduced BMD was significantly higher among 263 HIV-positive middle-aged women than a control group, 50% of whom were illicit drug users and had similar demographics (femoral neck BMD, 1.01 ± 0.13 versus 1.05 ± 0.13 g/cm², P = 0.001; lumbar spine BMD, 1.21 ± 0.17 versus 1.24 ± 0.17 g/cm², P = .04). Interestingly, this association was only present in non-black women. In 559 elderly men with or at risk of HIV infection, the same group found an independent effect of HIV on femoral neck BMD that was significant but modest (P = 0.05). However, in other studies, no evidence for an independent effect of HIV infection was demonstrated, although in one of these, low HIV plasma viral load and low CD4 lymphocyte nadir were independent risk factors for low BMD, suggesting an effect of therapy rather than the disease itself.

In many studies, low BMI has emerged as an independent risk factor for low BMD in HIV-infected individuals. In a meta-analysis,
Bolland et al.\textsuperscript{13} demonstrated that controlling for differences in weight between HIV-positive and control groups reduced or eliminated the apparent differences in BMD. However, BMD differences at the femoral neck, which is arguably the most important site in terms of predicting fracture risk, remained significant ($P = 0.013$).

\textbf{Does HAART increase the risk of osteoporosis?}

Protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) have been the agents most widely investigated as causes of reduced BMD in HIV-positive populations. However, consistent evidence for their effects is lacking and it is increasingly recognized that these may be drug rather than class-specific.\textsuperscript{14}

In their meta-analysis of 20 studies, Brown and Qaqish\textsuperscript{4} found that the prevalence of reduced BMD was significantly higher in antiretroviral-treated compared with antiretroviral-naive patients (OR = 2.5, 95\% CI 1.8, 3.7), and also in PI-treated groups compared with PI-untreated patients (OR 1.5, 95\% CI 1.2, 2.0), compared with patients never previously exposed to a PI (OR 1.8, 95\% CI 1.2, 2.6) or compared with other HAART in general (OR 1.5, 95\% CI 1.2, 7.2). However, measurements of BMD were often obtained soon after commencement of an HAART regimen, and consequently, BMD may have reflected worsening HIV disease which prompted the introduction of HAART, with a corresponding decrease in BMD, rather than the effects of therapy. In addition, as the authors point out, many of the studies included did not control for the severity of HIV disease. Clinicians may perceive PI-based HAART as a more effective regimen with increased toxicity, which they therefore reserve for patients with more severe disease, who already have an increased risk of osteoporosis.

Prospective studies of the effects of HAART on BMD have yielded conflicting results, stable, increasing or decreasing BMD being reported.\textsuperscript{12–18} However, the most recent studies suggest that HAART is associated with bone loss, at least during the first 1–2 years after treatment is initiated. Duvivier et al.\textsuperscript{16} randomized antiretroviral-naive patients into a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus a boosted PI arm, a boosted PI and two NRTIs arm or an NNRTI and NRTIs arm. At 48 weeks, the decrease in lumbar spine BMD was significantly greater in patients receiving either PI-containing regimen than in the NNRTI and NRTI only arm (mean $-4.4\%$, $-5.8\%$ and $-1.5\%$; $P = 0.007$ and 0.001, respectively). Their results contrast with those reported by Brown et al.,\textsuperscript{19} who randomized 106 ART-naive HIV-infected subjects to receive efavirenz (EFV) + zidovudine/
lamivudine (n = 32) or lopinavir/ritonavir (LPV/r) + zidovudine/lamivudine induction (n = 74) for 24–48 weeks followed by LPV/r monotherapy. At 96 weeks, both groups had comparable decreases in total body BMD (mean 2.5% and 2.3%, respectively). Nevertheless, the results may have been confounded by the late change of both groups to PI monotherapy, at any time between 24 and 48 weeks. Most recently, the effects of continuous versus intermittent ART on bone density have been reported from the INSIGHT SMART study.\(^\text{20}\) After a mean follow-up of 2.4 years, continuous ART was associated with significantly greater bone loss in the spine and hip than intermittent ART (mean differences 1.3% and 1.4%, \(P = 0.03\) and 0.002, respectively). Interestingly, in this study, fractures, reported as Grade 4 adverse events, were reported significantly more often in patients in the continuous than the intermittent therapy group.

Growing points–areas timely for developing research

**Mechanisms for the effects of HIV and HAART on bone**

The mechanical competence of bone is maintained by the process of bone remodelling, which consists of the removal of old bone by osteoclasts and its subsequent replacement with new bone by osteoblasts. In the young adult skeleton, the amounts of bone resorbed and formed are similar, thus maintaining bone mass. Bone loss may occur in osteoporosis as a result of increased resorption, decreased formation or a combination of the two. In age-related bone loss in women, both mechanisms play a role, whereas in men, reduced bone formation is the predominant change.\(^\text{21}\)

The cellular mechanisms underlying bone loss in HIV-positive individuals are not well defined, although in one study, reduced bone formation and turnover were reported in iliac crest biopsies.\(^\text{22}\) The association between chronic inflammatory conditions and osteoporosis is well documented and receptor activator of NF\(\kappa\)B ligand (RANKL), the key mediator of osteoclast activity, is produced by activated T cells.\(^\text{23}\) Even in the asymptomatic phase of HIV infection, levels of inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumour necrosis factor alpha (TNF\(\alpha\)) are increased, and these cytokines also stimulate bone resorption.\(^\text{23}\) TNF\(\alpha\) has also been shown to mediate apoptosis of human osteoblasts in response to HIV gp120.\(^\text{24}\) Gibellini et al.\(^\text{25}\) recently reported that levels of RANKL were higher in HIV-infected men and correlated with reduced BMD. However, in the study of Chirch et al.,\(^\text{26}\) BMD in seven HIV-positive individuals was not associated with levels of soluble TNF receptor 2.
Vitamin D insufficiency is common in HIV-positive populations, and while this is mainly due to privational causes, inhibition of 1-α-hydroxylase by TNFα may also contribute. Potential mechanisms by which antiretrovirals might negatively affect BMD have been identified in vitro. Some PIs have been shown to inhibit osteogenesis and increase osteoclastogenesis, whereas others may decrease bone loss. Using gene chip microarray analysis, Malizia et al. recently showed that exposure to the PIs nelfinavir and ritonavir increased the expression by osteoblastic cells of the inflammatory cytokines MCP-1 and IL-8. PIs may also inhibit 1-α-hydroxylase and reduce serum 1,25(OH)2D levels, which could have a detrimental effect on BMD. In addition, LRP5, a positive regulator of bone formation, is inhibited by PIs. Azidothymidine and other NRTIs have been found to stimulate osteoclastogenesis in vitro and to reduce BMD in mice. NRTIs have also been shown to cause mitochondrial damage and dysfunction due to their cross-inhibition of mitochondrial x-polypolymerase. This is thought to be the cause of raised lactate levels in some HAART-treated individuals, which have been linked to increased bone resorption. Finally, EFV may affect BMD via a reduction in vitamin D levels as a consequence of hepatic enzyme induction.

What are the treatments?

Lifestyle modifications recommended for HIV-positive individuals include cessation of smoking, avoidance of alcohol abuse, appropriate exercise and attention to diet and nutrition.

Bisphosphonates are synthetic analogues of inorganic pyrophosphate that inhibit bone resorption by increasing the apoptosis of osteoclasts. They can be administered orally as alendronate (10 mg daily or 70 mg once weekly), risedronate (5 mg daily or 35 mg once weekly) or ibandronate (150 mg once monthly). Intravenous formulations are also available as ibandronate (3 mg every 3 months) and zoledronate 5 mg once yearly). Oral bisphosphonates require a complex dosing regimen; they must be taken fasting, with the patient sitting or standing, with a large glass of plain water and the patient must remain upright for 30–60 min after taking the tablet and must not eat, drink or take other medications during that time. Upper gastrointestinal side effects may occur with oral bisphosphonates, particularly if the dosing regimen is not followed. An acute phase reaction occurs in up to one-third of the patients receiving their first intravenous bisphosphonate injection or infusion. Generic versions of alendronate are now available and their low cost makes them a first-line option in many individuals.
However, in the HIV-positive population, adherence is likely to be better with once yearly zoledronic acid treatment than with a weekly oral formulation, given the already high pill burden in this population. The optimal duration of bisphosphonate therapy has not been established. Bone loss resumes after treatment is stopped, but there are concerns that prolonged suppression of bone remodelling may be harmful to the skeleton. Atypical femoral stress fractures have been reported in a small number of patients receiving bisphosphonate therapy for osteoporosis, although it should be stressed that these are extremely rare. Osteonecrosis of the jaw has been reported mainly in patients receiving high doses of intravenous bisphosphonates for skeletal malignant disease and its incidence in patients undergoing bisphosphonate therapy for osteoporosis may not be higher than that of the background population. In post-menopausal women and men with osteoporosis, treatment is generally given for a minimum period of ~5 years and BMD measurement repeated at the end of that time. A decision can then be made, based on BMD and other risk factors, on whether to continue treatment or to stop treatment and continue to monitor.

Alendronate has been shown to be effective in terms of BMD changes in HIV-positive individuals in several small studies. A prospective, randomized, placebo-controlled, multicentre trial showed that in combination with calcium and vitamin D, alendronate treatment was associated with significant improvements in BMD in HIV-positive individuals when compared with the group treated with calcium and vitamin D alone. Once yearly infusions of zoledronic acid, 4 mg, have also been shown to have significant benefits on spine and hip BMD in HIV-infected men. A double-blind, randomized, controlled trial evaluated the effect of a single dose of zoledronic acid versus placebo in 30 HIV-positive men \( (n = 27) \) and women \( (n = 3) \). Treatment was associated with significant improvement in spine and hip BMD when compared with the placebo group. Testosterone replacement successfully increased BMD in a single study, although this is not generally indicated for the treatment of osteoporosis other than in clinically hypogonadal men. It should be emphasized that no study of bone-protective therapy in the HIV-positive population has been powered to show a reduction in fractures.

There is evidence for low vitamin D levels in a high proportion of HIV-positive individuals. In one study, the prevalence of moderate [serum 25-hydroxyvitamin D (25OHD) level ≤20 and >10 ng/ml] or severe (serum 25OHD ≤10 ng/ml) vitamin D deficiency was 36.8% and 10.5%, respectively, among 57 unselected HIV-positive outpatients. A recent study has examined the effect of colecalciferol supplementation in 20 vitamin D deficient HIV-1-infected patients. Fourteen weeks of treatment with 2000 IU/day normalized serum
25OHD levels and decreased serum PTH; however, when the dose was subsequently reduced to 1000 IU/day, serum 25OHD and 1,25(OH)2D levels decreased, suggesting that doses of up to 2000 IU/day are required to maintain normal vitamin D status.

What are the implications?

There is evidence that HIV is associated with reduced BMD and increased risk of fragility fracture.5,46 Detection and treatment of osteoporosis now has a central place in public health strategy,47 and the morbidity and mortality of fragility fractures, already considerable, is likely to be even greater among HIV-positive patients. In future, improvements in the treatment of HIV are likely to result in healthier HIV-positive populations with reduced prevalence of known risk factors for osteoporosis, including low body weight. Addressing these factors may prove to be the most effective strategy for protection of bone health in these populations, as the independent effects of HIV or HAART seem to be less pronounced.

Review of bone health should become part of routine care for all HIV patients, and those with additional risk factors for osteoporosis should be referred for dual energy X-ray absorptiometry.48 Bone-protective therapy with a bisphosphonate should be considered in individuals with a T-score ≤−2.5 and in those with a history of fracture, after exclusion of osteomalacia.

Sadly it may be some years before the evidence described becomes relevant to large areas of the developing world.

Conclusions

Many factors contribute to the increased prevalence of osteoporosis in HIV-positive populations, probably including independent effects of HIV infection and of HAART. Evidence from some studies that BMD is stable over time in HAART-treated populations is encouraging, but a detrimental effect of HAART on bone has also been demonstrated in some studies, at least during the first year or so of treatment. With effective treatments for osteoporosis available, it should be possible to identify high-risk individuals and prevent fragility fractures in the HIV-positive population.
References


