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Bone Loss in HIV Infection

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Opinion Statement

Human immunodeficiency virus (HIV) infection is an established risk factor for low bone mineral density (BMD) and subsequent fracture, and treatment with combination antiretroviral therapy (cART) leads to additional BMD loss, particularly in the first 1–2 years of therapy. The prevalence of low BMD and fragility fracture is expected to increase as the HIV-infected population ages with successful treatment with cART. Mechanisms of bone loss in the setting of HIV infection are likely multifactorial, and include viral, host, and immune effects, as well as direct and indirect effects of cART, particularly tenofovir disoproxil fumarate (TDF) and the protease inhibitors (PIs). Emerging data indicate that BMD loss following cART initiation can be mitigated by prophylaxis with either long-acting bisphosphonates or vitamin D and calcium supplementation. In addition, newer antiretrovirals, particularly the integrase strand transfer inhibitors and tenofovir alafenamide (TAF), are associated with less intense bone loss than PIs and TDF. However, further studies are needed to establish optimal bone sparing cART regimens, appropriate screening intervals, and preventive measures to address the rising prevalence of fragility bone disease in the HIV population.

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Conflicts of Interest

Dr. Caitlin A. Moran, Dr.› M. Neale Weitzmann, and Dr. Ighovwerha Ofotokun declare no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any new studies with human or animal involvement performed by the authors.

Compliance with Ethical Standards

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Keywords

HIV; osteopenia; osteoporosis; combination antiretroviral therapy; immune reconstitution; bisphosphonates

I. Introduction

HIV-infected individuals treated with combination antiretroviral therapy (cART) can expect to attain a near-normal life expectancy [1]; however, they will experience age-related comorbidities including cardiovascular disease, musculoskeletal abnormalities, and renal impairment at rates that exceed those of the general population [2, 3]. As the HIV population ages, the prevalence of these comorbidities in this population is expected to increase significantly [3]. Therefore, it is becoming increasingly important for clinicians caring for HIV-infected patients to be aware of the risks of noninfectious comorbidities in this population, as well as strategies to mitigate these risks.

Osteopenia and osteoporosis as defined by the World Health Organization criteria [femoral neck or lumbar spine T-score as measured by dual energy X-ray absorptiometry (DXA) between −1.0 and −2.5 (osteopenia) and less than or equal to −2.5 (osteoporosis)] [4] are associated with HIV infection itself, as well as with cART [5, 6]. Indeed, cART further aggravates the bone mineral density (BMD) loss associated with HIV infection: patients experience an additional 2% to 6% BMD loss in the first 1–2 years of cART, a rate of bone loss similar to that seen in postmenopausal osteoporosis [7, 8]. Because this higher prevalence of bone disease in the HIV population is accompanied by a clinically significant increased rate of bone fractures [9, 10], it is important to understand the mechanisms underlying HIV-associated bone loss, as well as current options to prevent further bone loss in this population. This review will focus on new evidence regarding the pathogenesis of HIV-associated bone loss due to both HIV infection itself and the effects of cART, as well as strategies for mitigating metabolic bone disease and fragility fractures in the HIV-infected population.

II. The scope and burden of HIV-associated bone loss

Current estimates suggest that the prevalence of osteopenia and osteoporosis in the setting of HIV infection ranges from 48% to 55% and 10% to 34%, respectively [11–13], and is expected to increase as the HIV population ages [3]. This high prevalence of bone disease is associated with an elevated rate of bone fractures despite the relatively young age of the HIV population [14]. The landmark population-based study by Triant *et al.*, which involved 8,525 HIV-infected patients and 2,208,792 HIV-uninfected controls, found that fracture prevalence among HIV-infected patients of both sexes was two- to four-fold higher than among the HIV-uninfected controls [9]. These findings were confirmed in more recent studies of fracture prevalence involving patients in the United States (U.S.) in the HIV Outpatient Study (HOPS) cohort [15], the Veterans Aging Cohort Study Virtual Cohort (VASC-VC) [16], and the Women's Interagency HIV Study (WIHS) cohort [17]. Internationally, a more recent Spanish population-based cohort study of 2,489 HIV-infected and 1,115,667 HIV-uninfected participants over the age of 40 demonstrated an overall age- and sex-adjusted hip

fracture hazard ratio (HR) for HIV infection of 4.7, with a stronger association in older age groups [10]. In Denmark, a case-control study using nationwide health registry data analyzed 124,655 non-traumatic fracture cases and 373,962 age- and sex-matched controls, and found an almost 9-fold increased risk for hip fracture among HIV-infected patients compared to their HIV-uninfected counterparts [18]. Taken together, these population-based studies demonstrate the high burden of fragility fractures in the HIV population, which is projected to increase as the HIV population ages.

III. Proposed mechanisms of HIV-associated bone loss

The maintenance of skeletal health involves ongoing bone remodeling that requires a balance between bone deposition mediated by mesenchymal stem cell (MSC)-derived osteoblasts and bone resorption mediated by monocyte-macrophage-derived osteoclasts [19]. The osteoblast-osteoclast balance is mediated by cross talk between these bone cells and immune cells [6]. Osteoclast differentiation is stimulated by the binding of receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) to RANK expressed on cells of the monocytic lineage. In physiological conditions RANKL is secreted predominantly by cells of the osteoblast lineage including osteoblast progenetors (MSCs), osteoblasts [19], and osteocytes, as well as by hypertrophic chondrocytes [20, 21]. The activity of RANKL is inhibited by osteoprotegerin (OPG), a decoy receptor of RANKL, which, under normal conditions, is produced predominantly by B cells in the bone marrow in response to T cell signaling, as well as by MSCs and osteoblasts. However, under inflammatory conditions, T and B cells are further activated to produce RANKL instead of OPG [22•, 23]. This production of RANKL and OPG by immune cells suggests a link between the skeletal and immune systems, the “immunoskeletal interface”. Furthermore, pro-inflammatory cytokines including interleukin (IL)-1, IL-6, IL-7, IL-17, macrophage-colony stimulating factor (M-CSF) and tumor necrosis factor (TNF)-α stimulate osteoclast differentiation either by promoting RANKL, stimulating expression of RANK, or by suppressing production of OPG, favoring enhanced bone loss. TNF-α further amplifies RANKL activity while interferon (IFN)-γ has direct inhibitory effects on osteoclast differentiation [19, 24••], but can potently stimulate osteoclastogensis through immune mediated signals. Many of these cytokines including IL-7 and TNF-α further disregulate bone turnover by suppressing osteoblast differentiation [24••]. Therefore, any perturbations in this complex “immunoskeletal interface” [25] that result in an increase in osteoclastic bone resorption relative to osteoblastic bone formation will lead to BMD loss.

The development of metabolic bone disease in the setting of HIV infection is likely multifactorial. Traditional risk factors for low BMD, including low body mass index (BMI), smoking, hypogonadism or menopause, and corticosteroid use are highly prevalent among HIV-infected individuals [12, 26–29]. However, individuals with HIV experience BMD loss beyond what would be expected from these traditional risk factors alone [30], and there is evidence that both the HIV virus itself, and treatment with cART, contribute to ongoing bone loss in the HIV population.

III.A Mechanisms of virus-associated bone damage

Data suggest that HIV has both direct and indirect effects on osteoblasts, osteoclasts, and their cross-talk regulation [31]. In a prospective cohort study by Hileman *et al.*, treatment-naïve, HIV-infected individuals experienced a greater rate of BMD loss than age, race, and sex matched HIV-uninfected controls over 48 weeks [32]. And studies of cART-naïve, HIV-infected individuals have shown that longer duration of HIV infection [26, 33], more advanced WHO HIV stage [34], and greater levels of HIV viremia [35] are all associated with greater BMD loss, suggesting that the virus itself and the inflammation associated with HIV infection have an effect on BMD.

III.A.i Effects of inflammation and adaptive immune dysregulation on bone— Markers of inflammation and immune activation are associated with BMD loss in HIV-infected individuals. Hileman *et al.* found that higher plasma levels of IL-6 were associated with greater BMD loss among HIV-infected, but not HIV-uninfected, participants [32]. In addition, in a cross-sectional analysis of 457 Tanner stage 5 behaviorally HIV-infected males and females aged 14–25 and seronegative controls, soluble CD14 (sCD14), a marker of macrophage activation, was greater in HIV-infected males than in HIV-uninfected males [36], and a negative correlation between bone mass and sCD14 was seen in both sexes [36]. Taken together, these results suggest that inflammation and innate immune activation play a role in HIV-induced bone loss.

HIV infection also causes dysfunction in adaptive immunity that results in bone loss. In HIV-uninfected persons, activated T cells have been shown to produce RANKL and stimulate osteoclastogenesis in a number of inflammatory conditions including rheumatoid arthritis [37] and postmenopausal osteoporosis [38]. In a cross-sectional study of 78 HIV-infected patients who underwent DXA screening, patients with low BMD (osteopenia or osteoporosis) had a greater frequency of activated $CD4^+$ ($CD4^+HLA\text{-}DR^+$) and activated $CD8^+$ ($CD8^+HLA\text{-}DR^+$) T cells; in a subset of 57 patients virologically suppressed on cART, those with low BMD continued to display a greater frequency of activated $CD8^+$, but not activated $CD4^+$, T cells, suggesting that some immune activation leading to decreased BMD persists despite virologic suppression [39]. However, the clinical significance of these findings is unclear. In a retrospective analysis of the AIDS Clinical Trials Group (ACTG) Longitudinal-Linked Randomized Trial (ALLRT), a longitudinal cohort of participants enrolled in other ACTG studies, markers of T cell activation ($CD8^+CD38^+HLA\text{-}DR^+$) were not associated with an increased incidence of fracture, although this study had low power to detect associations [40].

B cells are also affected by HIV infection. Our group has shown that B cells switch from OPG production to RANKL production in animal models of HIV infection [41], and that B cells isolated from cART-naïve HIV-infected individuals displayed increased RANKL production and decreased OPG production compared to B cells isolated from HIV-uninfected controls [22•]. Furthermore, these changes were associated with an increase in bone turnover markers and a decrease in BMD in HIV-infected individuals compared with HIV-uninfected controls [22•].

III.A.ii Direct effects of HIV on bone—There is also *in vitro* evidence that HIV directly affects bone remodeling. Human osteoblasts exposed to HIV protein p55-gag and envelope glycoprotein gp120 had decreased alkaline phosphatase activity, calcium deposition, and cell proliferation and viability [42, 43], while exposure of $CD3^+$ T cells to gp120 resulted in a significant increase of RANKL production and subsequent osteoclast differentiation [44, 45]. Furthermore, MSCs chronically exposed over 20 days to HIV proteins Tat and Nef *in vitro* exhibited premature senescence, increased oxidative stress, and mitochondrial dysfunction resulting in decreased osteoblastic differentiation [46]. These data suggest that the effect of HIV on BMD may be partially mediated by a range of HIV proteins; however, additional studies are needed to confirm these findings *in vivo*.

III.B Mechanisms of antiretroviral therapy-associated bone damage

There is compelling evidence that HIV-associated bone loss is paradoxically worsened by cART. In a meta-analysis by Brown and Qaqish, HIV-infected individuals on cART had a 2.5-fold increased odds of prevalent low BMD compared with those who were cART-naïve [47]. This effect is universal across all antiretroviral drug classes, although the magnitude of BMD loss may vary by drug regimen [5, 48–50]. Of particular interest is the observation that the vast majority of bone loss occurs within the first 1–2 years after cART initiation, with subsequent stabilization of BMD thereafter [51–53]. It also has been observed that a lower baseline CD4 count is associated with a greater degree of BMD loss after cART initiation [54•]. These data suggest that, in addition to the direct effects of specific antiretrovirals on bone, some of the bone loss seen immediately after cART initiation may be due to HIV disease reversal and immune reconstitution.

III.B.i Role of T cell restoration in cART-associated bone damage—Recently, our group has explored the role of immune reconstitution and T cell repopulation in BMD loss after cART initiation. Our group created an animal model of immune reconstitution by adoptive transfer of T cells into T cell knock-out mice to mimic cART-induced T cell re-expansion, and observed an increase in the osteoclastogenic cytokines RANKL and TNF-α, along with corresponding decreases in cortical and trabecular bone mass 12 weeks after adoptive transfer of T cells [24••]. These findings were confirmed in part in humans in a prospective cohort study of 20 cART-naïve HIV-infected participants initiating cART. A rapid increase in plasma bone turnover markers was observed as early as two weeks after cART initiation, and lasted through 24 weeks [55••]. Peak bone resorption was noted at around 12 weeks: the time at which T cell recovery after cART initiation reaches a significant level [56]. Therefore, it seems likely that in humans, as was described in the mouse model, T cell repopulation plays a role in cART-induced bone loss.

III.B.ii Tenofovir disoproxil fumarate-associated bone loss—Tenofovir disoproxil fumarate (TDF) is a prodrug of the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir (TFV). Both cART-naïve and virologically suppressed HIV-infected patients exposed to TDF experience 1–3% more bone loss than those exposed to other NRTIs in [57–61]. Additionally, reversible TDF-associated bone loss has been observed in healthy, HIV-uninfected men and women taking TDF for pre-exposure prophylaxis (PrEP) [62–64], thus confirming the effects of TDF on bone beyond what can be attributed to viral or immune

factors. Although there is some *in vitro* evidence that TDF directly affects osteoblast and osteoclast gene expression [65, 66], the putative mechanism of TDF-associated bone loss is phosphate wasting caused by proximal renal tubular dysfunction. TDF is metabolized to TFV in the plasma. In the kidney, TFV is taken up from the plasma by the organic anion transporter at the proximal tubular cells and is then excreted into urine in the tubular space at a slower rate than it is taken up [67, 68]. Accumulation of TFV in the proximal tubular cells can lead to proximal renal tubular dysfunction, the most severe form of which is a Fanconi-like syndrome (hyperphosphaturia, hyperaminoaciduria, and glucosuria) that can result in osteomalacia (poorly mineralized bone matrix), even with preserved glomerular function [67, 69, 70]. Milder TDF-associated renal tubular dysfunction and alterations in phosphate metabolism can still result in a reduction in BMD [71, 72]. Indeed, hyperphosphaturia has been correlated with BMD loss even in the setting of normal phosphatemia [73].

In contrast to TDF, tenofovir alafenamide (TAF) is an alanine ester prodrug of TFV whose pharmacokinetic properties result in greater concentrations of TFV in HIV-target cells with approximately 90% lower TFV plasma concentrations than are seen with TDF [68, 74, 75]. This lower plasma concentration results in less TFV uptake by the kidney and lower proximal tubule TFV concentrations, which in turn leads to less proximal tubule dysfunction [75] and subsequent BMD loss. In clinical trials, cART-naïve HIV-infected patients experienced less BMD loss when started on a TAF-containing regimen compared with a TDF-containing regimen [76, 77], and HIV-infected patients who were virologically suppressed on a TDF-containing regimen saw improvements in their renal function and BMD when switched to a TAF-containing regimen [78]. Whether the long-term bone effects of TAF are similar to those of other non-TDF NRTIs remains to be seen.

III.B.iii Protease inhibitor associated bone loss—The effects of protease inhibitors (PIs) on BMD are somewhat controversial: most, but not all, clinical studies point to an association between PI use and BMD loss [50, 79–83]. In randomized clinical trials, PI-based regimens are associated with a greater degree of BMD loss than either non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens [58, 84] or integrase strand transfer inhibitor (INSTI)-based regimens [85, 86]. The mechanisms behind PI-associated bone loss are unclear, and *in vitro* data are conflicting and vary by drug. Gibellini *et al.* demonstrated that treatment of osteoblasts with fosamprenavir (FPV), but not indinavir (IDV), saquinavir (SQV), atazanavir (ATV), tipranavir (TPV) or darunavir (DRV) results in an increase in OPG expression and subsequent decrease in RANKL production [87], conditions unfavorable for osteoclastic bone resorption. In contrast, Fakruddin *et al.* showed that, in human peripheral blood mononuclear cells (PBMCs), physiologic blocks to osteoclastogenesis are inhibited by ritonavir (RTV) and SQV, two PIs that have been associated with osteopenia, but not IDV and nelfinavir (NFV) [44]. Other *in vitro* studies have demonstrated that PIs can alter osteoblast gene expression [88], decrease osteoblast differentiation by MSCs [89], and increase osteoclast differentiation [45, 90, 91]. Given that the effects observed *in vitro* vary by specific drug, and are not all consistent with clinical observations, there are likely additional or alternative mechanisms by which PIs affect BMD.

In addition to the direct effects of PIs on osteoblasts and osteoclasts, there are data to suggest that a portion of the bone loss associated with PIs can be attributed to concomitant TDF use. In clinical trials of viremic and virologically suppressed HIV-infected patients on standard PI-based cART regimens, maintaining PIs while removing the TDF-containing NRTI backbone results in less BMD loss compared with continuing an NRTI-containing regimen [92–94]. Indeed, RTV has been shown to inhibit active TFV secretion by the proximal tubule, resulting in an increase of plasma TFV concentrations by 25–35% [95–97]. However, compared with other drug classes, PIs are associated with decreased BMD regardless of NRTI backbone [58, 84], suggesting that the mechanism of their effects go beyond alterations in TFV metabolism.

III.C Role of altered vitamin D metabolism in HIV-associated bone loss

Vitamin D is important for maintaining adequate serum calcium levels. Inadequate vitamin D (insufficiency and deficiency) can lead to secondary hyperparathyroidism, which in turn stimulates RANKL production that results in osteoclastogenesis and subsequent bone loss [98]. Likely due in part to chronic inflammation and viral replication [99], inadequate vitamin D is highly prevalent in the HIV-infected population, with estimates ranging from 24–87% in different cohorts and geographic locations [100–103]. cART can lead to further reduction of serum 25-hydroxyvitamin D [25-(OH)D] levels, with the greatest decrease seen with the NNRTI efavirenz (EFV) [101]. In addition, PIs have been shown to inhibit conversion of 25-(OH)D to the active metabolite 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] *in vitro* [104], but the clinical importance of these cART-associated alterations in vitamin D metabolism is unclear.

IV. Management of HIV-associated bone loss

Due to the complex pathogenesis of bone loss in the setting of HIV infection, screening, risk factor modification, prophylaxis, and treatment continue to present clinical challenges. Fortunately, there is emerging evidence that HIV-associated bone loss can be attenuated by a variety of interventions including the use of newer bone sparing cART regimens, calcium and vitamin D supplementation, and prophylaxis with bisphosphonates.

IV.A Screening for low BMD in HIV infection

Screening for osteopenia and osteoporosis in HIV-infected individuals remains challenging because current screening modalities, including the Fracture Risk Assessment Tool (FRAX) and DXA, are not validated in the relatively young HIV population. Current recommendations from the Osteo Renal Exchange Program (OREP) suggest that all HIV-infected men between the ages of 40–49 and all HIV-infected premenopausal women 40 years of age or older should undergo screening for 10-year fragility fracture risk with a FRAX assessment every 2–3 years, and that men 50 years of age and older, postmenopausal women, and others at high risk such as those with a history of fragility fracture or who are on chronic glucocorticoid therapy should undergo DXA screening, if available [105•]. European AIDS Clinical Society (EACS) guidelines are generally similar [106]. While these recommendations provide some guidance to practicing clinicians, they are limited by the availability of evidence. DXA and FRAX are each well validated in the general population

[107]; however, their utility in the HIV-infected population is less clear. As the OREP guidelines note, the WHO diagnostic T-score criteria for DXA were designed for postmenopausal women, and men 50 years of age and older, and may not be applicable to a younger, HIV-infected population [4, 105•]. Additionally, studies involving the VACS-VC show that each modality underestimates fracture risk in the setting of HIV infection, although FRAX improves when HIV is included as a cause of secondary osteoporosis [108, 109]. In HIV-infected men in the United Kingdom with a median age of 45 years, FRAX had a poor sensitivity and specificity for osteoporosis compared with DXA [110]. However, alternative methods of screening, such as bone turnover markers, are not practical in the clinical setting, and DXA is often not available in resource-limited settings. The development of a more accurate screening tool for fragility fracture in the setting of HIV infection is needed.

IV.B Prophylaxis and treatment

Several strategies exist for the prevention and management of osteoporosis in the setting of HIV infection. These include selection of cART regimens associated with less BMD loss, calcium and vitamin D supplementation, and potentially, prophylaxis with long-acting bisphosphonates.

IV.B.i Selection of cART regimen—It should first be noted that the benefits of cART far outweigh any risks of future bone disease, and current WHO guidelines recommend initiation of therapy in all HIV-infected persons regardless of CD4 count [111]. The selection of any cART regimen is complex and involves a number of viral and host factors. TDF and PIs, both of which are known to carry a greater risk of bone loss, remain important components of recommended first-line and salvage regimens [111, 112]. However, for HIV-infected patients at particularly high risk for fragility bone disease, it is reasonable to consider cART regimens that are not associated with a higher risk of bone loss, such as abacavir (ABC)-containing NRTI backbones and INSTI-based regimens [105•], or to avoid regimens containing both TDF and a PI. Furthermore, the development of TAF has allowed for the use of a TFV prodrug in some patients for whom TDF has been contraindicated, and may offer an additional option for those at high risk for bone disease. While its long-term effects on fracture are not known, TAF in the short-term has been associated with the same degree of bone loss as other TDF-sparing regimens [76], and is an attractive option for those in whom either ABC is contraindicated, or who have another indication for TFV, such as chronic hepatitis B infection. Although much of the cART-associated bone loss occurs in the first 1–2 years of therapy, there does appear to be some benefit in switching from TDF to TAF [78], and this strategy may be beneficial in those who develop additional risk factors for fragility bone disease while on cART.

IV.B.ii Calcium and vitamin D supplementation—In HIV-infected patients with vitamin D deficiency, supplementation with vitamin D has been shown to improve BMD and reduce PTH levels [113]. Furthermore, Overton *et al.*, in a prospective randomized, double-blind, placebo-controlled trial of cART-naïve HIV-infected individuals initiating TDF/emtricitabine (FTC)/EFV, who had baseline 25-(OH)D levels above 25 nmol/L, showed that calcium and vitamin D3 (cholecalciferol) supplementation attenuates BMD loss by about

50% at 48 weeks [114•]. Therefore, although there is little evidence for widespread use of vitamin D supplementation in the general population to prevent osteoporosis [98], it may be beneficial to prevent bone loss in HIV-infected patients who are initiating cART even in the absence of vitamin D deficiency. Further data on adequate dosing and duration of vitamin D supplementation are lacking and require further study as some data suggest that while a low concentration of vitamin D is needed to prevent osteomalacia, higher doses may block bone formation [115]. Besides, emerging data also seem to suggest that calcium supplementation may be associated with increase risk of CVD [116].

IV.B.iii Bisphosphonates—Bisphosphonates inhibit bone resorption, are the most widely used drugs in the treatment of postmenopausal osteoporosis, and are associated with a decreased risk of fracture in that population [117]. Data regarding their use in the HIV-infected population are also promising: bisphosphonates have been shown to improve BMD in HIV-infected men and women in a number of clinical trials [118–120]. In a meta-analysis of the effects of bisphosphonates in HIV-infected patients with low BMD, a mean increase in BMD of 2.85% at the lumbar spine, 1.18% at the femoral neck, and 2.12% at the total hip was seen at 48 weeks [121]. Interestingly, in a phase IIb trial of viremic, cART-naïve, HIV-infected patients without osteoporosis, our group demonstrated that a single infusion of zoledronic acid at the start of therapy with TDF/FTC + ATV/RTV prevented BMD loss at the lumbar spine, hip and femoral neck at 48 weeks [122••]. Although the long-term effects of bisphosphonates in the HIV population on clinically important outcomes such as fracture remain to be determined, these data are promising. Given the challenge of screening all HIV patients initiating cART, the inaccuracy of current screening tools, and the magnitude of bone loss associated with some of the cART regimens, this is a simple, safe and practical step to completely prevent cART-induced bone loss, especially for patients who are being treated with regimens associated with greater bone loss including TDF- and PI-containing regimens. Further study regarding the use of bisphosphonates for either prevention or treatment of HIV-associated bone loss is warranted.

IV.B.iv Other treatment modalities—There are fewer data regarding the use of other pharmacologic agents for the treatment of low BMD in the setting of HIV infection. Teriparatide is a human recombinant PTH used to treat severe osteoporosis in the general population, but its efficacy in HIV-infected individuals is unknown. There is one case report of successful teriparatide use in an HIV-infected man with severe osteoporosis [123] although robust data regarding its use in HIV-infected patients are lacking. In addition, the 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) simvastatin has been shown to increase osteoblast activity and decrease osteoclastogenesis, and is associated with increased fracture healing in *in vivo* animal models [124], while pravastatin has been shown to prevent PI-induced senescence in MSCs and restore osteoblastic potential *in vitro* [89]. Clinically however, in HIV-infected individuals on stable cART who had heightened immune activation, treatment with rosuvastatin for 96 weeks was not associated with any changes in BMD, although it was associated with improvement in lean body mass [125]. More data on the BMD effects of these medications in HIV-infected patients are needed.

V. Conclusions

HIV infection is associated with a clinically important loss of BMD that is compounded by treatment with cART. This problem is likely to increase as the HIV-infected population ages. Although much remains unknown about the pathogenesis of low BMD in HIV-infected individuals, current research suggests that immune reconstitution is responsible for a significant proportion of the bone loss seen after cART initiation, and that this effect can be mitigated by bisphosphonate therapy. Further research regarding optimal screening modalities and intervals, cART regimens, and treatment modalities are needed to stem the tide of bone loss and fragility fracture in the aging HIV population.

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• Of importance

•• Of major importance

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