Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2015 December ; 22(6): 446–451. doi:10.1097/MED.000000000000200.

Bone loss in HIV—a contemporary review

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Abstract

Purpose of the review—Because of antiretroviral therapy, people are living with HIV infection longer than ever before. As this patient group ages, it is expected that medical co-morbidities such as osteoporosis and fragility fractures will increase. The purpose of this review is to address the epidemiology and what is known regarding the pathogenesis of bone loss in people living with HIV infection with a focus on recently published literature.

Recent findings—HIV-infected individuals are at increased risk for low bone mineral density and bone fractures. The cause of bone loss in HIV is multifactorial including traditional risk factors some of which disproportionately affect HIV-infected individuals and alterations in bone metabolism due to antiretroviral therapy (ART), HIV viral proteins and chronic inflammation. Lifestyle modification, changing ART, calcium and vitamin D supplementation and pharmacologic treatment for osteoporosis may all be employed to abrogate bone loss in this patient group.

Summary—Clinicians should be aware of the contributors to bone loss in people living with HIV in order to recognize high risk individuals and to take appropriate steps to address modifiable risk factors to prevent future fracture.

Keywords

Human Immunodeficiency Virus; Osteoporosis; Antiretroviral Therapy; Systemic Inflammation

Introduction

Advances in antiretroviral therapy (ART) have had an impressive impact on AIDS-related mortality over the last two decades such that life expectancy nears that of the general population in developed countries[1]. As this patient group ages, it is expected that medical co-morbidities such as osteoporosis and fragility fractures will increase[2*]. As a result,

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Conflicts of interest: COH none were declared.

maintaining bone health has emerged as an important aspect of the long term care of people living with HIV infection. Patients and clinicians are interested in recognizing high risk individuals and understanding appropriate steps to address modifiable risk factors to prevent future fracture. Acknowledging that the cause of bone loss in HIV is a complex interplay of multiple factors is imperative to attainment of these goals. Therefore, the aim of this review is to address the epidemiology and what is known regarding the pathogenesis of bone loss in people living with HIV infection with a focus on recently published literature.

Prevalence of low bone mineral density and fracture in HIV

According to the World Health Organization, osteoporosis may be defined as a bone mineral density (BMD) that is 2.5 standard deviations below the young adult mean value, ie, a T-score at or below -2.5 and osteopenia as a T-score between -1 and -2.5 [3]. Osteoporosis determined by dual-energy x-ray absorptiometry (DXA) is a well-established predictor of future fracture in the general population[4], and this has recently been shown in HIV as well. Data combined from the HIV Outpatient Study (HOPS) and Study to Understand the Natural History of HIV/AIDS (SUN Study), both longitudinal cohort studies of HIV-infected adults in the United States, show that having a T-score -2.5 is associated with an adjusted risk of incident fracture of 4.02 (95% CI 2.02–8.01) compared with having a T-score -1 [5**].

Alarming, in a meta-analysis of cross-sectional studies evaluating BMD in HIV, the unadjusted odds of osteoporosis were 3.7 times higher for HIV-infected patients compared to uninfected controls and the prevalence of low BMD (T-score < -1) among the HIV-infected groups in the included studies ranged from 40%–87.5%[6]. Since this report, additional studies have continued to substantiate that low BMD is common in people living with HIV infection whether ART-treated[7*, 8*] or ART-naïve[9**, 10, 11]; and, in some[12**], but not all[13**, 14], comparative studies osteopenia and osteoporosis are more prevalent among HIV-infected individuals when compared with uninfected controls. Of greatest concern, however, are reports of heightened risk for fracture among people living with HIV. In a meta-analysis of studies evaluating fracture risk, the unadjusted incident rate ratio for any fracture was 1.58 (95% CI 1.25–2) compared with HIV-uninfected controls and the crude incidence of fragility fracture among HIV-infected groups ranged from 1–7.4 per 1000 person-years in the included studies[15]. Due to ART, people are living with HIV longer than ever before. This, coupled with the fact that low BMD and fractures are common in this patient group, is why determining the cause of bone loss in HIV is an area of active research.

Traditional risk factors

It is clear that traditional risk factors for bone loss contribute to low BMD in HIV. In fact, there is controversy regarding whether traditional risk factors such as low body weight entirely explain the increase risk seen in this patient group[16, 17]. In another meta-analysis of cross-sectional studies comparing BMD between HIV-infected and uninfected individuals, differences in body weight accounted in large part for differences in BMD[17]. Also, in a recent cross-sectional analysis from the AGE_{HIV} Cohort, a prospective observational study of predominately male ($>85\%$) HIV-infected and uninfected adults 45 years old, both osteopenia and osteoporosis were more prevalent in the HIV-infected

participants; however, after adjustment for body weight and smoking, HIV infection was no longer independently associated with BMD[13**]. Importantly, in both of these reports, participants were either young or predominately men who have sex with men (MSM) and therefore, the results may not be generalizable to all HIV-infected patients. It is interesting, however, that in the AGE_hIV study, the association between current body weight with BMD was stronger in the HIV-infected group than in controls. Further, within the HIV-infected group, the association between body weight and BMD was strongest in those with a history of a condition that signifies advanced immunosuppression according to the Centers for Disease Control and Prevention HIV staging classification system. This suggests that the effect of low body weight on osteoporosis risk may be greater among those with HIV infection. It is also important to note that both of these risk factors disproportionately affect those with HIV infection. In 2009, 42% (95% CI 40–45) of HIV-infected adults receiving medical care in the United States were current smokers which represented an adjusted prevalence difference of 17% (95% CI 14–20) compared with the US adult population[18**]. Further, low body weight is common among MSM and also typifies advanced HIV disease.

Other traditional risk factors highly prevalent among people living with HIV include hypogonadism[19] and vitamin D deficiency[20]. Male hypogonadism is common with advanced HIV and may continue to be present despite ART[19, 21, 22]. Low testosterone has been linked with reduced BMD in HIV infected men[23] and short term exogenous androgen has been shown to increase BMD in eugonadal men with AIDS wasting[24]. On the other hand, the extent to which vitamin D deficiency contributes to osteopenia and osteoporosis in the HIV population is largely unknown unlike in the general population where data from randomized, placebo-controlled trials show that vitamin D and calcium supplementation improves BMD and modestly decreases the risk of fracture[25–27]. However, in addition to usual risk factors for vitamin D deficiency such as dark skin and inadequate intake, certain commonly-prescribed antiretrovirals, particularly efavirenz (EFV), interfere with vitamin D metabolism and may lead to deficiency. Efavirenz reduces the expression of the cytochrome P450 enzyme CYP2R1 which is involved in converting vitamin D3 to 25-hydroxy-vitamin D (25(OH)D)[28]and upregulates CYP24 which converts active vitamin D to inactive metabolites[29, 30]. Human trials have shown greater decreases in 25(OH)D when initiating EFV-containing ART over non-EFV ART[31*, 32].

Finally, common risk factors for osteoporosis in the general population are also associated with low BMD in HIV, including older age and menopausal status. In the Menopause Study, a longitudinal cohort study of menopause and its sequelae in women with or at risk for HIV infection in Bronx, New York, HIV-infected women had lower BMD at both the femoral neck and lumbar spine compared with women at similar risk for HIV acquisition[33], and decline in BMD per year while similar between groups was most significant through the menopausal transition[34]. In a recent report, however, it was suggested that the combined effects of HIV and race on change in BMD vary among women in this cohort. HIV infection was not associated with bone loss among black women; however, HIV was associated with significantly greater bone loss at the total hip per year among non-black women[35*].

Hepatitis C co-infection

In a meta-analysis of studies evaluating BMD or incident fractures in HIV/HCV co-infected patients, the prevalence of osteoporosis was 22% with an unadjusted OR of 1.63 (95% CI 1.27–2.11) compared to those with HIV-mono-infection. Additionally the risks of all fractures, traumatic/high-energy fractures and fragility fractures were each about 2 fold higher for the HIV/HCV co-infected group compared to the HIV-monoinfected group[36*]. While it is not clear why hepatitis C infection increases the risk of low BMD, behavioral factors may explain in part the higher risk of fracture in this patient group.

Antiretroviral therapy

After ART initiation, systemic inflammation decreases markedly whereas bone turnover increases[37]. While this “re-coupling” of bone formation and resorption associated with decreased inflammation was initially believed to be beneficial to bone health, it is now established that ART initiation results in a 2–6% decrease in BMD over the first 96 weeks[38]. Therefore, even though bone formation increases with ART initiation, there is still a net loss of bone. In the Strategies for Management of AntiRetroviral Therapy (SMART) trial Body Composition substudy, the effect of intermittent vs continuous ART on markers of bone turnover and BMD were evaluated. Compared with continuous ART, interruption of ART resulted in reduction in makers of bone turnover and an increase in BMD at the hip and spine[39, 40]. Presently, it is not clear whether changes that occur after ART initiation result from alterations in the inflammatory/immune environment or direct antiretroviral effects. Bone loss after ART has been linked with lower pre-ART CD4+ cell count suggesting a role for pretreatment immunosuppression as a contributor[41]. On the other hand, protease inhibitors (PIs)[42**] and the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) appear to be associated with greater bone losses than other antiretrovirals suggesting that direct antiviral effects are likely playing a role as well.

Role of tenofovir

One suggested mechanism for the bone changes associated with TDF is that hypophosphatemia secondary to proximal renal tubular dysfunction triggers bone reabsorption in an attempt to liberate matrix phosphorus. In a prospective, cross-sectional study of Asian Americans with chronic hepatitis B infection, the renal threshold phosphate concentration or the ratio of maximal rate of renal tubular reabsorption of phosphate to GFR ($TmPO_4/GFR$), a measure of renal tubular reabsorption of phosphate, was similar between participants not on treatment, treated with TDF or treated with entecavir (ETV); however, the prevalence of abnormal $TmPO_4/GFR$ was greater in participants treated with TDF 18 months compared to those treated with ETV (48% vs 12.5%; $p=0.005$). Although, in this study there was no difference in the prevalence of osteoporosis between the three groups and $TmPO_4/GFR$ did not correlate with osteoporosis[43*].

As proof of the direct antiviral toxicity, TDF has been associated with decrease in BMD in individuals with and without HIV infection. In the Preexposure Prophylaxis Initiate (iPrEX) study, HIV-uninfected men and transgender women (N=2499) were randomized to receive emtricitabine (FTC) with TDF or placebo daily to evaluate this regimen for use in pre-

exposure prophylaxis against HIV infection. In the FTC/TDF group, spine BMD decreased most dramatically in the first 24 weeks with smaller further decreases to 96 weeks, and hip BMD initially decreased and then rebounded to near baseline by week 72. Net differences in percentage change in BMD between groups were significant at 24 weeks at both the spine and hip (spine: -0.91% ; $p=0.001$ and hip: -0.61% ; $p=0.001$)[44**]. Further, in HIV, studies comparing TDF-containing ART and ART without TDF in ART-naïve HIV-infected individuals have consistently shown that ART without TDF leads to less BMD decline over the first 48 to 96 weeks of treatment[45*, 46] as well as less increase in bone turnover markers[47*, 48]. Last, in virologically suppressed, HIV-infected participants, switching from a TDF-containing regimen to an alternative NRTI or an NRTI-sparing regimen also leads to improvement in bone turnover markers, including sclerostin, a selective regulator of bone formation through the Wnt pathway[49*] and results in increase in BMD[50*]. These studies confirm the heightened risk of bone loss with TDF, but also provide possible alternative ART combinations for high risk patients.

Currently in clinical trials, tenofovir alafenamide (TAF), a prodrug of tenofovir (TDV) that is metabolized intracellularly to TDV achieving higher active metabolite concentration in the peripheral blood mononuclear cells and lower plasma TDV than TDF, offers a promising alternative to TDF with regard to the bone toxicity[51**].

HIV infection and the host immune response

HIV viral proteins and the host immune response contribute to changes in the balance of bone formation and resorption. In vitro, HIV proteins Tat and Nef reduce the number of bone marrow mesenchymal stem cells available to differentiate into osteoblasts by inducing senescence of these cells through NF- κ B activation and inhibition of autophagy, respectively[52*]. Whereas, HIV proteins Tat and Rev increase monocyte differentiation into osteoclasts, as well as boost osteoclast resorption function by increasing reactive oxygen species and TNF- α production in osteoclast precursors[53*]. B cell dysfunction associated with HIV infection has also been suggested as a possible mechanism for bone loss in HIV. It has been shown that there is a higher frequency of RANKL-expressing B cells (resting memory and exhausted tissue-like memory B cells) and a lower frequency of OPG-expressing B cells (resting memory B cells) in HIV-infected compared to HIV-uninfected individuals. Further, RANKL/OPG ratio was correlated with total hip BMD, T- and Z-scores in the HIV-infected participants[54*].

Screening and management of bone disease in HIV

Presently, the Infectious Disease Society of America (IDSA), the European AIDS Clinical Society (EACS) and other HIV and bone experts recommend DXA screening for osteoporosis in HIV-infected postmenopausal women and men age ≥ 50 years[55**, 56, 57]. The Osteo Renal Exchange Program (OREP) recently added to these recommendations suggesting that it is reasonable to perform DXA for HIV-infected adults aged 40–49 years with a Fracture Risk Assessment Tool (FRAX) score of $> 10\%$ and for adults with major fragility fracture risk factors[58*]. These guidelines take into account the heightened risk of bone loss in HIV-infected adults.

In a randomized clinical trial, calcium plus vitamin D supplementation with ART initiation mitigated some of the bone loss sustained during the first year of therapy with TDF/FTC/EFV[59**]. Whether this strategy is generalizable to ART initiation with other agents is unclear.

The management of established low BMD in HIV is for the most part similar to that in the general population. Strength training has recently been shown to increase BMD in HIV-infected adults with lipodystrophy[60*]. Vitamin D and calcium supplementation increase, albeit modestly, spine and hip BMD in ART-treated, HIV-infected individuals[61]. For those with osteoporosis, bisphosphonates have been shown to be safe and effective in increasing spine and hip BMD in this patient group[61].

Recently, HMG-CoA reductase inhibitors or statins have been shown to have a beneficial effect on BMD in HIV-infected adults on ART. In the SATURN-HIV study, a randomized, double-blind, placebo-controlled trial of rosuvastatin in HIV-infected adults on stable ART with low density lipoprotein < 130 mg/dL and evidence of heightened systemic inflammation or immune activation, trochanter and total hip BMD modestly increased over 48 weeks in the rosuvastatin arm [percent change in BMD trochanter 0.9% (95% CI -0.9%-0.6%); total hip 0.6% (95% CI 0.0%–1.1%)] and these changes were significantly different than placebo[62*].

Conclusion

People living with HIV infection are at risk for bone loss to a greater extent than the general population. This is likely to contribute to greater fracture risk as this population ages and this has been suggested in longitudinal studies to date. Taking steps to identify high risk patients for targeted intervention is warranted.

Acknowledgments

This work was supported by the National Institutes of Health (K23HL116209 to COH and K23HD069199 to ARE). ARE has received research grants from Cubist Pharmaceuticals, GSK and BMS and serves as consultant for Gilead. GAM has received research grants from BMS, Gilead Sciences and GSK, has served as a consultant to BMS, GSK/Viiv, Gilead, ICON, has served as a speaker for BMS, and is on the DSMB for a Pfizer-sponsored trial.

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Key points

- Low bone mineral density is common in HIV-infected individuals whether antiretroviral therapy treated or antiretroviral therapy naive.
- The cause of bone loss in HIV is multifactorial and includes traditional risk factors for osteoporosis some of which disproportionately affect HIV-infected individuals and alterations in bone metabolism due to antiretroviral therapy, HIV viral proteins and chronic inflammation.
- Screening for low bone mineral density should be considered in HIV-infected postmenopausal women and men 50 years.
- Lifestyle modification, changing antiretroviral therapy, calcium and vitamin D supplementation and pharmacological treatment for osteoporosis, namely bisphosphonates, may be employed to abrogate bone loss in this patient group.