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REVIEW

HIV infection and osteoporosis

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In the past two decades, the life expectancy of people living with HIV infection has increased significantly, and osteoporosis has emerged as a significant comorbidity. In addition to traditional risk factors for fracture, specific factors related to HIV infection are also likely to contribute, including antiretroviral therapy. The heterogeneity of the HIV-infected population in terms of age and ethnicity presents many challenges to the prevention and management of bone disease, and further studies are required to establish optimal approaches to risk assessment and treatment.

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Introduction

According to the World Health Organization statistics, there were ~35 million people living with HIV in 2013, of whom 31.8 million were adults and 3.2 million were children (⩽15 years old). Of the infected adults, ~50% were women. In 2013, 2.1 million people were newly infected with HIV, and there were 1.5 million deaths due to AIDS. The vast majority (an estimated 24.7 million) of adults and children living with HIV reside in Sub-Saharan Africa, with 4.8 million from Asia and the Pacific region, 2.3 million from North America, western and central Europe and 1.6 million in Latin America.[1]

Over the past 10–15 years, there have been substantial advances in the treatment of HIV infection, and in developed countries where access to treatment is widely available life expectancy approaches normal. However, a number of comorbidities have emerged in the ageing HIV-positive population, one of which is osteoporosis. This review addresses current knowledge of the epidemiology, pathogenesis, pathophysiology and management of osteoporosis and fracture in HIV-infected individuals.

Worldwide, there is marked heterogeneity in the demographic characteristics of HIV-infected individuals in terms of age, gender, ethnicity, lifestyle and access to antiretroviral therapy (ART). Most of the studies of bone health and HIV infection have been conducted in Europe and North America, and extrapolation of the results to other populations may not be valid. In particular, few studies have been performed in Sub-Saharan Africa, where nearly 1 in 20 adults are HIV positive and access to ART is restricted.

Standard treatment of HIV infection involves the combination of at least three antiretroviral drugs, now generally prescribed as a single pill taken once daily (fixed-dose combination). Classes of ART include nucleoside transcriptase inhibitors (NRTIs), non-nucleoside transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase inhibitors. As discussed later in this review, initiation of most forms of ART is associated with significant bone loss, although the mechanisms underlying this are poorly defined.

HIV-infected individuals have both traditional and specific, HIV-related, risk factors for low bone mineral density (BMD) and fracture. In the former category, tobacco use, alcohol abuse, hypogonadism, exposure to trauma and low body mass index (BMI) may be more prevalent in HIV-infected individuals, particularly intravenous drug users. Risk factors specific to HIV infection include ART, chronic inflammation and comorbidities.

BMD in HIV-Positive Individuals

A number of cross-sectional studies have documented lower BMD in HIV-infected individuals when compared with non-infected controls.[2–13] In a meta-analysis, the prevalence of osteoporosis, defined as a BMD *T*-score $\leqslant -2.5$ at the spine and/or hip, was increased threefold and was higher in individuals treated with ART and those exposed to PIs when compared with their respective controls.[14] Most of these studies were conducted in North American, Australian and European populations, and few data are available for black African-infected individuals, who comprise the largest population of HIV-infected people worldwide. In a recent study in premenopausal South African women, no difference in BMD between infected and non-infected individuals was demonstrated; however, all of the HIV-positive women were ART-naive.[15]

Prospective studies of HIV-infected individuals initiating ART have shown a bone loss of between 2 and 6% in the hip and spine during the first 1–2 years of treatment.[16–23] Tenofovir-

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containing regimens have consistently been shown to be associated with the greatest bone loss,[20–23] and in one study the use of PIs was associated with greater bone loss in the spine,[18] although this finding has not been universal. ART-induced bone loss is accompanied by increases in biochemical markers of bone resorption and formation, implicating increased bone turnover as the mechanism of bone loss.[20] Nevertheless, most studies in individuals established on ART have demonstrated stable or increasing BMD, possibly reflecting the beneficial effects of long-term ART on general health and, in particular, on body weight.[24–31]

The mechanisms by which ART initiation results in bone loss have not been clearly defined. Stimulation of osteoclastogenesis and inhibition of osteoblast function by some PIs have been reported, and zidovudine, an NRTI, has also been shown to stimulate osteoclastogenesis.[32] Tenofovir may sometimes cause renal tubular dysfunction, and it is rarely associated with Fanconi syndrome and hypophosphataemic osteomalacia. Efavirenz, an NNRTI, is associated with an increased risk of vitamin D deficiency, possibly related to induction of cytochrome *P*450,[33] and suppression of 1α-hydroxylase and 25-hydroxylase activity has been reported with some PIs. Chronic immune reconstitution may also have a role in bone loss associated with ART initiation, as a result of increased circulating levels of proinflammatory, proresorptive cytokines.[34,35]

Interestingly, there is emerging evidence that adverse effects on bone may be reduced or absent with one class of ART drugs: the integrase inhibitors. In an open-label study of participants randomized to lopinavir/ritonavir + raltegravir or lopinavir/ritanovir + 2-3 nucleoside/nucleotide reverse transcriptase inhibitors as second-line therapy, bone loss in the spine and hip over 48 weeks was significantly less in those in the treatment arm containing the integrase inhibitor raltegravir.[36] In another 48-week study in which the effects of raltegravir were compared with tenofovir/emtricitabine in treatment-naive HIV-positive individuals, raltegravir therapy was associated with a significant increase in whole-body BMD (mean +11.3%), in contrast to significant bone loss in the other treatment group (mean −6.9%).[37]

Fracture Risk in HIV-Positive Individuals

Fracture prevalence and incidence in HIV-infected individuals have been studied in a number of cohorts, mainly from North America and Europe. The design, sample size and population characteristics of these studies have varied considerably, but despite this heterogeneity most have demonstrated increased fracture risk.

In participants of the Cohort of HIV at-risk Aging Men's Prospective Study (CHAMPS) from the United States, Arnsten *et al.*[12] reported a higher fracture risk in 328 HIV-infected men aged 49 years or older when compared with 231 non-infected controls, although this did not achieve statistical significance. Using data from a large US health-care system, Triant *et al.*[38] reported a significantly increased prevalence of all fractures in HIV-infected men and women ($n = 8525$); the prevalence of wrist and vertebral fractures was significantly higher in both genders, but increased prevalence of hip fracture was seen only in men. Comparison of ethnic groups demonstrated that fracture prevalence was higher relative to non-HIV-infected patients among African-American and Caucasian females and Caucasian males. Subsequent studies from the United States have mostly confirmed an association between HIV infection and increased fracture risk, including a large study from the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) and the US HIV Outpatient Study (HOPS).[39,40] In addition, two studies using Danish health registries[41,42] and one from a large population-based database from Catalonia, Spain[43] have reported increased fracture rates associated with HIV infection. The magnitude of increase in fracture risk has generally been modest; in the VACS-VC study, the adjusted hazard ratio (95% confidence interval) was 1.24 (1.11, 1.39), whereas in the two Danish studies an incidence rate ratio of 1.5 (1.4, 1.7) and odds ratio of 2.89 (1.99, 4.18) were reported. In the Spanish study, the age- and sex-adjusted hazard ratio for major fractures (defined as hip, clinical spine, pelvis, tibia, multiple rib and proximal humerus) was 2.7 (2.01, 3.5). The hazard ratio for hip fracture in this study was 6.2 (3.5, 10.9), but the number of hip fractures was small ($n = 12$) and these data should therefore be interpreted with caution.

Shiau *et al.*[44] performed a systematic review and meta-analysis of studies reporting fracture incidence in HIV-infected individuals. There was a significant increase in the risk of all fractures and of fragility fractures with incidence rate ratios of 1.58 (1.25, 2.00) and 1.35 (1.10, 1.65), respectively. There was, however, significant heterogeneity between studies of fragility fracture, and there was also wide variation in fracture rates across studies, likely owing to differences in the demographic characteristics of the populations studied.

A number of risk factors for fracture in HIV-infected individuals have been documented (**Table 1**). Tobacco use, older age and white race have been consistent risk factors across studies. Other risk factors identified in some, but not all, studies include alcohol or substance abuse, use of glucocorticoids, proton pump inhibitors or anticonvulsants, comorbidities and low BMI. Interestingly, female gender has not been identified as a significant predictor of fracture. In addition to these traditional risk factors, those specific to HIV infection have also been identified in some studies including ART and exposure to tenofovir. Coinfection with hepatitis C has also consistently emerged as a significant independent risk factor for fracture. A significantly increased risk of hip fracture was reported in a retrospective cohort study of Medicaid enrollees, with an adjusted hazard ratio for fracture in coinfected individuals versus HCV mono-infected individuals of 1.38 (1.25, 1.53).[45] In individuals enrolled in the Veterans Affairs' Clinical Case Registry, Maalouf *et al.*[46]

Table 1 Risk factors that have been identified in some studies for fracture in HIV-infected individuals

Traditional	*HIV related*
Age	Low CD4 count
Low BMI	ART exposure
Tobacco use	Hepatitis C coinfection
Alcohol or substance abuse	
Glucocorticoids	
Proton pump inhibitors	
Anticonvulsants	
Comorbidities	
Non-black or white race	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index. Adapted from Shiau *et al.*[44]

reported a significantly higher risk of osteoporotic fracture, defined as closed wrist, vertebral or hip fracture, in HCV/HIV coinfected versus HIV mono-infected individuals, with fracture rates of 2.57 and 2.07/1000 patient-years ($P < 0.0001$).

The available data thus indicate that there is a modest increase in fragility and non-fragility fracture risk associated with HIV infection. Most of the studies have been conducted in the United States and Europe and there are no data in the HIV-infected population in Sub-Saharan South Africa. More studies are also required to establish the incidence of vertebral fractures and to define more clearly the role of falls and trauma in the pathogenesis of fracture.

Pathophysiology of Bone Loss Associated with HIV Infection

The changes in bone remodelling and structure responsible for bone loss and increased bone fragility in HIV-positive individuals have not been clearly defined. Bone biopsy data are limited to one study in 22 HIV-positive, ART-naive young adults. When compared with biopsies obtained from a control group of healthy kidney donors, bone formation at both tissue and cellular levels was reduced.[47] Studies of bone turnover markers in treatment-naive HIV-infected individuals have not been reported; as discussed earlier in this review, initiation of ART is associated with an increase in biochemical markers of bone resorption and formation. There are few data on bone turnover markers in subjects established on long-term ART, but elevated levels were reported in African-American and Hispanic postmenopausal HIV-positive women.

Changes in bone microstructure, assessed using high-resolution peripheral quantitative computerized tomography, have been reported in HIV-positive individuals in several studies. In 22 HIV-infected premenopausal women, Calmy *et al.*[48] reported significantly lower tibial trabecular bone density and trabecular number, and a significantly lower cortical density in the radius when compared with non-infected controls. In 46 HIV-positive postmenopausal women, tibial cortical thickness and cortical area were significantly lower than control values, but no differences were seen in the radius.[49] Finally, Yin *et al.*[50] have recently reported reduced trabecular bone density in the tibia and radius and lower cortical and trabecular thickness in young American-African or Hispanic men.

Taken together, these data do not provide a complete picture of the mechanisms underlying bone loss in HIV-infected individuals. There is good evidence that the bone loss associated with initiation of most ART regimens is a consequence of increased remodelling rate, and some of the changes in bone microstructure that have been reported may result from this increase in bone turnover. However, whether abnormalities in bone remodelling persist in individuals stabilized on long-term ART is unknown.

Management of Bone Disease in HIV-Infected Individuals

Fracture risk assessment

Fracture risk assessment in HIV-positive individuals is based on similar principles to those used in the general population. The European AIDS Clinical Society (EACS) guidelines advise that BMD assessment by dual-energy X-ray absorptiometry (DXA), where available, should be considered in infected postmenopausal women and men aged $\geqslant 50$ years, particularly if clinical risk factors are present.[51] They also recommend the use of the Fracture Risk Assessment Tool (FRAX) in HIV-infected individuals $\geqslant 40$ years. Other secondary causes of osteoporosis should be excluded in those with low BMD and vertebral fracture assessment considered in those with height loss, kyphosis or low spine BMD.

Lifestyle advice

Lifestyle advice should be given where appropriate, particularly with respect to tobacco use, alcohol abuse and physical activity. In addition, nutritional measures aimed at achieving a normal body weight and adequate calcium intakes should be taken. There is no consistent evidence that the prevalence of vitamin D deficiency/insufficiency is higher in HIV-infected populations than in the general population, and the EACS guideline recommends that measurement of serum 25-hydroxyvitamin D levels should be considered in individuals with low BMD, fracture or risk factors for deficiency. Finally, risk factors for falling should be assessed and, where appropriate, addressed.

Pharmacological interventions

Of the pharmacological interventions currently approved for prevention of fracture in postmenopausal women and older men, only alendronate and zoledronic acid have been studied in HIV-infected individuals. In nearly all these studies, calcium and vitamin D supplements were also administered. These studies have been relatively small and conducted in selected populations, with BMD as the primary outcome and with insufficient power for fracture outcomes.

The effects of alendronate 70 mg once weekly have been investigated in several studies. In a systematic review of three randomized controlled trials of alendronate in osteopenic or osteoporotic HIV-positive individuals, significant gains in lumbar spine and hip BMD were reported after 1 and 2 years.[52] The number of fractures in these studies was small and insufficient to demonstrate effects on fracture risk. Significant BMD benefits have been demonstrated in two subsequent randomized controlled trials of once-weekly alendronate in HIV-positive individuals, but neither of these studies was powered to demonstrate fracture reduction.[53,54]

Intravenous zoledronic acid has also been investigated as a potential treatment option. In a randomized controlled trial conducted in 43 HIV-infected men with a BMD *T*-score < -0.5, increases in lumbar spine and total hip BMD in the treatment and control groups were 8.9% versus 2.6% and 3.8% versus 0.8% after two annual infusions of zoledronic acid, 4 mg.[55] In a 4-year extension of this study, persistence of the effects on BMD and biochemical markers of bone turnover was demonstrated for at least 5 years after the second dose.[56] Significant effects on spine and hip BMD were also reported by Huang *et al.*[57] after a single dose of zoledronic acid, 5 mg, in 30 men with osteopenia or osteoporosis.

Although intervention studies in HIV-infected individuals have generally been relatively small and short-term, the available data indicate BMD responses that are similar to those seen in non-infected postmenopausal women and older men treated with bisphosphonates. Because adherence to therapy may be particularly poor in HIV-positive individuals, zoledronic acid is likely to be the preferable option in many cases. However, it

should be emphasized that in this population the use of FRAX ± BMD to assess fracture risk has not been well validated and that the effects of treatment on fracture are unknown. Both the targeting of treatment and its efficacy therefore require further investigation. In addition, the long-term safety of bisphosphonates in HIV-infected individuals remains to be established.

Conclusions

In recent years, there has been increasing awareness of osteoporosis as a complication of HIV infection. The available evidence indicates that the risk of all fractures and of fragility fractures is modestly increased in HIV-infected individuals, although these studies are mainly limited to North America, Europe and Australia. The pathogenesis of increased bone fragility has not been clearly established, but it is likely to be multifactorial, with both traditional and HIV-related risk factors involved. Relatively little is known about the prevalence of bone disease in HIV-positive individuals in Sub-Saharan Africa, where the vast majority of HIV infection occurs, and this is an important area for future research.

Conflict of Interest

The author declares no conflict of interest.

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