

Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers

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Low bone mineral density (BMD) is prevalent in human immunodeficiency virus (HIV)-infected subjects. Initiation of antiretroviral therapy is associated with a 2%–6% decrease in BMD over the first 2 years, a decrease that is similar in magnitude to that sustained during the first 2 years of menopause. Recent studies have also described increased fracture rates in the HIV-infected population. The causes of low BMD in individuals with HIV infection appear to be multifactorial and likely represent a complex interaction between HIV infection, traditional osteoporosis risk factors, and antiretroviral-related factors. In this review, we make the point that HIV infection should be considered as a risk factor for bone disease. We recommend screening patients with fragility fractures, all HIV-infected post-menopausal women, and all HIV-infected men ≥ 50 years of age. We also discuss the importance of considering secondary causes of osteoporosis. Finally, we discuss treatment of the more severe cases of bone disease, while outlining the caveats and gaps in our knowledge.

INTRODUCTION

As the number of older human immunodeficiency virus (HIV)-infected persons expands, the importance of aging-related comorbidities, such as osteoporosis and fractures, has increased. This review describes the current knowledge of the epidemiology and pathogenesis of reduced bone mineral density (BMD) in HIV-infected patients, discusses the authors' recommendations regarding screening and treatment considerations, and highlights areas of controversy and uncertainty.

DEFINITIONS OF OSTEOPENIA, OSTEOPOROSIS, AND OSTEOMALACIA

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [1]. The diagnosis of osteoporosis can be based on a history of fragility fracture (a fracture resulting from trauma equivalent

or less than a fall from a standing position). Osteoporosis may also be diagnosed before a fracture occurs by measuring BMD by dual-energy x-ray absorptiometry (DXA). The World Health Organization (WHO) classifies BMD as Normal, Osteopenia, or Osteoporosis according to the number of standard deviations (SDs) below the mean BMD for a healthy, young (25–35 years of age), sex- and ethnicity-matched reference population (T-score) [2]. In post-menopausal women and men 50 years of age and older, a T-score less than or equal to -2.5 at the hip or spine is defined as osteoporosis. Osteopenia is defined as a T-score between -1 and -2.49 . In older populations, the risk of fracture approximately doubles for each SD decrease below the young normal mean [3]. For patients younger than 50 years of age, the Z-score (SD below a sex- and ethnicity-matched population of the same age) is preferred; a value less than or equal to -2.0 considered to be abnormal [4]. The diagnosis of osteoporosis in this younger population should not be made on the basis of BMD testing alone [4].

Osteomalacia refers to impaired mineralization of the bone matrix, most often caused by severe vitamin D deficiency. Although osteoporosis and osteomalacia are separate conditions with distinct etiologies and treatments, both may be associated with low BMD by DXA and fractures.

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LOW BMD IN HIV INFECTION

Low BMD has been reported in many cross-sectional studies involving younger [5–10] and older [11–14] HIV-infected individuals. In one meta-analysis, the prevalence of osteoporosis was 3 times higher among HIV-infected patients than among HIV-negative control subjects, especially among those receiving antiretroviral therapy (ART) [15]. Several studies have shown that BMD decreases by 2%–6% within the first 2 years after initiation of various ART regimens [16–18], a decrease in BMD similar to that sustained during the first 2 years of menopause [19]. BMD appears to be relatively stable in patients who receive established ART [20–22]. Importantly, studies reporting increased fracture rates in the HIV-infected population are starting to emerge, with rates 30%–70% higher than those among matched uninfected control subjects [23–26].

POTENTIAL ETIOLOGIES OF LOW BMD IN HIV INFECTION

The causes of low BMD in HIV appear to be multifactorial and likely represent a complex interaction between HIV infection, traditional osteoporosis risk factors exacerbated by consequences of chronic HIV infection (eg, poor nutrition and low weight), high rates of tobacco and alcohol use, low vitamin D levels, and ART-related factors [9, 22, 27–29]. ART-naive subjects [5, 15] have a high prevalence of osteopenia, which suggests that uncontrolled viremia can impact BMD, likely mediated by effects of systemic inflammation on bone remodeling. Specifically, HIV proteins increase osteoclastic activity [30] and decrease bone formation by promoting osteoblast apoptosis [31, 32]. Furthermore, elevated tumor necrosis factor (TNF) α increases osteoclast-mediated bone resorption without concomitant increases in bone formation [33].

Other comorbidities that are common in individuals with HIV infection also impact BMD. The prevalence of low vitamin D levels is 60%–75% in different HIV-infected cohorts [34–36], and hypogonadism also likely contributes [37]. Lipoatrophy may mediate bone loss through the complicated relationships between central signaling of adipocyte hormones [38, 39]. As in the general population [39], relative central fat accumulation has been associated with lower BMD in some HIV-infected populations [40, 41]. The mechanisms underlying this association deserve further attention.

Initiation of ART induces a marked and clinically significant loss of BMD (2%–6%), regardless of the initial choice of ART [16, 18, 27, 29, 42]. Although early studies suggested that bone loss was attributable to protease inhibitor (PI)-based ART [9, 43, 44], others have failed to confirm the association [45–47]. Of greatest interest for most clinicians, the nucleoside reverse-transcriptase inhibitor tenofovir (TDF) has been strongly associated with an acute decrease in BMD; in a recently presented

study, there was more bone loss in patients with HIV suppression who were switched to TDF than in those who were switched to abacavir (ABC) [27, 48]. Two prospective studies involving subjects who were initiating their first ART regimen showed that TDF-containing regimens led to a significantly larger decrease in spine and hip BMD than did ABC-containing regimens [42, 49]. In addition, in ACTG5224, use of regimens containing the PI atazanavir-ritonavir led to a greater decrease in lumbar spine—but not hip—BMD, when compared with use of efavirenz (EFV) containing regimens. The mechanisms involved in bone loss associated with particular ART regimens are not well understood. TDF may affect bone indirectly through proximal tubule toxicity, resulting in phosphate wasting and increased bone turnover [50], whereas EFV and PIs may affect BMD indirectly through vitamin D metabolism [51–55].

BONE DISEASE IN SELECTED POPULATIONS

Children and adolescents. Peak bone mass is achieved during adolescence and young adulthood and is a key determinant of bone mass in later life [56]. Thus, the effect of HIV infection and/or ART on this process is a critical area of research. Variation in the pattern and dynamics of skeletal growth complicate bone mass measurements in children and youth, and normative databases are insufficient [57, 58]. Techniques that are influenced by body size (eg, DXA) can be confounded by HIV-associated delays in growth [59–61]. Despite these caveats, almost all studies involving perinatally infected children have reported lower-than-expected bone mass [62–74], as well as hormonal and calcium deficiencies [66, 68, 75, 76]. Bone abnormalities may be worse in subjects who are receiving ART [65, 71], particularly TDF [70, 77]; in those with advanced HIV disease [64, 70, 75, 77]; and in pubertal males [78]. Optimal nutrition, exercise, and lifestyle changes should be emphasized in this population.

Resource-limited settings (RLS). More than 90% of HIV-infected people live in RLS, where nutritional deficiencies are also highly prevalent [79]. Access to effective ART has improved life expectancy for HIV-infected patients in RLS. Although the burden of metabolic bone disease has not been clarified in these populations, osteoporosis would be expected in an aging population. In addition, vitamin D deficiency is very prevalent across the globe [80–83] and may contribute to bone complications in RLS. Defining the prevalence of osteoporosis, fracture risk, and consequences of vitamin D deficiency in RLS is an important topic for investigation.

WHOM TO SCREEN FOR BONE DISEASE IN HIV?

Recently published guidelines for the management of low BMD in the general US population recommend a DXA for persons

of any age with a fragility fracture, women ≥ 65 years of age, and men ≥ 70 years of age (Figure 1) [4]. For those with an additional risk factor, the recommendation is to perform a DXA in younger post-menopausal women and men ≥ 50 years of age [4]. Although HIV infection is not listed as a condition that is associated with low BMD, we believe that current evidence supports the inclusion of HIV-infection among other risk factors. Thus, we recommend a DXA scan for all HIV-infected post-menopausal women and men ≥ 50 years. Our position is more aggressive than the recommendation from the Infectious Diseases Society of America that suggests a DXA for HIV-infected subjects ≥ 50 years of age with additional risk

factors for osteopenia and/or osteoporosis, although those factors are so prevalent that most HIV-positive patients would qualify [84]. If the results of the test do not warrant medical treatment, the test should be repeated every 2–5 years, depending on the proximity to thresholds for therapy. DXA scans in younger HIV-infected persons are probably not indicated, because the risk for fracture is low. One of the most powerful predictors of future fragility fractures in the general population is a history of fragility fracture [85]. Patients who have a history of fragility fracture should be evaluated by DXA regardless of age or sex, which is a diagnostic modality clearly underutilized in this population [86].

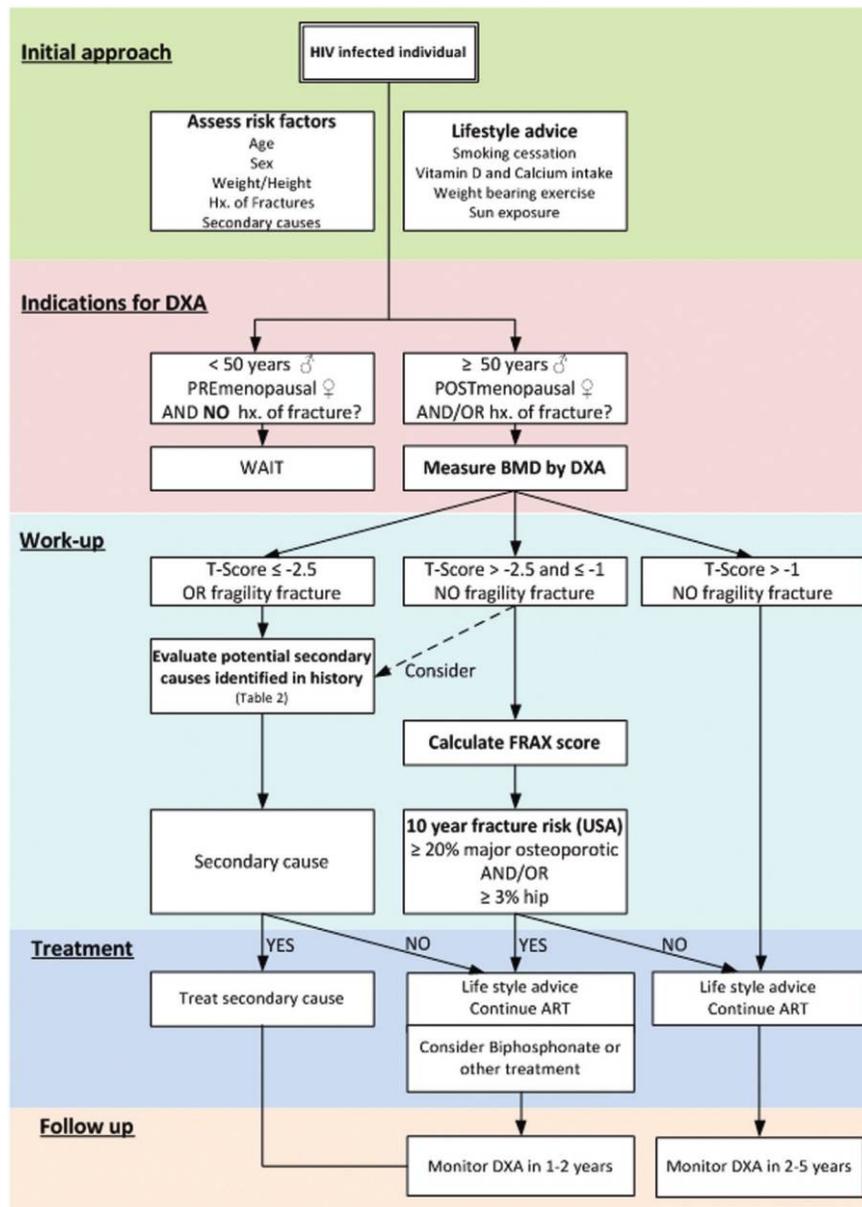


Figure 1. Approach to bone problems in patients with human immunodeficiency virus (HIV) infection (adapted from Dolin et al [126]). ART, antiretroviral therapy; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FRAX, Fracture Risk Assessment Tool; Hx, history.

Table 1. Conditions Associated With Osteoporosis and Fractures

Category	Condition(s)
Genetic disorders	Cystic fibrosis, hemochromatosis, idiopathic hypercalciuria
Hypogonadal states	Anorexia nervosa, early menopause, low testosterone (men), premenopausal oligomenorrhea , prolactinoma, Turner's and Klinefelter's syndromes
Other endocrine disorders	Acromegaly, adrenal insufficiency , Cushing's syndrome, diabetes mellitus (1 and 2), primary hyperparathyroidism, thyrotoxicosis
Gastrointestinal diseases	Bariatric surgery, celiac disease, gastrectomy, inflammatory bowel disease, malabsorption , primary biliary cirrhosis
Hematologic disorders	Hemophilia , leukemias and lymphomas, multiple myeloma, sickle cell disease , thalassemia, systemic mastocytosis
Pulmonary diseases	Emphysema , sarcoidosis
Infectious and inflammatory diseases	Rheumatoid arthritis, lupus
Lifestyle choices and/or habits	Alcohol (>3 drinks/day), dietary calcium deficiency, methadone/opiates, physical inactivity, tobacco use
Miscellaneous	Chronic metabolic acidosis , congestive heart failure, chronic infection, chronic kidney disease, depression , idiopathic scoliosis, immobilization, multiple sclerosis, organ transplantation, vitamin D deficiency
Medications	Anticoagulants, anticonvulsants, glitazones , antipsychotics, antiretrovirals , cyclosporines, tacrolimus, cytotoxic drugs, glucocorticoids , gonadotropin-releasing hormone agonists, lithium, excess thyroxine , methotrexate, proton pump inhibitors

NOTE. Conditions that are particularly relevant to patients with human immunodeficiency virus infection or AIDS are shown in bold.

WORK-UP TO RULE OUT SECONDARY CAUSES OF OSTEOPOROSIS

Secondary osteoporosis is osteoporosis that is caused or exacerbated by a specific disease process or medication. Table 1 includes a list of diseases, medications, and behaviors associated with low BMD and fractures in the general population. In postmenopausal women [87], premenopausal women [88, 89], and men <50 years of age [90] with low BMD in the general population, the prevalence of secondary causes is 44%–90%.

The most common secondary causes in men are hypogonadism, alcoholism, and glucocorticoid exposure, which together account for 40%–60% of cases [90], whereas premenopausal estrogen deficiency and glucocorticoid exposure are the most common secondary causes in women, accounting for 35%–40% of cases [88]. In HIV-infected individuals, low BMD has been linked most frequently to low body weight [91] but has also been linked to testosterone or estrogen deficiency, glucocorticoids, malabsorption, tobacco use, alcohol and opiate abuse, nadir CD4⁺ cell count, duration of HIV infection, lipodystrophy, insulin resistance, and hyperlactatemia [92, 93]. There are significant clinical consequences of secondary osteoporosis, because older women and men with metabolic disorders associated with secondary osteoporosis have a 2–3-fold higher risk of hip and vertebral fractures [94–96]. Fortunately, the majority of causes of secondary osteoporosis can be suspected or diagnosed on the basis of a thorough history and physical examination. However, if no cause is apparent, the tests summarized in Table 2 were

shown to have 92% sensitivity for detecting secondary causes of osteoporosis [87].

When vitamin D deficiency is pronounced, patients may experience osteomalacia, the diagnosis of which relies on a combination of clinical symptoms and biochemical abnormalities. Osteoporosis is asymptomatic until the development of a bone fracture, whereas severe osteomalacia can lead to bone pain, muscle weakness, and stiffness. Laboratory abnormalities include low calcium and phosphorus levels, low 25 hydroxyvi-

Table 2. Work-up for Secondary Causes of Osteopenia and/or Osteoporosis

History and physical examination with focus on secondary causes of osteoporosis
Perform complete blood count
Perform routine blood chemistry tests
Determine creatinine, blood urea nitrogen, total calcium, phosphate, albumin, and alkaline phosphatase levels
Determine serum 25-hydroxyvitamin D level
Perform parathyroid hormone and thyroid-stimulating hormone tests
Perform 24-hour urine test for calcium and creatinine
Determine total and free testosterone (for men)
Determine estradiol, follicle-stimulating hormone, luteinizing hormone, and prolactin levels in young amenorrheic women
Simultaneous serum phosphate and creatinine, spot urine phosphate, and creatinine to calculate the fractional excretion of phosphate (for patients receiving tenofovir)

NOTE. Adapted from Dolin et al [126].

tamin D (25[OH]D) levels, and elevated alkaline phosphatase and parathyroid hormone (PTH) levels.

WHO SHOULD BE TREATED FOR OSTEOPOROSIS?

After evaluation and treatment of secondary causes of reduced BMD, we recommend pharmacologic treatment of osteoporosis for post-menopausal women and men ≥ 50 years with a T-score of the total hip, femoral neck, or lumbar spine less than or equal to -2.5 or in those with a history of fragility fracture, in accordance with the most recent guidelines from the National Osteoporosis Foundation [4]. For those with osteopenia, the 10-year risk for both major osteoporotic fracture (hip, shoulder, wrist, and clinical vertebral combined) and hip fracture alone [98] should be calculated, using the WHO Fracture Risk Assessment Tool (FRAX) [97]. If the 10-year risk of all osteoporotic fracture is $\geq 20\%$ or risk of hip fracture is $\geq 3\%$ (the cost-effective threshold set in the United States), consideration should be given to starting pharmacologic therapy. In patients with osteopenia who have a history of height loss, plain radiographs of the thoracic and lumbar spine or use of a DXA with vertebral fracture assessment software may be useful to further risk-stratify patients, because clinically silent vertebral fractures are common and would trigger the use of pharmacologic therapy, regardless of the FRAX score or BMD. In addition, all subjects with osteopenia, regardless of FRAX score, deserve a work-up for secondary causes of bone loss and non-pharmacologic interventions. It should be noted that the FRAX has not been validated in HIV-infected persons, and there is concern that the FRAX-derived 10-year risk of fracture may under-estimate risk in HIV-infected patients [98].

GENERAL GUIDELINES FOR GOOD BONE HEALTH

In practice, it is important to focus on factors important to bone health, including adequate nutrition, particularly calcium and vitamin D intake. Because of the high prevalence of low BMD in HIV infection, we recommend that HIV-infected subjects receive 1000–1500 mg of calcium and 800–1000 IU of vitamin D daily. The amount of daily sun exposure sufficient for maintaining vitamin D levels without increasing the risk of skin cancer is unknown. Muscle strengthening and balance exercises to prevent falls should also be recommended. In post-menopausal women, exercise that puts a physical load on the bone was shown to improve BMD and reduce fracture [99]. Thirty minutes of weight-bearing exercise (including jogging or walking) at least 3 days a week has been recommended [100]. Smoking cessation and limitation of alcohol intake are strongly recommended.

Treatment of secondary causes. If a secondary cause of low

BMD is identified, specific treatment addressing the underlying problem should be instituted. Of the conditions listed in Table 1, vitamin D deficiency and phosphate wasting deserve special consideration.

Vitamin D can be replaced by vitamin D₂ (ergocalciferol) or the more bioavailable vitamin D₃ (cholecalciferol) [101, 102]. A standard repletion regimen does not exist for healthy adults. Examples of replacement regimens [103, 104] include D₂ 50,000 IU weekly for 8–12 weeks and then monthly thereafter or D₃ 2000 IU daily for 12 weeks then D₃ 1000–2000 IU daily. In general, we prefer daily dosing of vitamin D for 25(OH)D concentrations >15 ng/mL. For those with lower 25(OH)D concentrations, particularly those with secondary hyperparathyroidism or evidence of osteomalacia, high dose loading can be considered. However, there are limited data evaluating the effect of vitamin D loading strategies (eg, D₂ 50,000 IU weekly for 8–12 weeks) on fracture risk and that very high yearly loading doses (500,000 U vitamin D₃ each year) may be associated with an increased risk of fractures and falls [105]. Measurements of 25(OH)D at the end of replacement intervals should be considered to ensure adequate levels. The goal should be to achieve 25(OH)D level of >32 ng/mL, although some experts recommend levels in the 40–50 ng/mL range [104]. An incremental dose of D₃ of 40 IU will increase 25(OH)D by 0.4 ng/mL [106]. Vitamin D deficiency may attenuate the efficacy of bisphosphonates and increase the risk of bisphosphonate-related hypocalcemia [107, 108]. Vitamin D deficiency should therefore be corrected prior to initiation of bisphosphonates therapy, particularly intravenous therapy.

Phosphate wasting, if severe, may cause osteomalacia. Effective treatment of osteomalacia may rapidly reverse low BMD. In a TDF-treated patient with fragility fracture or Z-score less than or equal to -2.0 , discontinuation of TDF should be considered in the presence of urinary phosphate wasting and hypophosphatemia. For patients with significant hypophosphatemia, calcium (1–2 g/day) and phosphorous (1–2 g/day) should be given to remineralize the bone, and any concomitant vitamin D deficiency should be corrected.

SPECIFIC PHARMACOLOGIC INTERVENTIONS

Bisphosphonates. Bisphosphonates are considered to be first-line therapy. These medications bind to the bone matrix and inhibit osteoclast-mediated bone resorption. In numerous randomized, placebo-controlled trials, they have been shown to reduce the risk of fracture in patients without HIV infection [109]. Oral bisphosphonates are given either weekly (alendronate) or monthly (risedronate and ibandronate). Intravenous bisphosphonates include ibandronate (given every 3 months) and zoledronic acid (given yearly). All reduce the risk of vertebral fractures, and all but ibandronate lower the risk of non-spine

(hip) fractures [109]. Intravenous formulations should be considered for those who do not tolerate or are noncompliant with oral bisphosphonates. Both alendronate and zoledronic acid has been evaluated in HIV-infected patients in 48-week randomized controlled trials and have shown effects on BMD and tolerability that were similar to those found in the general population [110–113].

Adverse effects of bisphosphonates. Oral bisphosphonates may be associated with esophageal irritation and dyspepsia, are poorly absorbed, and must be taken on an empty stomach. Patients should be instructed to administer with a glass of water, to remain upright, and not to eat or drink anything for at least 30 min [114]. Osteonecrosis of the jaw has been reported in patients who received bisphosphonates, although the incidence is very rare (<1 case per 100,000 person-years) [115]. The most consistent risk factor is recent prior dental surgery or extraction [116]. Therefore, patients who require dental work should have this work completed and be given time to heal before bisphosphonate initiation [116]. Atrial fibrillation and esophageal cancers have been associated with bisphosphonate use in some trials [117]; however, there is insufficient evidence to establish a causal relationship [118]. In addition, there is concern about the potential adverse effects of chronic suppression of bone turnover with bisphosphonates, which may prevent the repair of microdamage to the bone architecture and compromise bone strength and, paradoxically, predispose to fracture in some patients [119]. There have been recent reports of unusual femur fractures (sub-trochanteric) in patients who received long-term bisphosphonates [120]. Nevertheless, 10-year data with alendronate in post-menopausal women showed continued increases in BMD and no increase in the risk of fracture over time [121, 122]. Given the prolonged effects of bisphosphonates and the uncertainty of their long-term safety, the optimal duration of treatment with bisphosphonates is unclear, but some experts recommend discontinuation after 5 years with careful observation [123]. Because HIV-infected subjects are now expected to live for many decades, the decision as to when to start or stop therapy is difficult and deserves to be investigated in long-term clinical trials.

Second-line osteoporosis therapies. In postmenopausal women, osteoporosis can be effectively treated with estrogen-replacement therapy. However, because of the risk of cancer (breast and endometrial), cardiovascular disease, and deep-vein thrombosis, these therapies cannot be recommended as first line treatment. In postmenopausal women, the selective estrogen receptor modulator raloxifene may be a reasonable alternative to bisphosphonates, because it does not increase the risk of breast cancer [85]. Intranasal calcitonin has relatively low efficacy, compared with that of bisphosphonates. An analogue of PTH, teriparatide, stimulates new bone formation by increasing the number and/or activity of the bone-forming osteoblasts, but it should be

reserved for patients with severe osteoporosis and those who have experienced treatment with bisphosphonates. PTH should not be used concomitantly with bisphosphonates [124]. These therapies have not been specifically evaluated in HIV-infected patients.

Antiretroviral changes in patients with low BMD. Although certain ART regimens may be associated with greater decreases in BMD, there is currently no evidence to suggest that switching ART will improve BMD and reduce fracture risk in HIV-infected patients.

Role of tenofovir in osteoporosis. Although TDF exposure has been associated with increased bone loss in HIV-infected patients initiating ART [27, 42, 49] and those receiving suppressive ART regimens [48], there have been no properly powered studies to date that have linked TDF use to fracture. Ongoing studies investigating the use of TDF for HIV prophylaxis and for the treatment hepatitis B infection will be useful in determining the effect of TDF use, independent of HIV infection or the host inflammatory response. At this juncture, there is insufficient evidence to recommend against TDF use in a patient with known low BMD prior to ART initiation. However, alternative ART choice or closer bone monitoring after TDF initiation may be considered for subjects with fragility fractures or known osteoporosis. Additional investigation into the mechanisms and clinical impact of TDF use on bone health is required.

Monitoring osteoporosis treatment. DXA should be monitored 1–2 years after initiation of osteoporosis therapy [57]. If BMD is stable or improved, consideration can be given to less frequent monitoring. If BMD decreases, compliance, procedures for taking the drug, or underlying secondary causes should be re-evaluated. Bone turnover markers decrease by 30%–50% within 6 weeks after initiation of bisphosphonates [125], although a relationship between changes in these markers and changes in BMD has not been demonstrated in individuals with HIV infection [110]. The use of bone markers in this setting has not been addressed in the current guidelines [57].

Referral to a specialist. Consultation with an experienced endocrinologist or rheumatologist should be considered when: (1) the osteoporosis is unexpectedly severe, (2) there are significant secondary causes contributing to low BMD, and (3) in cases of treatment intolerance or failure.

Conclusion. Low BMD is very common among HIV-infected subjects. BMD decreases further after ART initiation. Fracture rates are increased among older HIV-infected patients. The pathogenesis of low BMD in individuals with HIV infection remains only partially elucidated, and studies aimed at clarifying the mechanisms underlying bone loss related to ART initiation are urgently needed. Better understanding of the mechanisms of bone loss would permit targeted interventions to prevent ART-induced bone loss and mitigate fracture risk

among aging HIV-infected patients. We recommend aggressive screening and treatment of the more-severe cases, while outlining the caveats and gaps in our knowledge.

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