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Vitamin D and Bone Loss in HIV

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Abstract

Purpose of review—Bone health has become an increasingly important aspect of the care of HIV-infected patients as bone loss with antiretroviral therapy (ART) initiation is significant and osteopenia and osteoporosis are highly prevalent. Vitamin D is tightly linked to calcium balance and bone health and vitamin D deficiency is common in HIV. This review outlines the epidemiology of vitamin D deficiency in HIV, summarizes our current understanding of the relationship between vitamin D and bone loss in HIV and the impact of vitamin D supplementation in this patient group.

Recent findings—While data are conflicting as to whether vitamin D deficiency is more prevalent among HIV-infected individuals than in the general population, there are several reasons for why this patient group may be at heightened risk. Studies linking vitamin D deficiency to bone loss in HIV are limited; however, data from randomized clinical trials suggest a benefit of vitamin D supplementation for the prevention of bone loss with ART initiation and for the treatment of bone loss with bisphosphonate therapy.

Summary—There are too limited data to recommend universal screening of vitamin D status or supplementation to all HIV-infected individuals. However, testing 25-hydroxyvitamin D levels in those at risk for deficiency and treating patients found to be deficient or initiating antiretroviral therapy or bisphosphonate therapy should be considered. Further study on vitamin D supplementation is needed regarding the potential benefit on immune activation and restoration in this patient group.

Keywords

Vitamin D; Osteoporosis; HIV infection; Antiretroviral therapy

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Conflicts of interest

COH has served on a medical advisory board for Gilead Sciences. GAM has received research grants from BMS, Gilead Sciences and GSK, has served as a consultant to BMS, GSK, Janssen, Merck and Gilead, as a speaker for BMS, GSK and Tibotec and on the DSMB for a Pfizer-sponsored trial. ETO has no conflicts of interest.

Introduction

Vitamin D deficiency is common in people living with HIV infection(1, 2). While data are conflicting as to whether vitamin D deficiency is more prevalent among HIV-infected individuals than in the general population(2, 3*), there are several reasons for why this patient group may be at heightened risk for low vitamin D levels and its consequences. Beyond traditional risk factors, such as inadequate dietary intake, malabsorption syndromes and lack of sun exposure, specific antiretrovirals used in the management of HIV(4) and chronic HIV-associated immune activation(5, 6) have been associated with alterations in vitamin D levels. In non-HIV-infected populations, vitamin D supplementation has been linked with improvement in bone mineral density (BMD) and fracture prevention(7, 8). This is important because both low BMD and fracture are common in HIV-infected individuals. This review outlines the epidemiology of vitamin D deficiency in HIV, summarizes our current understanding of the relationship between vitamin D and bone loss in HIV and the impact of vitamin D supplementation in this patient group with a focus on recently published literature.

Physiology of vitamin D

The physiology of vitamin D and parathyroid hormone (PTH)-vitamin D axis for maintenance of calcium balance and normal bone health have been extensively reviewed(9–12). Briefly, most vitamin D in the circulation comes from conversion of cholesterol precursor 7-dehydrocholesterol in skin to vitamin D (D_3) after exposure to sunlight. Dietary sources of vitamin D (D_2 and D_3) are limited to oil-rich fish such as salmon, mushrooms, fortified foods such as milk and cereal, or vitamin D supplements. After vitamin D enters the body, it is rapidly hydroxylated in the liver by 25-hydroxylase to its major circulating form 25-hydroxyvitamin D [$25(OH)D$]. Assessment of total vitamin D status is best determined by measuring $25(OH)D$ levels as the serum half-life is long, i.e. three weeks, and production in the liver is primarily dependent on substrate concentration(13). Subsequently, $25(OH)D$ is hydroxylated a second time by 1α -hydroxylase in the kidneys to make the hormonal or active form of vitamin D, $1,25$ -dihydroxyvitamin D [$1,25(OH)_2D$]. $1,25(OH)_2D$ has a short half-life, i.e. 4–6 hours, and binds to the vitamin D receptor (VDR) in target tissues. It then enters the nucleus to bind to vitamin D response elements (VDRE) on DNA to regulate gene transcription(14). The hydroxylation of $25(OH)D$ to $1,25(OH)_2D$ is tightly regulated by PTH, calcium and phosphorus to prevent the development of hypercalcemia. Additionally, $1,25(OH)_2D$ induces 24-hydroxylase gene expression to metabolize $25(OH)D$ and $1,25(OH)_2D$ to inactive forms and limit excess calcium release by bone resorption.

The main function of vitamin D is to maintain calcium homeostasis. $1,25(OH)_2D$ binds the VDR in intestinal cells to stimulate calcium and phosphorus absorption. It also binds the VDR in osteoblasts to stimulate expression of receptor activator of nuclear factor κB ligand (RANKL) which interacts with receptor activator of nuclear factor κB (RANK) to induce osteoclast maturation to ultimately mobilize calcium from the bone. Last, calcium reabsorption in the kidney is stimulated by $1,25(OH)_2D$ under the influence of PTH. In fact, each of these actions work in concert with PTH to regulate calcium concentrations. Outside of the effect on calcium homeostasis and bone, vitamin D has a multiplicity of additional

effects. Many other tissues in the body have 1α -hydroxylase and can convert 25(OH)D to $1,25(\text{OH})_2\text{D}$ to act locally as a paracrine/autocrine hormone(10, 14). VDR activation affects levels of inflammatory cytokines and elicits potent immunomodulatory effects(15, 16). Thus, vitamin D regulates many factors important for health and pertinent to the HIV-infected population.

The optimal 25(OH)D level remains controversial and varies depending on the physiologic processes being evaluated(17, 18). Furthermore, consensus is lacking for the optimal vitamin D level for persons of African descent, a racial group that is disproportionately affected by HIV infection(19). Despite this debate, many authorities currently define vitamin D deficiency as $25(\text{OH})\text{D} < 20 \text{ ng/ml}$ (or 50 nmol/L)(17, 18) and vitamin D insufficiency as $25(\text{OH})\text{D} \text{ level} < 30 \text{ ng/ml}$ (or 75 nmol/L)(18).

Vitamin D deficiency in HIV

Numerous studies have reported the prevalence of low vitamin D in HIV-infected individuals. These reports consistently demonstrate a high prevalence of vitamin D deficiency, but rates vary widely across studies. The variance is due to different cutoffs used to define deficiency, locations at different latitudes or varying proportion of participants with dark skin, advanced immunodeficiency or antiretroviral therapy (ART) use. In recent publications, the prevalence of $25(\text{OH})\text{D} < 30 \text{ ng/mL}$ in HIV-infected adults mostly ART-treated was 72% in Spain(20), 71% in Thailand(21*), 70% in the US(2), 54% in Australia(22*), 24% in one study in Brazil(23*) and 83% in another(24). In ART-naïve HIV-infected adults, 59% had $25(\text{OH})\text{D}$ levels $< 20 \text{ ng/mL}$ in London(25). The data can be compared to the general adult population for the 2005–2006 National Health and Nutrition Examination Survey, wherein 41.6% of adult participants, including 82% of blacks, had $25(\text{OH})\text{D}$ levels $< 20 \text{ ng/mL}$ (26). Vitamin D status may be more important to characterize in HIV-infected children/youth, as peak bone mass is not attained until age 25. The prevalence of $25(\text{OH})\text{D} < 30 \text{ ng/mL}$ in perinatally-infected children and young adults on ART was 43% in Thailand(27*), but reported in 96% in a Parisian cohort(28). In the US, 87% of behaviorally-infected(1) and 56% of perinatally-infected(29) children and young adults had $25(\text{OH})\text{D} < 15 \text{ ng/mL}$. Clearly, there are a substantial proportion of the HIV-infected population with Vitamin D deficiency.

Studies comparing $25(\text{OH})\text{D}$ in HIV-infected individuals with uninfected controls have reported conflicting data(1–3*, 28–30*, 31–34) likely confounded by numerous clinical and HIV-related parameters, so it is challenging to confirm whether low vitamin D is more common with HIV infection. In fact, many studies indicate that vitamin D levels are similar for HIV-infected and uninfected cohorts (1, 2, 28, 31, 32, 34). For example, among the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN Study) participants, a cohort of HIV-infected adults in the US on contemporary ART, the prevalence of vitamin D insufficiency or deficiency ($25(\text{OH})\text{D} < 30 \text{ ng/mL}$) was 70.3% (95% CI 68.1–74.9%) compared to a prevalence of 79% (95% CI 76.7–81.3%) in National Health and Nutrition Examination Survey (NHANES) participants, a nationally representative sample of adults in the US, matched by age, race and sex(2). Nevertheless,

some HIV-infected patients are clearly at heightened risk for vitamin D deficiency and its consequences.

Traditional risk factors certainly play a role. In most studies, African descent and dark skin tone are associated with lower 25(OH)D levels(2, 3*, 20, 22*, 25, 28–30*, 31, 32). It is well established that HIV disproportionately affects African American individuals in the US and in the world. According to the Centers for Disease Control, in 2014, the rate of HIV infection in the US was 49.4 per 100,000 population in African Americans, higher than any other racial group and 8 times higher than whites(35). While the relevance of vitamin D deficiency to osteoporosis in African Americans has been questioned(19, 36*), race is certainly a factor associated with vitamin D levels among HIV-infected patients. Another frequently associated traditional risk factor is relative exposure to sunlight captured across studies as UV index, location, season or use of sunscreen(1–3*, 22*, 23*, 25, 27*, 29, 30*, 31, 32). It is possible that HIV infection, specifically advanced disease, may result in a more sedentary lifestyle and therefore less sun exposure. Dietary intake is the other primary mechanism to increase vitamin D levels. Studies are mixed with regard to whether HIV-infected individuals consume adequate levels(1, 24). Malabsorption related to HIV-related changes in the gastrointestinal tract may be highly relevant in the setting of HIV infection, as well. On the other hand, just as in the general population(37), high body mass index and obesity are associated with low vitamin D in HIV(2, 23*, 29, 32).

Beyond traditional risk factors, issues specific to HIV contribute to vitamin D deficiency. The enzymes responsible for vitamin D metabolism are cytochrome P450 monooxygenases. Some antiretrovirals, specifically the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz and protease inhibitors (PIs), interact with some of these enzymes and have been linked with changes in vitamin D levels. Efavirenz is a potent inducer of the CYP3A4 (25-hydroxylase) and CYP24 (24-hydroxylase) enzymes which catalyze hydroxylation of vitamin D₃ to 25(OH)D₃ and catabolism of 1,25(OH)₂D to inactive forms, respectively(38). Use of efavirenz has been linked with vitamin D deficiency in several cross-sectional studies(2, 21*, 39*). Also, in ART-naïve HIV-infected adults, initiation of ART with an efavirenz-containing regimen resulted in a decrease in 25(OH)D levels and progression to severe vitamin D deficiency (25(OH)D < 10 ng/mL)(4, 40), a finding that may be even more pronounced in patients over 50 years of age(41). Last, it has been suggested that efavirenz use may make it more difficult to achieve sufficient levels of 25(OH)D with vitamin D supplementation(42) although recent studies do not support this idea(43, 44*). The clinical relevance of the effect of efavirenz on vitamin D status is unclear as long term studies evaluating efavirenz use, 25(OH)D levels, BMD and fracture rates are not available; however, cross-sectional studies have linked efavirenz use with low BMD in this patient group(39*).

Protease inhibitors inhibit 25-hydroxylase and 1 α -hydroxylase in hepatocyte and monocyte cultures, enzymes responsible for hydroxylation of vitamin D₃ to 25(OH)D₃ and 25(OH)D₃ to 1,25(OH)₂D₃, respectively(45). While there is biologic plausibility for PI-containing regimens to contribute to low vitamin D levels, recent clinical studies have failed to confirm that PIs increase vitamin D deficiency risk. A lower risk of having 25(OH)D < 30 ng/mL was reported in patients on PI-monotherapy compared with no treatment(20) and in a pilot

study of oral high dose cholecalciferol in postmenopausal HIV-infected women with $25(\text{OH})\text{D} < 20 \text{ ng/mL}$, use of PIs was not associated with inability to replete to sufficient levels(46*). However, PI use has been associated with lower $1,25(\text{OH})_2\text{D}$ levels in HIV-infected adults with $25(\text{OH})\text{D} < 20 \text{ ng/mL}$ (47*). Thus, PIs may block the generation of the active vitamin D metabolite with potential important consequences for bone health.

The nucleotide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) has been linked with increased PTH levels, phosphate wasting by the kidney and low BMD in treated HIV-infected patients(48–51), but there is no direct evidence that this occurs through alterations in vitamin D metabolism. However, vitamin D status may modify the effect of TDF on PTH levels(48, 52) and on BMD(47*). In small study where HIV-infected participants initiated ART with regimens containing TDF/FTC or ABC/3TC, PTH levels were significantly higher in the TDF/FTC group early after ART initiation and remained above normal limits through 48 weeks. At week 24 and 48, TDF/FTC users with $25(\text{OH})\text{D}$ levels $< 30 \text{ ng/mL}$, had the highest PTH levels suggesting suboptimal baseline $25(\text{OH})\text{D}$ levels increase the risk of secondary hyperparathyroidism among TDF users(48). In another study, TDF use was associated with lower hip BMD compared to non-TDF users, a difference that was more pronounced in those with $25(\text{OH})\text{D} \geq 20 \text{ ng/mL}$ (47*). It is possible that TDF-induced proximal renal tubular dysfunction resulting in urinary loss of phosphate may stimulate an increase in PTH levels. Increased PTH may result in increased conversion of $25(\text{OH})\text{D}$ to active $1,25(\text{OH})_2\text{D}$ with resultant decrease in circulating $25(\text{OH})\text{D}$ (53).

In addition to specific antiretroviral therapy agents, chronic HIV-associated inflammation and immune activation may also contribute to low vitamin D. In vitro, monocytes stimulated with HIV viral envelope protein gp120 and LPS increased expression of CYP27B1, the enzyme that catalyzes the conversion of $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$. In macrophages, stimulation with LPS led to enhanced expression CYP24A1, the enzyme that inactivates $1,25(\text{OH})_2\text{D}$. The authors of this study hypothesize that these immune cells convert and utilize active vitamin D to regulate immune response leading to increased vitamin D consumption and lower available $25(\text{OH})\text{D}$ (6). Further, it has been suggested that excess TNF α which typifies chronic HIV infection results in an inhibition of the usual stimulatory effect of PTH on the renal 1α -hydroxylase(5, 54). In clinical studies, vitamin D levels have been associated with markers of systemic inflammation in some(55*), but not all recent studies(56*). In HIV-infected individuals on ART, higher $25(\text{OH})\text{D}$ levels were associated with lower TNF α levels; although vitamin D supplementation did not alter the levels of inflammatory markers tested(55*). Perhaps, there is an inherent genetic component to the regulation between vitamin D and systemic inflammatory markers. Future studies can explore these relationships.

Vitamin D and bone in HIV

In recent studies, the prevalence of osteopenia ranges from 33–58% and osteoporosis from 2–13% among the HIV-infected participants(57–63). When compared to the general population, HIV-infected persons are more likely to have low BMD (34, 58, 61, 64, 65). Strikingly, the risk of bone fracture appears to be higher in people living with HIV as well. In a meta-analysis of studies evaluating fracture risk with HIV infection, the crude incidence

rate ratio for all fractures was 1.58 (95% CI 1.25–2) for HIV-infected participants compared to controls and the incidence of fragility fracture among HIV-infected groups ranged from 1–7.4 per 1000 person-years in the included studies(66). Since this report, additional studies have continued to substantiate this heightened fracture risk(67, 68).

The causes of bone loss in HIV are still being elucidated and include traditional risk factors for osteoporosis(59, 69), wasting syndrome and hypogonadism associated with advanced AIDS(70), direct ART toxicity and immune activation both with chronic HIV infection(71) and with T-cell repopulation after ART initiation(72, 73). The contribution of vitamin D deficiency is largely unknown unlike in the general population where data from randomized clinical trials have shown improvement in BMD and fracture risk with vitamin D supplementation(7, 8). Recently, in a cross-sectional study of HIV-infected adults in Africa, higher vitamin D levels were associated with higher total hip BMD, but there was no association with spine BMD. In this study having a Z score < -2 on DXA was present in 17 and 5% at the lumbar spine and total hip, respectively, and vitamin D deficiency was present in only 15% of participants(39*). Also, analysis of baseline data from the HIV UPBEAT study, a prospective, cohort study of HIV-infected and -uninfected participants from similar demographic backgrounds, showed that after adjustment for traditional osteoporosis risk factors, 25(OH)D levels were not associated with BMD(34).

Supplementation trials provide some insight, but there are only a few reporting on change in bone markers or BMD and none large enough to study fracture risk. Supplementation of HIV-infected patients with 25(OH)D < 75 nmol/L with cholecalciferol 300,000 IU, led to a decrease in bone turnover markers, including bone specific alkaline phosphatase, pyridinoline, desoxypyridinoline, and 25(OH)D levels increased significantly after three months(74).

With regard to BMD as an endpoint, trials evaluating the effect of alendronate for the treatment of low BMD in HIV have used vitamin D and calcium supplementation as the comparison/control arm(75, 76). In the larger study by McComsey GA, et al, BMD increased in the lumbar spine, total hip and femoral neck by 1.1% (p=0.08), 1.31% (p=0.03) and 1.24% (p=0.07) in the vitamin D plus calcium group over 48 weeks(75). Also, in this study, having a 25(OH)D < 32 ng/mL was associated with a greater BMD response to alendronate(77**). This latter point reinforces the importance of vitamin D supplementation to optimize the impact of bisphosphonate therapy on BMD. While these studies suggest that vitamin D supplementation modestly increases BMD in HIV-infected adults with low BMD, they were not primarily designed to test the effect of vitamin D as they utilized a low dose, i.e. 400 IU/day, and excluded individuals with severe vitamin D deficiency. In a recent randomized clinical trial to evaluate the effect of vitamin D₃ (4000 IU/day) and calcium (1000 mg/day) supplementation on bone loss associated with ART initiation over 48 weeks, those participants randomized to vitamin D₃ and calcium had a smaller percent decline in total hip BMD than placebo [-1.36% (IQR -3.43 to 0.5%) vs -3.22% (IQR -5.56 to -0.88); p=0.004]. Similar results were seen in spine BMD. Median change in 25(OH)D in the vitamin D arm was 61.2 nmol/L (IQR 36.4 to 94.3 nmol/L). Vitamin D and calcium at the doses provided in the study were well tolerated with no hypercalcemia(78**). Importantly,

this finding may not be generalizable to all ART regimens or be solely related to the vitamin D supplementation.

Unfortunately, limited data are available in HIV-infected youth, a group at risk for failing to reach peak BMD. In a 96 week, randomized placebo controlled trial in children perinatally-infected, the effect of cholecalciferol (100,000 IU given every 2 months) with calcium (1000 mg/day) on bone mass accrual was evaluated. While 25(OH)D levels increased only in the active treatment arm, bone mass increased in both groups without between group differences(79). In this study, youth with severe vitamin D deficiency were excluded. Eckard et al recently presented a randomized, active-control, double-blind trial investigating two different monthly vitamin D₃ doses [60,000 or 120,000 IU/month] vs a control arm of 18,000 IU/month in HIV-infected youth on ART with baseline 25(OH)D = 30 ng/mL. After 12 months of supplementation, 25(OH)D increased from 17 (11, 21) ng/mL to 31 (22, 37) ng/mL in the control group and from 18 (14, 22) ng/mL to 42 (33, 53) ng/mL in the combined medium and high dose groups (within and between groups $p < 0.001$), but there were no differences between groups in changes in BMD or bone markers(80**). Notably, supplementation decreased markers of T-cell activation and exhaustion and monocyte activation regardless of the dose; although, participants given the highest dose showed the greatest improvements(81). Collectively, these studies suggest that there is a role for vitamin D supplementation in HIV-infected patients initiating ART and while undergoing treatment with alendronate for low BMD, but the effect of supplementation outside of these two settings is unclear. Vitamin D supplementation may offer extra-skeletal benefits in HIV, including on immune activation, which in the long term may positively impact bone accrual, but further studies are needed.

Screening and clinical management of vitamin D deficiency

Guidelines for clinicians on the screening and management of vitamin D deficiency vary. The European AIDS Clinical Society guidelines recommend checking vitamin D status in HIV-infected persons with a history of low BMD and/or fracture and in those at high risk for fracture and to consider checking vitamin D status in persons with dark skin, dietary deficiency, those avoiding sun exposure, with malabsorption, obesity, chronic kidney disease and on efavirenz or PIs. Further, these guidelines recommend vitamin D supplementation for those with 25(OH)D < 10 ng/mL and to consider with 25(OH)D < 20 ng/mL if the patient has low BMD or increased PTH(82). The Endocrine Society Clinical Practice Guidelines are not specific to HIV infection, but are similar. For screening, these guidelines recommend checking vitamin D status by measurement of 25(OH)D levels in at risk individuals defined as above, but also including those with hepatic failure, granuloma-forming disorders, lymphomas and on anticonvulsants, glucocorticoids, antifungals, cholestyramine. These guidelines recommend vitamin D replacement for individuals with 25(OH)D < 30 ng/mL(18). Finally, the Institute of Medicine suggests that 25(OH)D levels of 20 ng/mL cover the requirements for skeletal health of at least 97.5% of the population and caution supplementing to levels higher than 50 ng/mL(17). Taken together and with the available literature regarding vitamin D in HIV, at risk HIV-infected individuals should be screened for vitamin D deficiency using 25(OH)D levels. Supplementation with vitamin D should be

considered in HIV-infected individuals initiating ART, starting bisphosphonate therapy for low BMD or with vitamin D deficiency.

Conclusion

In conclusion, vitamin D deficiency is common in people living with HIV infection. Beyond traditional risk factors, specific antiretroviral agents and chronic HIV-associated immune activation likely contribute to low vitamin D in this patient group. As in the general population, there is an association between low vitamin D and low BMD in HIV-infected individuals; and, while the data are limited, vitamin D supplementation appears to be safe and beneficial especially for the prevention of bone loss with ART initiation and in conjunction with bisphosphonate therapy for treatment of low BMD. Because of the high prevalence of osteopenia and osteoporosis in the aging HIV population, screening for vitamin D deficiency with serum 25(OH)D levels and strong consideration for vitamin D supplementation should be made for both the treatment and prevention of bone disease in HIV-infected patients.

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Key Points

- Vitamin D deficiency is common in HIV-infected individuals and is linked with traditional risk factors, specific antiretrovirals including efavirenz and protease inhibitors, and chronic activation of the immune system.
- Limited evidence suggests low vitamin D levels are related to low bone mineral density in HIV-infected individuals, but data regarding the effect on fracture risk are lacking.
- Vitamin D supplementation with calcium does decrease bone loss after antiretroviral therapy initiation and is important during bisphosphonate therapy for low bone mineral density in HIV-infected adults, but requires further study in other scenarios.
- The link between vitamin D supplementation and modification of immune activation is intriguing and requires further study.