Perspective

Challenges in the Management of Osteoporosis and Vitamin D Deficiency in HIV Infection

Until 2013, the National Osteoporosis Foundation guidelines did not include HIV infection and highly active antiretroviral therapy as osteoporosis risk factors that should trigger dual-energy x-ray absorptiometry (DEXA) screening for low bone mineral density (BMD) in older adults, but numerous data indicate that individuals with HIV infection are at early and increased risk for osteoporosis and fracture. For this reason, experts support the use of DEXA screening for HIV-infected postmenopausal women and men older than 50 years. Factors contributing to increased risk of low BMD in individuals with HIV infection include inflammation, effects of antiretroviral therapy, and numerous patient risk factors, including vitamin D deficiency. Workup for low BMD should include assessment for fracture risk and secondary causes of low BMD, including vitamin D deficiency, hyperparathyroidism, subclinical hyperthyroidism, hypogonadism, and phosphate wasting. Bisphosphonates are the preferred treatment to prevent fracture in low BMD but are not appropriate for treating osteomalacia, which is characterized by vitamin D deficiency and phosphate wasting. This article summarizes a presentation by Todd T. Brown, MD, PhD, at the IAS–USA continuing education program held in Atlanta, Georgia, in April 2013.

Keywords: *HIV, bone mineral density, osteoporosis, fracture, vitamin D, deficiency, tenofovir, bisphosphonates, osteomalacia*

The risk of vertebral, hip, or wrist fracture in the general population dramatically increases after approximately age 65 years in women and age 70 years in men. These fractures are associated with increased mortality and morbidity. The 2008 US National Osteoporosis Foundation (NOF) guidelines recommended dual-energy x-ray absorptiometry (DEXA) screening of bone mineral density (BMD) to detect osteoporosis for people with a history of fragility fracture, women aged 65 years or older and men aged 70 years or older, and postmenopausal women and men aged 50 years to 70 years if there is concern based on risk factor profiles. HIV infection and antiretroviral therapy were not listed among the risk factors.

Numerous studies, however, have shown that HIV-infected persons are at increased risk for osteoporosis, with a meta-analysis showing an overall prevalence of osteoporosis of 15% in an HIV-infected population with an average age of 41 years and a 3.68-fold increased risk of osteoporosis compared with their HIV-uninfected counterparts.[1] Further, a study in the Massachusetts General Hospital/Partners Healthcare System involving 8528 HIV-infected persons and more than 2 million HIV-uninfected persons showed a substantially increased prevalence of fracture in HIV-infected persons (Figure 1).[2] The increase in risk was observed after approximately age 30 years in men and age 40 years in women; the difference in prevalence rates between HIV-infected and HIV-uninfected persons continued to increase with age, suggesting an HIV-age interaction with regard to fracture risk. Given these findings, Dr Brown and colleagues recommended in 2010 that DEXA screening be used for all HIV-infected postmenopausal women and men older than 50 years.[3] The 2013 NOF guidelines finally list HIV infection and antiretroviral therapy among the risk factors that should prompt DEXA screening in older individuals.

Assessing BMD and Fracture Risk

Consider the case of patient A, a 62-year-old white man who was referred to the Johns Hopkins Lipodystrophy Clinic because of body fat changes. His HIV infection was diagnosed in 1987 and he had a CD4+ cell count nadir of 22/µL. He is receiving tenofovir, emtricitabine, and efavirenz. He has a history of hypogonadism and transdermal testosterone, a history of chronic obstructive pulmonary disease, and a 60 pack-year smoking habit. He has received numerous steroid courses but has no history of fracture and no height loss. On DEXA, his T scores were -2.2 for lumbar spine

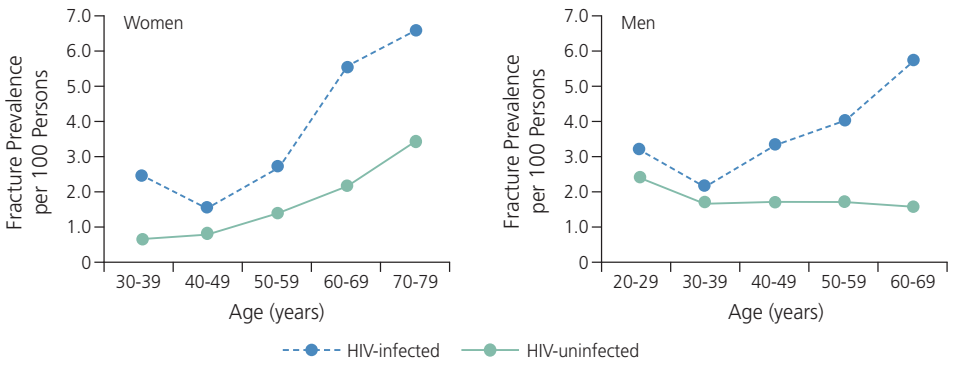

Figure 1. Fracture prevalence in HIV-infected and HIV-uninfected men and women in the Massachusetts General Hospital/Partners Healthcare System, 1996-2008. Adapted from Triant et al.[2]

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L1-L4, -2.1 for the femoral neck, and -2.3 for total hip.

According to the World Health Organization (WHO) guidelines, osteoporosis is defined by a T score below -2.5, osteopenia by a score between -1.0 and -2.5, and normal by a score above -1.0. The risk of fracture is estimated to increase 1.5- to 3.0-fold for each standard deviation decrease in T score. It is important to note that T scores are valid only in older individuals. Z scores (ie, the number of standard deviations from age-matched controls) are used in premenopausal women and men younger than 50 years of age, with a Z score below -2.0 indicating low BMD. Patient A is thus considered to have osteopenia, not osteoporosis. However, it is important to keep in mind that low BMD explains only approximately half of fracture risk.

As with many of the other metabolic complications in HIV infection, the pathophysiology of bone changes in HIV-infected patients is multifactorial but appears to include inflammation and the presence of HIV viral proteins, such as TAT and Vpr, that result in increased bone resorption and decreased bone formation. With regard to factors associated with medication use, tenofovir and certain HIV protease inhibitors (eg, ritonavir-boosted atazanavir and ritonavir-boosted lopinavir) have deleterious effects, and a 2% to 6% decrease in BMD has been observed 96 weeks after initiation of antiretroviral therapy, even in the context of viral suppression and reduced levels of inflammatory markers. Patient risk factors include low body weight, smoking, alcohol use, opiate use, coinfection with hepatitis C virus, physical inactivity, hypogonadism, and low vitamin D levels.

Given these considerations, what should be the next step in managing and treating patient A? The 2013 NOF guidelines recommend treatment for postmenopausal women and men aged 50 years and older who have hip or vertebral fractures; individuals with BMD T scores at or below -2.5 at the femoral neck, total hip, or spine on DEXA; and those with T scores between -1 and -2.5 (osteopenia) at these sites *and* a 10-year hip fracture probability of 3% or higher or a 10-year all major osteoporosis–related fracture probability of 20% or higher based on the WHO Fracture Risk Assessment Tool (FRAX®) model. FRAX assessment includes age, sex, weight, height, history of fracture, parental history of hip fracture, current smoking habits, glucocorticoid use, rheumatoid arthritis status, secondary osteoporosis status, alcohol ingestion per day, and femoral neck BMD. In the case of patient A, his 10-year risk of major osteoporotic fracture was 18% (under the treatment threshold) and his risk of hip fracture was 4.10%, making him a candidate for bisphosphonate or other treatment to reduce fracture risk.

However, before starting a patient on bisphosphonate treatment, potential secondary causes of low BMD must be evaluated. Those that should be evaluated in all patients include vitamin D deficiency, hyperparathyroidism, subclinical hyperparathyroidism, hypogonadism, and phosphate wasting, the latter of which can occur in patients receiving tenofovir. Other potential causes include idiopathic hypercalciuria, celiac sprue, multiple myeloma, mastocytosis, and Cushing syndrome.

Among these conditions, severe vitamin D deficiency and phosphate wasting are of particular note because low BMD occurring in either of these settings may be related to osteomalacia, the most important differential diagnosis in low BMD. Osteomalacia is characterized by impaired bone mineralization. The collagen matrix is normal but is not mineralized with calcium phosphate crystals. It can be accompanied by weakness, fracture, pain, anorexia, and weight loss. Osteomalacia needs to be treated not with bisphosphonates but with vitamin D and calcium and possibly phosphate replacement (if the cause is phosphate wasting). Consideration should be given to switching patients off tenofovir if they have phosphate wasting. Bisphosphonate treatment in this syndrome could actually inhibit bone mineralization.

Low Vitamin D

Consider the case of patient B, a 51-year-old white man diagnosed with HIV infection in 2001 who had a CD4+ cell count nadir of 30/µL. His plasma HIV RNA level is less than 50 copies/mL on tenofovir, emtricitabine, and efavirenz, but his CD4 + cell count remains low at 150/µL to 250/µL. He drinks 3 to 4 glasses of wine per day and is a former smoker. His sister has osteoporosis but no history of fracture. Patient B has had 2 traumatic fractures during recreational activities (boating and glade skiing). On DEXA, his T scores are -2.9 for L1-L4 (Z score, -2.5), -1.4 for the femoral neck (Z score, -0.6), and -0.8 for total hip (Z score, -0.4). On FRAX assessment, his 10-year risks are 4.7% for all osteoporotic fracture and 0.5% for hip fracture, low risks not indicative of a need for bisphosphonate treatment.

Secondary workup shows a low 25-hydroxyvitamin D level of 15 ng/mL. The rest of the secondary workup is normal: parathyroid hormone (PTH) of 44 pg/mL, calcium (Ca^{2+}) of 9.5 mg/dL, thyroid-stimulating hormone of 1.8 mU/L, free testosterone of 61 pg/mL, serum phosphate of 3.0 mg/dL, and fractional excretion of phosphate of 10%. Although vitamin D is low, it is not in the single digits, a level commonly seen in osteomalacia. Osteomalacia would also be accompanied by elevated PTH and elevated alkaline phosphatase. Patient B has vitamin D deficiency but not osteomalacia.

Vitamin D deficiency is defined as a level less than 20 ng/mL, with vitamin D inadequacy defined as a level from 20 ng/mL to 30 ng/mL. Vitamin D deficiency is very common in the general population, occurring in association with inadequate physical activity, inadequate exposure to sunlight, high body mass index, and other factors. In HIV-infected individuals, medications also play a role. For example, patients initiating antiretroviral therapy that includes efavirenz have been found to have a 5 ng/mL reduction in vitamin D levels compared with patients starting antiretroviral therapy without efavirenz.[4] This reduction is approximately

half the difference observed in the general population between summer and winter in some parts of the world, and approximately one-third that observed between white persons and black persons.

The optimal regimen for replacing vitamin D is unclear. Popular approaches are to provide replacement with ergocalciferol (D_2) at 50,000 IU once or twice per week for 8 weeks to 12 weeks or cholecalciferol (D_3) at 2000 IU/day and maintenance with ergocalciferol at 50,000 IU once or twice per month or cholecalciferol at 1000 IU/day to 2000 IU/day. It is of interest that a study examining very high replacement doses found that they did not provide protection from falls or fractures. In this study, 2256 women aged 70 years or older were randomized to receive 500,000 IU of vitamin D_3 once yearly each fall or to receive placebo and were followed up for 3 years to 5 years.[5] After the initial spike in vitamin D levels in those receiving replacement, levels declined but remained in the target range of 30 ng/mL to 50 ng/mL for all or most of the year. However, women receiving the annual high replacement dose had a statistically significant 16% increase in risk for falls (hazard ratio [HR], 1.16; $P = .003$) and a borderline statistically significant 26% increase in risk for fracture (HR, 1.26; $P = .06$). The explanation for this unexpected result is unclear, although it may be that the body's response to such a large replacement dose is to catabolize the vitamin D and eliminate it without sufficient conversion to the biologically active 1,25-dihydroxyvitamin D form.

Dr Brown's approach to vitamin D replacement is to check a patient's 25-hydroxyvitamin D levels if BMD is low or the patient has a history of falls. If levels are greater than 30 ng/mL, the patient is given vitamin D_3 at 1000 IU/day. For levels of 20 ng/mL to 30 ng/mL, a patient is given vitamin D_3 at 2000 IU/day. For levels of 15 ng/mL to 20 ng/mL, replacement is given with ergocalciferol at 50,000 IU a week for 8 weeks followed by vitamin D_3 at 2000 IU/day. For levels less than 15 ng/mL, patients receive replacement with ergocalciferol at 50,000 IU once or twice a week for 8 weeks to 12 weeks followed by vitamin D_3 at 2000 IU/day. More aggressive replacement should be used if PTH or alkaline phosphatase levels are elevated or if a patient has signs or symptoms suggestive of osteomalacia.

For management of patient B, plain films were taken of the thoracic and lumbar spine. The vitamin D deficiency was addressed by ergocalciferol replacement with 50,000 IU once a week for 12 weeks, followed by vitamin D_3 at 2000 IU/day along with 1000 mg/day of calcium. He was advised to continue exercising but perhaps avoid glade skiing.

Treatment for Low BMD

If patient B were 71 years old instead of 51 years old, there would be greater incentive to treat low BMD with a bisphosphonate, because the additional 20 years of age confers a much higher risk of fracture at the same BMD value. Management in the 71-year-old patient B would include calcium and vitamin D supplementation, smoking cessation (if he were still smoking), reduction in alcohol intake, weight-bearing exercise, and assessment of fall risk. Fall risk assessment may be as simple as asking "Are you worried about falling?" People can recognize if they are at risk for falls and change the way in which they move in their environment. Patients who acknowledge being afraid of falling and those who are otherwise at increased risk should be given a referral for physical therapy for strength and balance training.

As in the general population, the initial, preferred treatment for low BMD in individuals with HIV infection is a bisphosphonate. Women may also be treated with selective estrogen receptor modulators, and those with hot flashes can be treated with estrogen. PTH analogues are an additional option. Comparative characteristics of available bisphosphonates are shown in the Table. Alendronate and zoledronate have the best efficacy, reducing fracture risk by approximately 30% to 40%. BMD changes with risedronate are less than those with alendronate, and ibandronate has not yet been shown to reduce the risk of nonvertebral fracture. Alendronate is the only bisphosphonate currently available in generic form and is less expensive. Oral bisphosphonates are associated with gastrointestinal side effects. Adherence can be an issue, in which case the once-yearly zoledronate is an attractive option.

There is concern about how long and how often patients should take

Table. Comparison of Efficacy, Cost, Adherence, and Associated Adverse Effects of Selected Bisphosphonates

Consideration	Alendronate	Risedronate	Ibandronate	Zoledronate
Efficacy	High	Medium	Low	High
Cost (for 1 year)	$350	$1200	$1200	$1100
Level of adherence	Low	Low	Oral: low Intravenous: high	High
Gastrointestinal side effects	Yes (20%)	Yes (20%)	Oral: yes Intravenous: no	No
Osteonecrosis of the jaw	Yes	Yes	Yes	Yes
Acute phase reaction	No	No	Oral: no Intravenous: yes	Yes (approximately 10%)
Esophageal cancer	Unclear	Unclear	Unclear	No
Oversuppression of bone turnover	Yes	Yes	Yes	Yes

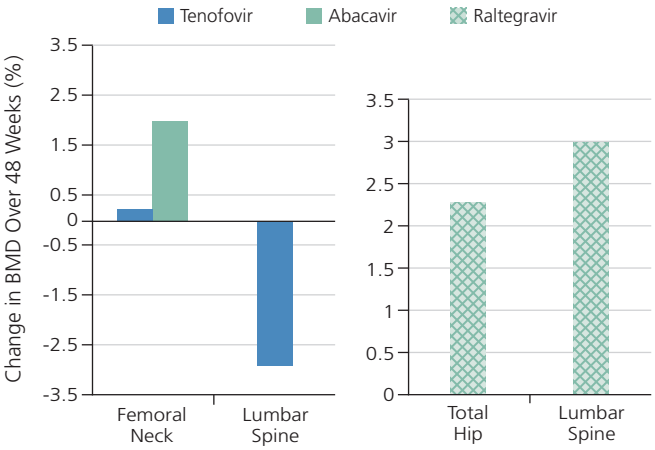

Figure 2. Effects on bone mineral density (BMD) of switching from tenofovir to abacavir (left) or to raltegravir (right) in patients with low BMD. Adapted with permission from Negredo et al and Bloch et al.[6,7]

bisphosphonates, and when they should take a drug holiday from treatment. Bisphosphonates suppress bone turnover, which is necessary for repair of microfractures that can occur with simple everyday wear and tear. As a result, prolonged use of bisphosphonates can in rare instances result in increased risk of fracture, particularly in subtrochanteric areas at the top of the femur, below the hip. Similarly, all bisphosphonates have been associated with osteonecrosis of the jaw, although this is a rare occurrence. Given the potential long-term risks, there is some belief that patients should be given a drug holiday after approximately 5 years or after 10 years in those with very low BMD. There are also concerns regarding atrial fibrillation, acute phase reactions with intravenous bisphosphonates, and esophageal cancer, although the risks of such effects are not yet well defined.

The 71-year-old patient B is receiving tenofovir. Although he has no evidence of phosphate wasting, consideration might be given to drug substitution. Recent studies have shown improvements in BMD with substitution for tenofovir in patients with low BMD (Figure 2). A study conducted over a 48-week period that randomized patients to switch from tenofovir to abacavir or remain on tenofovir showed that switching to abacavir use resulted in a marked increase in femoral neck BMD compared with continued tenofovir use; no change in lumbar spine BMD was seen in those patients switching to abacavir and it decreased in those who continued tenofovir.[6] In a single-arm study of a nucleoside analogue reverse transcriptase–sparing regimen, tenofovir was replaced with raltegravir, which resulted in marked increases in total hip and lumbar spine BMD over the 48-week study period.[7]

Conclusions

DEXA screening is recommended in HIV-infected men older than 50 years and HIV-infected postmenopausal women. In general, guidelines for treatment of low BMD in HIV-infected patients are the same as those established for the general population. It is important to consider secondary causes of low BMD, particularly vitamin D deficiency and phosphate wasting. The absolute risk of fracture should be used to help guide decisions in management and treatment.

Presented by Dr Brown in April 2013. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Brown in July 2013.

Financial Affiliations: Dr Brown has served as an advisory board member for Bristol-Myers Squibb and EMD Serono and as a consultant for Abbott Laboratories, Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, and ViiV Healthcare and has received grants awarded to his institution from Merck & Co, Inc, and GlaxoSmithKline.

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Top Antivir Med. 2013;21(3):115-118