Bone Health and Human Immunodeficiency Virus Infection

Jason J. Schafer,[1]* Kristine Manlangit,[1] and Kathleen E. Squires,[2]

[1]Department of Pharmacy Practice, Jefferson School of Pharmacy, Thomas Jefferson University, Philadelphia, Pennsylvania; [2]Division of Infectious Diseases, Thomas Jefferson University Hospital and Professor of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Low bone mineral density is common among persons with human immunodeficiency virus (HIV) infection, and studies reporting increased fracture rates in this patient population are emerging The causes of low bone mineral density, osteoporosis, and fractures in persons with HIV are likely multifactorial, involving traditional risk factors, HIV infection, and exposure to antiretroviral treatment. Specific antiretrovirals such as tenofovir may cause a greater loss of bone mineral density compared with other agents and have recently been linked to an increased risk for fracture. As a result, recent treatment guidelines suggest that clinicians consider avoiding tenofovir as initial therapy in postmenopausal women. Evaluating bone mineral density and vitamin D status in persons with HIV may be important steps in identifying those requiring pharmacotherapy; however, the appropriate timing for bone mineral density and vitamin D screening is uncertain, as is the appropriate method of replacing vitamin D in HIV-positive patients who are deficient. Further study is necessary to definitively determine the approach to evaluating bone health and managing low bone mineral density and vitamin D deficiency in patients with HIV infection.

KEY WORDS human immunodeficiency virus, osteoporosis, osteopenia. bone health, vitamin D.
(**Pharmacotherapy 2013;33(6):665–682) doi: 10.1002/phar.1257**

Several investigations have reported the presence of low bone mineral density (BMD), osteoporosis, and an increased risk of fracture in persons with human immunodeficiency virus (HIV) infection.[1–5] Similar to cardiovascular disease, insulin resistance, and chronic kidney disease, low BMD in patients with HIV may occur more frequently and have an earlier onset compared with the general population.[6] Although it is difficult to determine the definitive cause of low BMD in patients with HIV, it is likely the result of complex interactions between traditional risk factors (low body weight, lack of physical activity, tobacco use, and alcohol use), HIV infection, and antiretroviral therapy (ART).[1–5] In this article, the epidemiology of low BMD, osteoporosis, and fragility fractures in patients with HIV infection will be discussed, as well as the investigations that have examined potential mechanisms of disease. Current recommendations for osteoporosis screening and the management of bone loss in patients with HIV will also be evaluated.

Epidemiology

The prevalence of low BMD among patients with HIV has been evaluated in multiple investigations.[1–3, 7] The findings of these studies repeatedly suggest a greater incidence of osteopenia and osteoporosis in patients with HIV infection compared with their noninfected counterparts. This was recently demonstrated in an observational case-control analysis of patients

*Address for correspondence: Jason J. Schafer, Jefferson School of Pharmacy, Thomas Jefferson University, 901 Walnut Street, Suite 901, Philadelphia, PA 19107-5233; e-mail: jason.schafer@jefferson.edu.

enrolled in the Study to Understand the National History of HIV/AIDS (SUN) cohort.[1] The SUN cohort prospectively followed patients with HIV infection who were receiving treatment at participating clinics in Denver, Minneapolis, Providence, and St. Louis. After enrollment in the cohort, BMD was assessed using dual-energy x-ray absorptiometry (DEXA) scanning, and results were compared with HIV-negative controls. Control patients were matched in a 1:1 manner to cases according to age, race, sex, and body mass index (BMI). They were also currently enrolled in the National Health and Nutrition Examination Study III (NHANES). Patients had a mean age of 41 years and an average BMI of 26.4 kg/m^2. Most patients were male (88%), 60% were white, and 28% were black. The majority of patients were receiving ART (75%) and had an undetectable viral load (60%); 12% were treatment naïve. Overall, patients with HIV infection (625 patients) were more commonly diagnosed with osteopenia (51.7% vs 29.1%) or osteoporosis (9.8% vs 1%) compared with uninfected controls.[1] Prolonged duration of HIV infection (odds ratio [OR] 1.58, 95% confidence interval [CI] 1.09–3.55, p=0.023), age greater than 45 years (OR 1.79, 95% CI 1.14–2.73, p=0.006), low BMI (OR 3.91, 95% CI 2.24–6.89, p<0.001), and baseline CD4$^+$ cell count below 200 cells/mm^3 (OR 2.10, 95% CI 1.16–3.78, p=0.013) were specifically associated with osteoporosis. Strengths of this investigation included a large number of patients from multiple centers and the presence of a control group in the analysis. The data from this study, however, have only been presented as an abstract, and therefore may be limited. In particular, the assessment of antiretroviral factors including individual agents and duration of therapy was unclear.

Findings similar to the SUN cohort were demonstrated in a cross-sectional analysis of 492 patients with HIV infection in the French Aquitaine cohort.[7] The median age of patients was 43 years, 73% of patients were male, and nearly all patients (93.1%) were receiving ART (80% nucleoside reverse transcriptase inhibitors, 28.7% nonnucleoside reverse transcriptase inhibitors [NNRTIs], and 52% protease inhibitors). Total body, lumbar spine, and femoral neck BMD measurements revealed the presence of osteopenia or osteoporosis in 54.6% and 33.7% of men with HIV infection, respectively. Among women, 51.1% were diagnosed with osteopenia, and 8.3% had osteoporosis. On logistic regression analysis, risk factors for the presence of reduced BMD were very similar to those demonstrated in the SUN cohort. Specifically, older age (OR 2.03, 95% CI 1.33–3.08, p=0.0009) and low BMI (OR 14.4, 95% CI 3.68–56.71, p=0.0001) were associated with osteoporosis in men with HIV, whereas older age (OR 1.69, 95% CI 1.10–2.60, p=0.02) and low CD4$^+$ cell nadir (OR 1.43, 95% CI 1.10–1.85, p=0.008) were associated with osteoporosis in women. Although this study is limited by its cross-sectional design and absence of a control group, the findings are supportive of those demonstrated in the SUN cohort.

The findings from the SUN and Aquitaine cohorts also support those of a recent large meta-analysis of 20 cross-sectional studies.[2] The analysis included studies designed to evaluate the prevalence of reduced BMD among patients with HIV between 2000 and 2005. Of 884 patients with HIV, 67% had reduced BMD and 15% had osteoporosis, a value consistent with a 3 times greater risk for osteoporosis than HIV-negative controls. In addition, these investigators found that compared with treatment-naïve patients, those being treated with ART had a 2.4-fold greater risk (OR 2.38, 95% CI 1.2–4.8) of developing osteoporosis, a result that suggests a contributing role of ART in reducing BMD.

The clinical implications of a reduction in BMD include bone fragility and an increased risk for fracture. Recently, an association between HIV infection and the occurrence of fragility fractures has been demonstrated. A retrospective observational cohort study evaluated the fracture incidence (vertebral, wrist, and hip) among 8525 patients with HIV and 2,208,792 HIV-negative patients in a large health care system.[3] Compared with HIV-negative patients, a greater proportion of patients with HIV infection included in the analysis were male (65.2% vs 44.1%). Among both men (5554 patients) and women (2971 patients) with HIV infection, a higher proportion was younger than 60 years old (83.8% vs 44.3% for men 79.1% vs 49.8% for women), a greater proportion was African-American (17.9% vs 6.1% for men, 30.6% vs 6.4% for women), and a lower proportion was Caucasian (55.1% vs 64.3% for men, 39.3% vs 62.6% for women). The overall rate of fracture was 2.87 and 1.77/100 persons for patients with HIV and HIV-negative patients, respectively (p=0.002). Women with HIV infection had a higher prevalence of vertebral (0.81 vs 0.45,

p=0.01) and wrist fractures (1.31 vs 0.83, p=0.01)/100 persons, but they had a similar prevalence of hip fractures (0.47 vs 0.56, p=0.53). In contrast, the fracture prevalence for men with HIV infection was greater in all categories compared with noninfected controls including vertebral fractures (1.03 vs 0.49, p<0.0001), hip fractures (0.79 vs 0.45/100 persons, p=0.001), and wrist fractures (1.46 vs 0.99, p=0.001). Fracture prevalence for both men and women with HIV were significantly higher across all age categories (30–79 yrs) and increased with age at all sites including the wrist, hip, and spine. Overall, this large observational study provides strong evidence to suggest a greater prevalence of fracture among patients with HIV infection compared with noninfected patients across both sexes and among various age groups. The population-based nature of this study, however, prevented the evaluation of fracture risk factors including the roles of antiretrovirals as well as some traditional fracture risk factors such as smoking, alcohol use, low BMI, and receipt of other drugs affecting bone metabolism such as corticosteroids.

In a separate, prospective cohort, investigators from the HIV Outpatient Study (HOPS) also found a greater rate of fracture in patients with HIV.[4] This multicenter study (10 HIV specialty clinics in 8 cities in the United States) evaluated age- and sex-standardized fracture rates for 5826 patients with HIV from 2000–2008. Most patients were male (79%), and many were receiving ART (73%), with a median time since diagnosis of 5.3 years (interquartile range [IQR] 1.3–9.9), median HIV viral load of 11,305 copies/ml (IQR < 400–35,560) and median $CD4^+$ cell count of 372 cells/mm^3 (IQR 196–579). The median age of the patients was 40 years (IQR 38–51), and the median BMI was 24.4 kg/m^2 (IQR 22.3–27.4). Overall, 233 patients (4%) experienced a first-time fracture during the study period. Fracture rates/10,000 persons increased significantly from 57.7 in 2000 to 84.8 in 2002 (p=0.01) but stabilized thereafter, with 89.9 in 2008. In patients aged 25–54 years (87% of all HOPS patients), however, rates of fracture significantly increased throughout the study period from 110/10,000 persons in 2000 to 160/10,000 persons in 2008 (p=0.01). These trends could reflect a true increase in the number of fractures, as patients with HIV infection experienced improved survival during this period. In contrast, they could also be related to an improvement in the capture of fracture data over time or, according to study investigators, an increasing awareness of bone health issues in the HIV population.

In addition to the above evaluation, age- and sex-standardized fracture rates observed in the HOPS cohort were compared with rates observed in over 2.5 million patients from the general population using data from the National Hospital Ambulatory Medical Care Survey (NHAMCS). In this analysis, HOPS patients were more likely to experience fractures at fragility sites (wrist, spine, and femoral neck) and had a higher annual fracture rate than NHAMCS patients (60–90 vs 25–45 fractures/10,000 persons). Also, in patients aged 25–54 years, standardized fracture rates were consistently higher among HOPS patients. In the multivariable risk factor analysis, increasing age (hazard ratio [HR] 1.43 for every 10 yrs, 95% CI 1.03–1.98), hepatitis C coinfection (HR 1.99, 95% CI 1.01–3.90), and BMI less than 18.5 kg/m^2 (HR 3.72, 95% CI 1.14–12.09) were all associated with fragility fractures among patients with HIV. There were no observed associations between the risk of fracture and ART exposure, although an evaluation of specific ART agents was not performed. The risk factor analysis was also limited by a lack of BMD data. Investigators were unable to collect BMD measurements reliably and therefore its contribution to fracture risk could not be assessed properly. Despite these limitations, this large multicenter prospective study supports the results of risk factor analyses performed in other studies of patients with HIV and provides substantial evidence for an overall increased rate of fracture in this population.

Another recent study also evaluated fracture related risk factors among patients with HIV infection.[5] This study investigated male patients enrolled in the Veterans Aging Cohort Study (VACS) between 1997 and 2009 and included 119,318 patients, with approximately 33% (40,115 patients) being HIV-positive. Each patient with HIV infection enrolled in the VACS was followed prospectively for an average of 6 years and matched to two HIV-negative veterans by age, race-ethnicity, sex, and site. The majority (66%) of patients enrolled were less than 50 years old at baseline, and more than half (55%) were African-American or Hispanic. Many comorbid conditions were less common among patients with HIV including coronary artery disease and diabetes mellitus (p<0.0001), although alcohol abuse, drug abuse, current smoking, liver disease, renal disease, and lower

BMI (25 kg/m^2 vs 28 kg/m^2) were all more common in this group ($p<0.0001$). Among men with HIV, 30% had a serum HIV viral load of less than 1000 copies/mL at baseline, and most received ART (75%) during the study period for an average duration of 3 years. Many patients received therapy with a regimen containing a protease inhibitor (37%).

During the study period, there were 1615 fragility fractures (496 hip, 322 vertebral, and 797 upper arm), with a significant difference in the incidence of these fractures identified between patients with HIV infection and the control group (2.5 vs 1.9/1000 person-yrs, $p<0.0001$). Traditional risk factors were again associated with fragility fractures and included older age, white race, alcohol abuse, liver disease, current corticosteroid use, smoking, and proton pump inhibitor use. Having HIV was also associated with an increased fracture risk after adjusting for traditional factors (HR 1.24, 95% CI 1.11–1.39) but was attenuated when BMI was included in the analysis (HR 1.10, 95% CI 0.97–1.25). This finding suggests that HIV infection may not be directly responsible for fractures in men with HIV, but rather is associated with a lower BMI, which can increase fracture risk particularly in patients with other risk factors. In addition, current protease inhibitor use was also associated with fragility fractures (HR 1.41 95% CI 1.16–1.70) in this study. Although this finding indicates a potential role for protease inhibitors in the risk for fracture, the investigators suggest interpreting this result with caution since the use of protease inhibitors may have been a marker for greater HIV disease severity during much of the study period. The investigators also did not evaluate individual protease inhibitors or duration of protease inhibitor therapy and suggest that additional longitudinal evaluations will be necessary to make more definitive conclusions.

Overall, the available epidemiological data demonstrate an increased prevalence of osteoporosis and incident fractures among patients with HIV. They also confirm that several established risk factors for bone loss (older age, low body weight, substance abuse, diabetes, hepatitis C coinfection) are present in this population and have been associated with an increased fracture risk. Many studies also suggest a role for HIV infection alone as a contributing factor to both accelerated bone loss and an increasing risk for fracture. The underlying mechanisms associating HIV infection with bone loss have been thoroughly investigated.

HIV Infection and Bone Loss

The potential link between HIV infection and bone loss can be described in part by the concept of osteoimmunology. Osteoimmunology is a discipline that describes the interface between the immune system and the skeletal system and recognizes that various components of the immune response can have an important impact on regulating bone homeostasis.[8] For example, during HIV infection, levels of various inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), are elevated as part of the immune response but can also stimulate bone resorption.[9] The most important cytokines involved in bone homeostasis are receptor activator of nuclear factor–κ B ligand (RANKL), which stimulates osteoclast production, and osteoprotegrin (OPG), which is released by mature osteoblasts and counteracts the activity of RANKL. Importantly, it has been demonstrated that activated T cells secrete RANKL. Correspondingly, RANKL levels were recently found to be elevated in a cohort of ART-naïve men with HIV and low BMD.[10] The induction of RANKL secretion by activated T cells during HIV infection is likely the result of T cell interactions with the HIV surface protein GP120.[11] This protein has also been found to interact with osteoblast cell membrane receptors and induce TNF-α–mediated osteoblast apoptosis.[9] The overall loss of osteoblasts coupled with an increase in RANKL-mediated osteoclast production provides a potential rationale for the bone losses observed among patients with HIV.

Independent of RANKL secretion, T cells may have additional mechanisms for affecting bone remodeling during HIV infection. The first involves the active secretion of a second osteoclast-stimulating cytokine called secreted osteoclastogenic factor of activated T cells (SOFAT).[12] The second involves CD4$^+$ T-cell depletion during HIV infection and subsequent disruption of essential T cell and B cell interactions. Under basal physiologic conditions, B cells are a critical source of OPG and are therefore important for maintaining bone homeostasis.[13] During HIV infection, both B cell function and interaction with CD4$^+$ T cells can be compromised, leading to diminished B cell OPG production.[14]

Taken together, the above mechanisms suggest a significant impact of HIV infection on bone remodeling. The impact of each of these mechanisms alone or in combination is uncertain. The ongoing study of osteoimmunology in the context of HIV infection is necessary to truly understand the primary mechanisms of disease.

Antiretroviral Therapy and Bone Loss

If HIV infection alone is associated with losses in BMD, it would be reasonable to conclude that controlling HIV with ART could prevent and/or perhaps reverse HIV-associated BMD losses; however, the Strategies for Managing Antiretroviral Therapy (SMART) study has suggested otherwise.[15] In this investigation, patients with HIV and a $CD4^+$ cell count greater than 350 cells/mm^3 (5472 patients) were randomized to receive either continuous ART (2752 patients) or $CD4^+$ cell count–guided ART interruptions (2720 patients) over a 4-year period between 2002 and 2006. Patients receiving ART interruptions were found to have an increased risk of death and opportunistic disease, and, as a result, this study was terminated early. Before termination, a substudy was developed to evaluate the effects of the two treatment strategies on BMD (214 patients). Each patient (continuous ART = 98, intermittent ART = 116) had BMD assessments at baseline and annually thereafter using DEXA scanning of the total hip and DEXA scanning with quantitative computed tomography (qCT) of the lumbar spine. The median age of patients was 44 years, and the median time for follow-up was 2.4 years. Use of thymidine analogues (zidovudine and stavudine) was common (58.7%) in this patient population, as was use of protease inhibitors (45.2%) and NNRTIs (49%). Treatment groups were well balanced, although there was a higher proportion of women (24.5% vs 14.7%) and current smokers (51% vs 41.4%) in the continuous ART group, and those receiving continuous ART were more likely to have viral suppression (54.1% vs 37.9%).

With continuous ART, hip BMD decreased by 0.8%/year ($p<0.001$), whereas spine BMD decreased by 0.4%/year ($p=0.04$) and 2.4%/year ($p<0.001$) measured by DEXA and qCT scanning, respectively. In addition, patients receiving continuous ART reported more grade 4 fractures than patients in the comparator group (HR 4.91, 95% CI 1.1–22.5, $p=0.04$).[15] In the ART interruption group, BMD measurements remained stable or increased after 1 year. Overall, estimated differences in BMD changes (continuous ART vs ART interruption) through the follow-up period were 1.4% (95% CI 0.6–2.3%, $p=0.002$) for hip BMD, 1.3% (95% CI 0.1–2.4%, $p=0.03$) for spine BMD measured by DEXA scanning, and 3% (95% CI 0.8–5.2%, $p=0.007$) for spine BMD measured by qCT. The treatment effect of these BMD changes were consistent and did not vary according to age, sex, race, or other risk factors such as low BMI, smoking, alcohol use, nadir $CD4^+$ cell count, or viral load. Other risk factors for BMD losses that were evaluated included individual ART agents. Interestingly, no consistent associations could be identified with specific agents when all BMD measurements were included. For instance, lopinavir-ritonavir, zidovudine, and stavudine were all associated with BMD decreases in the spine but not the hip.

The results of the SMART study, although limited by a small sample size and modest follow-up time, provide substantial evidence for BMD losses in association with ART. The findings from this study have been supported by the results of additional studies, and together these data suggest that a clinically significant loss of BMD (2–6%) should be expected during the first 1–2 years after ART initiation irrespective of antiretroviral choices, a rate of bone loss similar to that observed in perimenopausal women.[16–18] Additional data suggest that bone losses with ART appear to stabilize after this initial time period and may even begin to recover, though are not likely to return to baseline levels.[19, 20]

Although the association between BMD losses after ART initiation is well established, the association between ART and fracture risk found in the SMART study has not been consistent in other investigations. Most recently, a large case-control study of patients with HIV evaluated fracture risk factors among 2477 patients with a fracture and 9144 matched controls.[21] Patients were enrolled between 1997 and 2008, were mostly men (72.2%), and had an average age of 40 years. Although traditional risk factors were again strongly associated with bone disease and fractures in this cohort, overall exposure to ART significantly reduced fracture risk (OR 0.64, 95% CI 0.58–0.71, $p<0.0001$). The reduced risk was demonstrated across multiple drug classes and was found with any duration of ART exposure. Moreover, an incremental reduction of fracture risk occurred with an increasing duration of ART. Interestingly, an initial exposure (0–3 mo) to some ART agents (nevirapine,

abacavir, didanosine, nelfinavir, ritonavir and stavudine) led to an initial increased risk for fracture that declined over time and actually became protective against fracture with continued exposure. Other agents had no impact on fracture risk over time (atazanavir, enfuvirtide, fosamprenavir, indinavir, lopinavir, tipranavir, and zalcitabine) and some consistently reduced fracture risk (efavirenz, emtiricitabine, lamivudine, tenofovir, and zidovudine). A few agents were associated with an increased fracture risk (darunavir [16 patients] and delavirdine [20 patients]) but very few case patients were exposed to these agents, and additional study is warranted before definitive conclusions can be made. Overall, the major finding of this study indicates that despite possible BMD losses early after ART initiation, overall ART exposure may be protective against fractures long term. It may also indicate that early BMD losses may stabilize over time, and continuous losses related to ART do not occur. Importantly, multiple longitudinal analyses have demonstrated BMD stabilization over time with the continued use of ART, despite early losses.[16, 22, 23] As a result, it appears that the most significant bone loss for patients with HIV infection occurs during an acute period of time after ART initiation.

The reason for bone loss in the acute period of time after ART initiation is likely multifactorial but may include immune reconstitution (or T cell recovery) and its impact on the RANKL-OPG system. In a recent study, investigators hypothesized that a relationship may exist between bone turnover and the significant recovery of T cells after ART is started.[24] A total of 20 ART-naïve patients were given therapy with tenofovir-emtricitabine plus lopinavir-ritonavir and observed for changes in bone turnover markers for 24 weeks. During the study period, concentrations of osteoclastic cytokines, including both serum TNF-α (+70%) and RANKL (+150%), were increased compared with baseline. Elevations in these markers may be the direct result of an increasing number of available T cells with ART, leading to increased bone resorption.[24] Elsewhere, it has been demonstrated that levels of OPG are significantly decreased after ART initiation.[25] The imbalance between RANKL and OPG induced by ART and immune reconstitution may compound the imbalance already present due to HIV infection alone, resulting in additional BMD losses. This hypothesis requires further study to determine the definitive causes of BMD losses in this setting.

Individual Antiretroviral Agents and Bone Loss

Although the initiation of ART has been consistently correlated with an initial decline in BMD, it appears that some ART agents may cause a more pronounced decrease than others. In vitro, certain protease inhibitors have been found to impact bone homeostasis by inhibiting osteoclast and/or osteoblast differentiation, whereas other studies have noted an inhibition of 1-α-hydroxylase associated with protease inhibitors that can lead to a reduction in calcitriol.[26–29] Despite the identification of these mechanisms, the results of clinical trials evaluating protease inhibitors and BMD losses have been conflicting, and definitive associations have not been established.[17, 30, 31]

Efavirenz, an NNRTI, has also been associated with BMD losses.[32–34] These losses may be the result of efavirenz-mediated induction of active vitamin D metabolism to inactive compounds through cytochrome P450 pathways. In a recent study, vitamin D levels were measured from stored blood samples in 87 ART-naïve patients before initiating therapy with efavirenz-containing (51 patients) or non–efavirenz-containing (36 patients, 89% taking protease inhibitors) HIV treatment regimens.[33] The median concentration was 22 ng/mL (IQR 13.4–30), and 33% of patients had hypovitaminosis (serum 25-hydroxyvitamin D [25-OH-D] level $\leq$ 15 ng/mL). After 6–12 months of ART, repeat vitamin D level measurements were obtained. Relative to patients receiving non–efavirenz-containing regimens, those receiving efavirenz had a mean $\pm$ SD 5.3 ng/mL $\pm$ 1.5 decline in vitamin D level (p=0.001) after adjustments were made for baseline levels, race, and season (summer vs other seasons). Also, on multivariate analysis, the risk of hypovitaminosis after ART initiation was significantly higher in patients receiving efavirenz (OR 1.8, 95% CI 1.2–2.8, p=0.007).

Similarly, in a cross-sectional analysis of 843 patients with HIV infection seen in a large clinic in London and receiving ART (78% protease inhibitor-based, 31% NNRTI-based), efavirenz (OR 1.0003 per day of exposure, 95% CI 1.0001–1.0004, p=0.001) but not other ART agents was associated with severe vitamin D deficiency (25-OH-D level $<$ 10 ng/mL).[34] Furthermore, correcting for season, nadir $CD4^+$ cell count, and ethnicity, patients exposed to efavirenz for 30–90 days had significantly lower vitamin D levels compared with those exposed for less than 30 days (8.6 ng/mL vs 13.9 ng/mL, p=0.04).

Overall, based on current data, it appears that the initiation of efavirenz can be accompanied by lower vitamin D concentrations; however, current studies are limited by their cross-sectional designs and their inability to study the effects of efavirenz on vitamin D deficiency over time. Also, clinical data establishing specific links between efavirenz, vitamin D deficiency, and actual BMD losses are not available, and additional research is needed in this area.[32–35]

Perhaps the most compelling data from investigations evaluating a link between a specific antiretroviral agent and BMD losses have occurred with tenofovir. This agent has been associated with proximal tubule toxicity that can result in phosphate wasting, hypophosphatemia, and decreased bone mineralization.[36] Clinically, multiple trials comparing tenofovir with non–tenofovir-containing regimens have consistently found this agent to be associated with significant decreases in BMD.[16, 20, 37] Of interest, BMD losses with tenofovir have been observed in various clinical scenarios and patient populations. These include adults initiating their first antiretroviral regimen,[16, 20, 37] treatment-experienced children (8–16 yrs old) initiating tenofovir for the first time,[38] adults with virologic suppression who have switched to a new regimen containing tenofovir,[39, 40] postmenopausal women receiving tenofovir-containing regimens,[41] and HIV-seronegative men randomized to receive tenofovir and emtricitabine for preexposure prophylaxis.[42] Compared with non–tenofovir-containing regimens, the increased BMD losses with tenofovir-containing regimens have ranged from 0.5–2%, depending on the BMD measurement site and the study population.[17] The greatest declines may occur in young children (~10 yrs old), perhaps due to the accelerated rate of bone turnover present in this population.[38] Overall, given the consistency with which this link has been observed across a variety of settings and patient populations, it appears that greater BMD losses should be expected with tenofovir exposure.

The clinical significance of these BMD losses has been uncertain until a recent study demonstrated an association between tenofovir and an increased risk for fracture.[31] This was a retrospective cohort study that evaluated 56,660 male veterans with HIV (mean follow-up time of 5.4 yrs) and their cumulative exposures to antiretrovirals between 1988 and 2009. The majority of patients (57%) entered the cohort during the highly active antiretroviral therapy (HAART) era (1996–2009), and most had been exposed to ART on entry (86%). A total of 951 individual patients had at least one osteoporotic fracture during the study period (124 vertebral, 486 wrist, 341 hip). Aside from traditional risk factors such as increasing age (HR 1.50/10-yr increase, 95% CI 1.37–1.64, p<0.0001), and BMI less than 20 kg/m^2 (HR 1.48, 95% CI 1.18–1.87, p=0.007), which were again strongly associated with incident fractures, cumulative use of tenofovir during the HAART era was independently associated with fracture risk (HR 1.12, 95% CI 1.03–1.21, p=0.011). This risk increased even further when tenofovir was combined with a boosted protease inhibitor (HR 1.16, 95% CI 1.04–1.30). Boosted protease inhibitor exposure alone was also associated with an increased risk for fracture (HR 1.08, 95% CI 1.01–1.15, p=0.026), but unlike tenofovir exposure, this association did not remain statistically significant when multivariate analyses controlled for both the presence of traditional fracture risk factors as well as concomitant ART exposures (HR 1.09, 95% CI 1.00–1.20, p=0.051). The findings of this study require confirmation with additional prospective analyses but do indicate the potential for not only BMD losses with tenofovir, but also an increased risk for fracture. Current HIV treatment guidelines do not suggest removing or replacing tenofovir from a current regimen, nor do they suggest avoiding tenofovir as initial therapy in older men as a result of this study. At the very least, however, monitoring for BMD changes in older men receiving tenofovir may be warranted.

In contrast, recent HIV treatment guidelines do suggest that clinicians consider avoiding tenofovir in postmenopausal women with HIV, as a clinically significant decline in BMD may be observed.[43] This suggestion is based on data from a recent longitudinal study analyzing BMD changes among 128 postmenopausal women (73 HIV positive) at two New York medical centers between 2002 and 2007.[41] Women with HIV in this study were younger (56 vs 59 yrs, p<0.05) and had a lower BMI (28 vs 31 kg/m^2, p<0.01) than their HIV-negative counterparts. The average duration of HIV infection was 8.6 years, and most patients (78%) were receiving ART for more than 3 years. At baseline, BMD adjusted for age, race, and BMI, was significantly lower in women with HIV at the lumbar spine (p=0.02), total hip (p<0.01), distal radius (p=0.03), and ultradistal radius (p=0.02). Measurements of BMD were performed annually after enrollment and uncovered higher rates of bone loss in

women with HIV, including statistically significant BMD changes as indicated by T scores at the lumbar spine (−1.2 vs −0.5, p=0.0009), distal radius (−1.1 vs −0.3, p=0.006) and ultradistal radius (−1.2 vs −0.7, p=0.02). In a multivariate analysis, HIV status was independently associated bone loss after adjustments were made for traditional risk factors. Among patients receiving ART, bone loss could not be correlated with protease inhibitor use or NNRTI use at any site. In contrast, the annual rate of bone loss was found to be greater for patients receiving tenofovir (12 patients) versus non–tenofovir-containing regimens (45 patients) at the lumbar spine (−2.8 vs −0.7, p=0.01), the distal radius (−2.3 vs −0.8, p=0.02), and the ultradistal radius (−2.2 vs −1.0, p=0.01). The rate of bone loss in the lumbar spine specifically remained greater in the tenofovir group after adjustments for traditional risk factors such as older age, white race, and low BMI (p=0.01). Despite the BMD losses associated with HIV and tenofovir in this study population, no significant differences were found in the rate of incident fractures between women with HIV (10%) and HIV-negative women (8%). Again, the results of this study require confirmation with additional prospective analyses of larger study populations but have impacted recommendations for therapy in postmenopausal women with HIV infection.[43]

Screening for Osteoporosis in Persons with HIV

Recent recommendations for the screening and management of osteoporosis in patients with HIV have been developed.[44] These recommendations are based on the National Osteoporosis Foundation (NOF) guidelines for preventing and treating osteoporosis in the general population, with a few key differences. The NOF recommends evaluating for osteoporosis by using a BMD DEXA scan for all of the following patients: adults aged 50 years and older who have sustained a fragility fracture, women aged 65 years and older, and men aged 70 years and older.[45] They also suggest screening in younger postmenopausal women and men aged 50 years or older when other risk factors for premature bone loss are present. These risk factors currently do not include HIV or ART but do include a comprehensive list of lifestyle factors, genetic factors, hypogonadal states, and various endocrine, gastrointestinal, hematologic, and autoimmune diseases. In contrast, the recent recommendations for patients with HIV include HIV as a significant risk factor for osteoporosis and therefore recommend DEXA screening in all HIV-positive men aged 50 years or older and all postmenopausal women.[44] The overall risks and benefits of this approach have not been established, but the screening of all postmenopausal women with HIV may be particularly important, given the greater bone losses and increased bone turnover markers found in this population compared with HIV-negative controls.[41]

Similar to the general population, a diagnosis of osteopenia (T score between −1 and −2.5 at the femoral neck or spine) or osteoporosis (T score of the hip, femoral neck or spine ≤ −2.5) in a patient with HIV infection warrants evaluation and management of secondary causes.[44, 45] These can include, but are not limited to, vitamin D deficiency, hyperthyroidism, adrenal insufficiency, kidney disease, poor nutrition, and the use of concurrent drugs linked to low BMD such as glucocorticoids and proton pump inhibitors.

Vitamin D Deficiency

Similar to the general population, vitamin D deficiency is common in patients with HIV. In an analysis of baseline data from the SUN cohort (672 patients), a total of 70.3% (95% CI 68.1–74.9%) of patients were either vitamin D deficient or insufficient (serum 25-hydroxyvitamin D levels < 30 ng/mL) compared with 79.1% (95% CI 76.7–81.3%) of U.S. adults.[46] Factors associated with low vitamin D levels in this cohort were similar to those often found in the general population and included the following: black race (OR 4.51, 95% CI 2.59–7.850), Hispanic ethnicity (OR 2.78, 95% CI 1.31–5.90), hypertension (OR 1.88, 95% CI 1.10–3.22), lack of exercise (OR 3.14, 95% CI 1.80–5.47), and a higher BMI (OR 1.04, 95% CI 1.00–1.09). Low vitamin D levels were also associated with exposure to efavirenz (OR 1.98, 95% CI 1.18–3.34), an association that has been found in other observational studies.[32–35] Consistent with other investigations, the results of the SUN cohort do not suggest that vitamin D deficiency is more common in patients with HIV compared with the general population.[35, 47–49] In addition, it is not apparent that HIV alone is a risk factor for developing low vitamin D levels. Rather, the risk factors for vitamin D deficiency in those with and without HIV appear to be similar.

The clinical consequences of low vitamin D levels can be significant. In addition to its

impact on bone health, deficiency in the general population has been associated with hypertension, cardiovascular disease, insulin resistance, malignancy, cognitive impairment, and even all-cause mortality.[50–53] Importantly, for the HIV population, vitamin D is also an immune modulator, and deficiency has been associated with disease progression and death.[54] These associations have not been firmly established, and the overall benefit of vitamin D replacement is unclear for the treatment or prevention of non-musculoskeletal conditions.[55] The overall prevalence of vitamin D deficiency among patients with HIV, in addition to its potential clinical consequences, underscores the importance of developing a validated approach to the assessment and management of vitamin D deficiency in this patient population.

Unfortunately, consensus recommendations for the screening of vitamin D deficiency in patients with HIV are not available. For instance, whereas the European AIDS Clinical Society recommends universal screening for vitamin D deficiency in all patients with HIV at baseline and at 2-year intervals, the Endocrine Society recommends only targeted screening for those at a higher risk for deficiency, including those patients receiving HIV drugs.[55, 56] These discrepant recommendations are likely the result of a shortage of evidence from randomized controlled trials demonstrating clinical and/or cost-effective benefits to vitamin D screening in patients with HIV.

Without consensus recommendations or sufficient evidence to direct vitamin D screening in patients with HIV, the approach to screening should follow recommendations for the general population. The Endocrine Society and NOF agree that vitamin D screening in the general population should be performed in select patients, most commonly as part of the work-up for secondary causes of osteoporosis or fragility fractures.[45, 55] They also recommend against universal vitamin D screening, as the feasibility, cost-effectiveness, and overall health benefits of this approach have not been demonstrated.

When screening is indicated, measuring 25-OH-D levels is preferred. Levels less than 30 ng/mL (75 nmol/L) are generally considered insufficient, whereas levels less than 20 ng/mL (50 nmol/L) represent vitamin D deficiency.[55] To maximize bone health and muscle function in all adults from the general population, both the Institute of Medicine and the Endocrine Society recommend a daily intake of vitamin D between 600 and 800 IU depending on age and sex.[55, 57] In patients who meet criteria for deficiency, the current guidelines recommend vitamin D repletion with 50,000 IU of vitamin D_2 or D_3 once a week for 8 weeks to achieve a level greater than 30 ng/mL. Patients should then receive maintenance therapy with 1500–2000 IU daily. In patients with insufficiency, daily maintenance therapy with 1500–2000 IU is recommended.[55]

Importantly, the dosing strategies recommended for vitamin D repletion in current guidelines have not been validated in patients with HIV, and data from controlled trials evaluating vitamin D replacement in this population are limited.[58, 59] One recent trial randomized 45 adults with HIV and baseline 25-OH-D levels less than 20 ng/mL to oral vitamin D_3 4000 IU/day or placebo for 12 weeks.[58] All patients had an undetectable viral load and had been receiving a stable ART regimen at study entry. At baseline, 25-OH-D levels were very low (median 9.0 ng/mL, range 7.1–13.1), and after 12 weeks of therapy, these levels had only a modest improvement (+4.6 ng/mL [range −1.3 to +7.4 ng/mL] for the vitamin D group vs –1.8 ng/mL [range −2.9 to +0.1 ng/mL] for the placebo group, p=0.018). This improvement was similar whether patients were receiving efavirenz-based (change of 4.6 ng/mL [range −0.9–7.0 ng/mL]) or non–efavirenz-based regimens (change of 5.1 ng/mL [range −1.1–8.5 ng/mL]). Overall, the results of this study are difficult to interpret since the vitamin D replacement strategy did not coincide with current guidelines. All patients in the study were vitamin D deficient and according to guidelines should have received repletion with 50,000 IU of vitamin D_2 or D_3 once weekly for 8 weeks. Furthermore, this study and others of similar design are limited by a small sample size, short duration of follow-up, and variable dosing strategies.[58, 59] Based on the limited data available, the current understanding of vitamin D replacement in patients with HIV is incomplete. Additional studies are necessary to identify the most appropriate method of vitamin D repletion in this population. Until data are available, it would be reasonable for clinicians to provide vitamin D replacement to their patients with HIV according to current guidelines for the general population.

Calcium Intake

In addition to adequate vitamin D intake, the NOF, the Endocrine Society, and the Institute of

Medicine recommend adequate calcium intake as a strategy to reduce fracture risk.[45, 55, 57] Recent recommendations for the adequate intake of elemental calcium suggest 1000 mg/day for men aged 31–70 years, 1000 mg/day for women aged 31–50 years, 1200 mg/day for women aged 51–70 years, and 1200 mg/day for both men and women over age 70 years.[57] It is important to note that these recommendations were developed for the general population and have not been validated in patients with HIV.

Calcium supplementation can be considered for reaching the recommended level of intake, although increasing dietary consumption should be the first-line approach.[45] Supplementation can occur with the use of agents containing calcium carbonate (containing 40% elemental calcium), calcium citrate (21%), calcium lactate (18%), calcium gluconate (9%) or various phosphate salts (23–39%). Calcium carbonate contains the most elemental calcium, is well tolerated, and is absorbed when administered with a meal. Levels of intake that surpass current recommendations and reach 2000 mg/day or more of calcium can increase the risk of adverse events such as the occurrence of kidney stones.[57] Also, concern has been raised given the recent findings of an increased risk for cardiovascular events with calcium supplementation, but definitive associations have not been made.[60]

Managing Osteoporosis in Persons with HIV

After evaluating and managing secondary causes of osteoporosis, pharmacologic therapy should be administered to the following patients: postmenopausal women or men aged 50 years and older with a T score of the hip, femoral neck, or spine of −2.5 or less (osteoporosis) and patients with a history of a fragility fracture.[44, 45] Also, those with osteopenia (T score between −1 and −2.5 at the femoral neck or spine) should receive treatment when their calculated 10-year probability of a hip fracture or major osteoporosis-related fracture is at least 3% or 20%, respectively, using the World Health Organization Fracture Risk Assessment Tool (FRAX).[45] The FRAX system uses classic risk factors to calculate a 10-year probability of fracture and identify patients who require close BMD monitoring and/or pharmacologic intervention. Of note, the FRAX system has not been fully validated in patients with HIV infection, and preliminary investigations in this group have found an underestimation of bone loss and fracture risk.[61, 62] These studies suggest that the underestimated risk may be due to factors that are unique to patients with HIV who are not captured in the FRAX assessment. Further study is necessary to define the role of the FRAX system in patients with HIV infection.

Bisphosphonate Therapy

Patients meeting criteria for pharmacologic treatment should receive therapy with a bisphosphonate or a second-line agent in combination with adequate calcium and vitamin D intake.[45] Bisphosphonates are approved by the United States Food and Drug Administration (FDA) for the prevention and treatment of postmenopausal osteoporosis. They decrease bone resorption by inhibiting the action of osteoclasts in areas of increased bone turnover.[63] Several studies have shown the efficacy of using bisphosphonates such as alendronate and zoledronic acid to improve BMD in patients with HIV infection (Tables 1 and 2).[64–71]

Alendronate

Alendronate is FDA-approved for the treatment and prevention of osteoporosis in postmenopausal women.[72] It is also approved as a treatment to increase bone mass in men with osteoporosis.[72] A number of investigations have evaluated the efficacy of alendronate in increasing BMD in patients with HIV infection (Table 1).[64–68] Treatment groups in all studies received oral alendronate 70 mg/week. In all but one study,[68] patients receiving alendronate had a significant increase in BMD of the lumbar spine.

The most recent investigation was a 96-week, placebo-controlled study of 44 individuals with HIV and osteoporosis.[64] This study found a significant increase in BMD at the lumbar spine in patients who received alendronate 70 mg once/week in combination with calcium and vitamin D compared with patients taking calcium and vitamin D alone (7.1% vs 1.0%, p=0.0003). Similar results were found in a separate prospective, randomized, placebo-controlled trial of 82 men and women with HIV and decreased BMD.[65] This study reported that administration of weekly alendronate in combination with calcium and vitamin D for 1 year significantly increased lumbar spine BMD again compared with calcium and vitamin D supplementation alone (3.4% vs 1.1%, p=0.03). A third prospective study, a randomized, open-label trial of 31 patients with

Table 1. Summary of Alendronate Efficacy Studies in Patients with Human Immunodeficiency Virus Infection

Intervention	Study Duration (wks)	Patient Population	Results[a]	p Value
Alendronate 70 mg/week + calcium 500 mg–vitamin D 400 IU/day vs placebo + calcium 500 mg–vitamin D 400 IU/day[64]	96	44 patients with T score ≤ –2.5: (95% men)	alendronate 7.1% vs placebo 1%	0.0003
Alendronate 70 mg/week + calcium 1000 mg–vitamin D 400 IU/day vs placebo + calcium 1000 mg–vitamin D 400 IU/day[65]	48	82 patients with T score ≤ −1.5: (71% men)	alendronate 3.4% vs placebo 1.1%	0.03
Alendronate 70 mg/week + calcium 1000 mg–vitamin D 400 IU/day vs placebo + calcium 1000 mg–vitamin D 400 IU/day[66]	48	31patients with T score ≤ −1.0: (87% men)	alendronate 5.2% vs placebo 1.3%	0.007
Alendronate 70 mg/week + dietary counseling vs placebo + dietary counseling[67]	96	25 patients with T score ≤ −2.5	alendronate 24% vs dietary counseling 0%	0.015
Alendronate 70 mg/week + calcium 1000 mg–vitamin D 500 IU/day vs placebo + calcium 1000 mg–vitamin D 500 IU/day[68]	52	41 patients with T score ≤−1.0	alendronate 4% vs placebo 3.7%	NS (p value not supported)

NS = not significant.
[a]Percent increase in T score at the lumbar spine.

Table 2. Summary of Zoledronate Efficacy Studies in Patients with Human Immunodeficiency Virus Infection

Intervention	Study Duration	Patient Population	Results[a]	p Value
Zoledronate 5-mg i.v. infusion × 1 + calcium 1000 mg–vitamin D 400 IU/day vs placebo infusion × 1 + calcium 1000 mg–vitamin D 400 IU/day[69]	12 mo	30 patients with T scores of −1.5 to −3.5	Zoledronate 3.7 ± 4.1% vs placebo 0.7 ± 3.1%	0.04
Zoledronate 4-mg i.v. infusion/yr + calcium 400 mg/day + vitamin D 1.25 mg/mo vs placebo infusion/yr + calcium 400 mg/day + vitamin D 1.25 mg/mo[70]	2 yrs	43 patients with T scores < −0.5	Zoledronate 8.9% vs placebo 2.6%	<0.001
	4-yr extension study[71]	35 patients	Zoledronate group had further increase of 3.7% (0.3–7.0%)	0.03

[a]Percent increase in T score at the lumbar spine.

HIV infection and osteopenia or osteoporosis has also been performed.[66] This study again found a significant increase in the lumbar spine BMD after 48 weeks of treatment with alendronate plus vitamin D and calcium compared with vitamin D and calcium alone (5.2% vs 1.3%, p=0.007). Lastly, a small, open-label study of 25 adults with HIV and osteoporosis also showed significant improvements in BMD in patients treated with once-weekly alendronate plus dietary counseling compared with dietary counseling alone (24% vs 0%, p=0.015).[67]

Although these studies have found that alendronate improves BMD in patients with HIV infection, its effect on decreasing osteoporotic fractures was not evaluated due to one or more of the following reasons: small sample size, short duration of the study, or patients were relatively younger and thus less prone to experiencing fractures. Nonetheless, these studies show that alendronate is an effective treatment option in patients with HIV infection and osteoporosis.

The recommended dose of alendronate is 10 mg/day or 70 mg/week.[72] The tablet must be taken with 6–8 oz of plain water at least 30 minutes before the first food, drink, or drug treatment for the day. Patients should be advised to not lie down for at least 30 minutes after taking the drug to decrease the occurrence of adverse effects.

Zoledronic Acid

Zoledronic acid is approved for the treatment and prevention of osteoporosis in postmeno-

pausal women.[73] It is also approved for the treatment and prevention of osteoporosis in men and women who receive glucocorticoid therapy for at least 12 months.[73] Two trials have demonstrated its efficacy in increasing BMD in patients with HIV infection.[69, 70] In both trials, patients in the treatment group received intravenous zoledronic acid once/year; all patients received calcium and vitamin D supplementation. The first trial was a randomized, double-blind trial conducted in 30 men and women with HIV and osteopenia or osteoporosis who were followed for 12 months after administration of zoledronic acid or placebo infusions.[69] The study found a significant increase in BMD at the hip (mean ± SD 3.2 ± 2.2% vs −1.8 ± 9.3%, p=0.016) and lumbar spine (3.7 ± 4.1% vs 0.7 ± 3.1%, p=0.04) in the zoledronic acid group compared with the placebo group. The second trial was a 2-year, randomized, placebo-controlled trial of 43 men with HIV and T scores below −0.5.[70] The trial found that BMD significantly increased at the lumbar spine with zoledronic acid plus calcium and vitamin D compared with calcium and vitamin D supplementation alone (8.9% vs 2.6%, p<0.001). An extension of this trial showed that between 1 year and 5 years after the second zoledronic acid dose, lumbar spine BMD increased another 3.7% (0.3–7.0%; p=0.03).[71]

Overall, these studies demonstrated an improvement in BMD with zoledronic acid in patients with HIV infection. Unfortunately, both studies were small and included mostly male patients. As a result, findings may not be generalizable to all patients with HIV infection. In addition, the annual cost associated with once-yearly zoledronic acid might deter patients from receiving this drug (~$1000/yr vs ~$160/yr for alendronate). Nevertheless, zoledronic acid is effective and offers good tolerability and a low drug burden, which makes it a viable therapy option for some patients.

The recommended treatment dosage of zoledronic acid for the general population is a 5-mg intravenous infusion administered over at least 15 minutes once/year.[73] Acetaminophen may be used as premedication to prevent acute-phase reaction symptoms such as fever, chills, flushing, bone pain, and myalgias.

Ibandronate

Ibandronate is approved for the prevention and treatment of postmenopausal osteoporosis.[74] No clinical trials have been conducted to determine the efficacy of ibandronate in increasing BMD in patients with HIV infection. The dosages of oral ibandronate are 2.5 mg/day or 150 mg/month. Patients with osteoporosis and a high pill-burden may benefit from the 3-mg intravenous injection preparation, which is administered every 3 months. The tablet must be taken with 6–8 oz of plain water at least 30 minutes before the first food, drink, or drug treatment for the day. Patients should be advised to not lie down for at least 60 minutes after taking the drug to decrease occurrence of adverse effects.[74]

Risedronate

Risedronate is approved for the treatment and prevention of osteoporosis in postmenopausal women.[75] It is also approved as a treatment to increase bone mass in men with osteoporosis.[75] No clinical trials have been conducted to determine the efficacy of risedronate in increasing BMD in patients with HIV infection. Dosage forms of risedronate are available for daily, weekly, or monthly administration. Health care providers who are concerned with increasing the pill burden for patients receiving multidrug regimens with daily or weekly administration of bisphosphonates may opt to prescribe risedronate 75 mg on two consecutive days of the month or 150 mg once/month. As with alendronate and ibandronate, the tablet must be taken with 6–8 oz of plain water at least 30 minutes before the first food, drink, or drug treatment for the day. Patients should be advised to not lie down for at least 30 minutes after taking the drug to decrease occurrence of adverse effects.[75]

Adverse Effects of Bisphosphonates

The most common adverse effects of bisphosphonates are gastrointestinal disturbances.[63] Oral bisphosphonates—alendronate, ibandronate, and risedronate—share similar gastrointestinal side effects: difficulty swallowing, inflammation of the esophagus, and gastric ulcer.[63] In a study that evaluated the incidence of upper gastrointestinal irritation in postmenopausal women with osteoporosis, the proportion of patients taking alendronate who experienced upper gastrointestinal adverse effects that were serious or led to drug discontinuation was 20.3%.[76] Treatment with ART can also cause gastrointestinal adverse effects.[77] Thus, caution

is warranted when initiating bisphosphonates in patients with active upper gastrointestinal problems who are receiving ART. Gastrointestinal adverse effects may be minimized with proper administration of tablets or by using intravenous formulations.

When using intravenous infusions, transient fever and flu-like symptoms may be experienced (10% with ibandronate and 44% with zoledronate).[73, 74] Premedication with acetaminophen may be considered to prevent these symptoms. Osteonecrosis of the jaw is a rare but serious complication seen in patients receiving usual doses of bisphosphonates.[72] Known risk factors of osteonecrosis of the jaw include invasive dental procedures, diagnosis of cancer, concomitant chemotherapy, concomitant use of corticosteroids, poor oral hygiene, and comorbid disorders.[72] Patients who receive zoledronic acid may be at a higher risk for developing atrial fibrillation compared with patients receiving placebo (1.3% vs 0.4%).[73] Other adverse effects of bisphosphonates include electrolyte imbalances (hypocalcemia, hypophosphatemia, and hypomagnesemia), musculoskeletal pain (4.1% with alendronate, 10% with zoledronic acid, nearly 6% with ibandronate, and as high as 24% with risedronate), and headache (2.6% with alendronate, 5.8% with ibandronate, and 18% with risedronate).[72–75] Cases of ocular inflammation, such as uveitis and scleritis have been reported rarely during postmarketing use but were not observed in clinical trials.[78]

Recent reports have associated bisphosphonate use with atypical fractures of the femoral shaft.[79] In response, a review of 284 records of 14,195 women in three large, randomized bisphosphonate trials suggested that the occurrence of atypical femur fractures was very rare, even among women who had been treated with bisphosphonates for as long as 10 years (HR 1.03, 95% CI 0.06–16.46 for 3–5 yrs of alendronate use, HR 1.50, 95% CI 0.25–9.00 for 3 yrs of zoledronic acid use, and HR 1.33 95% CI 0.12–14.67 for 5–10 yrs of alendronate use).[79]

Duration of Bisphosphonate Therapy

Due to concerns about the long-term efficacy and safety of bisphosphonate use, data from randomized trials on bisphosphonates were reviewed by the FDA and showed little benefit of continued bisphosphonate treatment beyond 5 years in the general population.[80] Similarly, a review of treatment extension trials, in which the duration of treatment ranged from 6–10 years, was unable to demonstrate additional fracture prevention benefits associated with continued bisphosphonate therapy.[81] Recommendations on the optimal duration of bisphosphonate use are not available. Thus, clinicians should assess individual risks and benefits when considering continued treatment with these agents. Age, history of fracture, and BMD score are patient factors to be considered when deciding whether or not to continue therapy. Patients with a low risk for fracture (i.e., younger patients, no fracture history, and BMD close to normal) may be considered for discontinuation of bisphosphonate therapy after 3–5 years.[81]

Monitoring of Bisphosphonate Therapy

Current osteoporosis management guidelines recommend BMD testing be performed using DEXA scans for patients on bisphosphonates 2 years after initiating therapy and every 2 years thereafter.[45] However, definitive evidence supporting this recommendation is not available. The Agency for Healthcare Research and Quality reports that, to date, no randomized controlled trials have directly compared various schedules of serial BMD monitoring during bisphosphonate therapy and in relation to fracture prediction.[82] Nonetheless, until further guidance is provided, patients with and without HIV infection who are receiving therapy for osteoporosis should be monitored according to current clinical guidelines.

Alternative Therapies

Calcitonin

Calcitonin is approved for the treatment of osteoporosis in women who have been postmenopausal for at least 5 years.[83] It lowers serum calcium and phosphate levels by inhibiting osteoclastic bone resorption. It is available as an intravenous or intranasal solution. A study evaluating the efficacy of calcitonin in postmenopausal women found a nonsignificant increase of 0.8% in BMD versus baseline after 2 years.[84] Similarly, in a separate randomized clinical trial that evaluated efficacy of calcitonin as treatment in established postmenopausal osteoporosis, minimal changes in BMD were also noted.[85] Overall, calcitonin appears to be less effective compared with other agents that inhibit bone resorption but may be considered as a therapy option in women who cannot tolerate other agents. Impor-

tantly, calcitonin has not been studied for the treatment of osteoporosis in patients with HIV infection. The most commonly reported adverse effects in patients treated with calcitonin nasal spray included rhinitis (12%), epistaxis (3.5%), and sinusitis (2.3%).[83]

Estrogen

Estrogen is approved for the prevention of osteoporosis in postmenopausal women.[86] It is also approved for the relief of vasomotor symptoms and vulvovaginal atrophy due to menopause.[86] Results of the Women's Health Initiative trial demonstrated that combination estrogen and progestin increase BMD compared with placebo (3.7% vs 0.14%, $p<0.001$) and reduce the risk of fracture in healthy, postmenopausal women (HR 0.76, 95% CI 0.69–0.83).[87] The trial also reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein phlebitis during the 5 years of treatment with estrogen and progestin. Combination estrogen and progestin therapy may be considered for postmenopausal women requiring relief from vasomotor symptoms. However, when estrogen therapy is to be used solely for the prevention of bone loss in postmenopausal women, the FDA recommends that nonestrogen pharmacotherapy should be considered first.[45] Furthermore, the efficacy and safety of using estrogen therapy for the prevention of bone loss in patients with HIV infection has not been evaluated. Common adverse reactions in patients treated with combination estrogen and progestin include abdominal pain, asthenia, back pain, headache, flatulence, nausea, depression, pruritus, breast pain, dysmenorrhea, and leukorrhea.[86]

Raloxifene

Raloxifene is approved for the prevention and treatment of osteoporosis in postmenopausal women.[88] It is a selective estrogen receptor modulator, which acts as an agonist at skeletal and cardiovascular receptors but as an antagonist in the breast and the uterus. A study that compared the efficacy of alendronate to raloxifene in improving BMD in postmenopausal osteoporosis found that lumbar spine BMD increased 4.8% with alendronate and 2.2% with raloxifene ($p<0.001$).[89] Raloxifene is inferior in efficacy to alendronate but may be an alternative in women who cannot tolerate bisphosphonates and have increased risks for breast and uterine cancer. Like calcitonin, it has not been studied in patients with HIV and osteoporosis. Common adverse reactions (> 2%) considered to be related to raloxifene include hot flashes, leg cramps, peripheral edema, flu-like syndrome, arthralgia, and sweating.[88] An increased risk of deep vein thrombosis and pulmonary embolism has also been reported with raloxifene; thus, raloxifene should be avoided in women with a history of thromboembolism.

Teriparatide

Teriparatide is approved for the treatment of osteoporosis in postmenopausal women and men at a high risk of fracture.[90] It is also approved for the treatment of glucocorticoid-induced osteoporosis.[90] Teriparatide is a recombinant form of parathyroid hormone, which directly stimulates bone formation. Data from a meta-analysis of eight randomized controlled trials of postmenopausal women identified a 2.48% increase in spine BMD from baseline, which is supportive of the agent's overall efficacy.[91] Although teriparatide has not been studied in patients with HIV, it is a potential option for patients receiving long-term glucocorticoid therapy who are at high risk of fracture. The most common adverse effects (>10%) in patients treated with teriparatide include arthralgia, pain, and nausea.[90]

Denosumab

Denosumab is approved for the treatment of osteoporosis in postmenopausal women at a high risk of fracture.[92] It is a monoclonal antibody that binds to RANKL. Binding of this drug blocks the interaction between RANKL and its receptor, RANK, preventing osteoclast formation and further bone resorption. A randomized controlled trial of 912 men with prostate cancer and androgen deprivation showed a significant increase in BMD of the lumbar spine (5.6% vs −1%, $p<0.001$) after 24 weeks of denosumab and a decreased incidence of fracture compared with placebo.[93]

The role for denosumab in patients with HIV infection is unknown. Clinical trial data in this population are currently unavailable, and the immunologic consequences of inhibiting RANK in patients with HIV are uncertain. In addition to its presence on osteoclasts, the RANK receptor also rests on the surface of certain

macrophages. The binding of RANKL to RANK in this setting helps to facilitate T cell interactions with monocytes and dendritic cells. As a result, disrupting the RANKL-RANK pathway with denosumab could be concerning in patients with compromised immunity and will require further study before it can be recommended in patients with HIV. The most common adverse effects (≥ 25% of patients) in patients receiving denosumab therapy are fatigue or asthenia, hypophosphatemia, and nausea.[92]

Nonpharmacologic Interventions

Lifestyle factors that may increase the development of bone disease in patients with HIV include tobacco and alcohol use, low physical activity, and low body weight. Modification of lifestyle factors should be given special attention by health care providers, as these risk factors are highly prevalent in patients with HIV infection.[44]

In the general population, current smoking significantly increases the risk for fractures in men and women by 13%, independent of BMD.[94] In a study that evaluated men who used Veterans Health Administration services for HIV from 1988–2009, tobacco use was found to be independently associated with a 31% increase in osteoporotic fractures.[31] Smoking is detrimental to overall health, regardless of HIV infection status, and smoking cessation should be encouraged in all patients to prevent fractures, bone disease, and other comorbid conditions.

Alcohol consumption is common among individuals with HIV, with rates of heavy drinking twice the rate found in the general population.[95] Although moderate alcohol consumption (≤ 3 drinks/day for men and ≤ 2 drinks/day for women) has not been found to negatively affect bone health in the general population, excessive alcohol consumption could lead to osteoporosis and fractures.[45] In addition, alcohol consumption contributes to nonadherence of ART. More specifically, consuming 5 drinks/week or more is predictive for having an unsuppressed HIV viral load due to nonadherence.[96]

Physical activity can increase BMD in the general population and has been shown to improve psychologic status and cardiopulmonary fitness in patients with HIV infection.[97–99] Currently, there are no data demonstrating the benefit of physical activity for bone health among patients with HIV, but a combination of endurance and resistance exercises has been recommended in this population to improve or maintain cardiovascular, metabolic, and muscle function.[99]

Several studies have found that low body weight and reduced lean mass can account for low BMD in men and women with HIV.[100, 101] A meta-analysis that evaluated correlations between body weight and BMD in patients with HIV infection found that, on average, patients with HIV were 5.1 kg lighter than controls (95% CI −6.8 to −3.4 kg, $p<0.001$) and BMD was lower at all sites by 4.4–7.0% ($p<0.01$).[100]

Factors that may contribute to weight loss in patients with HIV infection include reduced caloric intake, opportunistic infections, gastrointestinal disease, malignancies, and other endocrine or metabolic conditions.[102] Other than a decrease in BMD, uncontrolled weight loss and wasting in patients with HIV could lead to increased mortality, accelerated disease progression, and impairment of strength and functional status. As a result, education on adequate nutrition and physical activity should be emphasized.

Conclusion

Low BMD and osteoporosis are common among aging patients with HIV infection. Similar to other primary care conditions, low BMD among patients with HIV is likely due to complex interactions between traditional risk factors, HIV infection, and ART. Certain antiretroviral agents in particular have been more commonly linked to BMD losses, including tenofovir, which has also been linked to an increase risk for fragility fractures. Evaluating BMD and vitamin D deficiency in patients with HIV may be important steps in identifying patients who require pharmacotherapy. However, the appropriate timing for BMD and vitamin D screening is uncertain, as is the appropriate method of replacing vitamin D in patients with HIV who are deficient. Further study is necessary to definitively determine the appropriate methods for the complete evaluation of bone health and management of low BMD in patients with HIV infection. Future studies should focus on the cost-effectiveness of current osteoporosis screening and management recommendations for patients with HIV as well as the role of vitamin D deficiency screening and replacement for fracture prevention. Until data and guidance are definitive, HIV practitioners should adhere to guidelines that are currently available for patients with HIV and follow recommendations for the general population when specific guidance is not available for the HIV population.

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