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Vitamin D Deficiency and Altered Bone Mineral Metabolism in HIV-infected Individuals

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Abstract

Although patients with HIV infection are living decades longer than before with the advent of combination antiretroviral therapy, they have an increased rate of co-morbidities associated with chronic HIV, such as osteoporosis, cardiovascular disease, and immune dysfunction. Many of these complications are known to be affected by vitamin D status in the general population. Thus, the high rate of vitamin D deficiency among HIV-infected patients is alarming. Many observational and cohort studies have demonstrated that vitamin D deficiency is associated with these HIV-related complications, but randomized, placebo-controlled trials are limited. This paper reviews recent data on vitamin D deficiency in HIV infection.

Keywords

HIV/AIDS; 25-hydroxyvitamin D; vitamin D deficiency; bone; immune system; cardiovascular disease

INTRODUCTION

Much attention has been given to the field of vitamin D in HIV-infected patients over the last few years, as research has shown that the prevalence of vitamin D deficiency in the HIV-infected population, as determined by blood concentrations of 25-hydroxyvitamin D (25(OH)D), is very high and widespread. Studies have demonstrated >90% of subjects with HIV have concentrations <30 ng/mL, a level suggested to be optimal for vitamin D status [1-7].

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Compliance with Ethics Guidelines

Conflict of Interest

Allison Ross Eckard has received research funding from Bristol-Myers Squibb, Cubist Pharmaceuticals, and GlaxoSmithKline and has served as an advisor for Gilead.

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Human and Animal Rights and Informed Consent

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

Although the life expectancy of HIV-infected patients is approaching that of the general population as the result of the use of potent antiretroviral therapy (ART), HIV-infected patients are at a higher risk than the general population for complications like osteoporosis, non-AIDS-defining malignancies, and cardiovascular disease (CVD). Notably, many of the complications related to chronic HIV infection represent disease processes where vitamin D is known to play an important role [8-12]. In addition, vitamin D has long been known to play a key role in the immune system, making it even more important to be studied in the HIV-infected population.

The pathophysiology of vitamin D and the prevalence and risk factors of vitamin D deficiency in HIV are discussed only briefly here, but can be found in greater detail elsewhere [13, 14]. This paper will primarily focus on the most important recent developments in the field of vitamin D in HIV infection.

PHYSIOLOGY OF VITAMIN D

The main function of vitamin D is to maintain serum calcium concentrations in a physiologically-acceptable range [7]. Specifically, this occurs when 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$), the active form of vitamin D, interacts with its nuclear receptor, the vitamin D receptor (VDR) in the small intestinal cells. This interaction increases the absorption of dietary intake of calcium from only 10-15% to 30-40% and enhances phosphorus absorption by an additional 20%. When calcium absorption is low, serum-ionized calcium levels decrease which stimulate the parathyroid glands to produce parathyroid hormone (PTH). Parathyroid hormone increases tubular reabsorption of calcium, and enhances the expression of the plasma membrane protein receptor activator of NF- κ B ligand (RANKL) on osteoblasts to increase the production of mature osteoclasts which in turn mobilize calcium from bone, restoring serum calcium concentrations to a normal range. Parathyroid hormone also mobilizes phosphorus from bone, as well as decreases kidney phosphorus reabsorption which causes phosphaturia. Both calcium and phosphorus promote bone mineralization.

Most vitamin D found in circulation comes from the skin after exposure to ultraviolet-B radiation. Dietary sources of vitamin D are limited to fortified foods, fatty fish or supplements. After vitamin D enters the body, it circulates bound to vitamin D binding protein (DBP) and is rapidly converted by the liver to its major circulating form, $25(\text{OH})\text{D}$. In general, $25(\text{OH})\text{D}$ concentrations are the best indicator of overall vitamin D status. Under the influence of PTH, $25(\text{OH})\text{D}$ is converted by 1- α -hydroxylase ($1\alpha\text{-OHase}$) in the kidney to make the hormonal form of vitamin D, $1,25(\text{OH})_2\text{D}$.

Many other tissues in the body also have $1\alpha\text{-OHase}$ and can convert $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$ to act locally as a paracrine/autocrine hormone [15]. $1,25(\text{OH})_2\text{D}$ binds to the VDR and enters the nucleus to bind to vitamin D response elements (VDRE) on DNA to regulate transcription of hundreds of genes. Thus, vitamin D regulates many factors important for optimal health, not limited to bone metabolism.

VITAMIN D DEFICIENCY AND HIV-SPECIFIC FACTORS

The Role of Efavirenz—While the causes of vitamin D deficiency in HIV are multifactorial, including inadequate diet and darker skin pigmentation, certain commonly-prescribed antiretroviral medications, particularly efavirenz (EFV), have been shown to interfere with normal vitamin D metabolism [3, 6, 16]. Efavirenz appears to accelerate the catabolism of 25(OH)D through the upregulation of 24-OHase, the enzyme that breaks down 25(OH)D [17], or through the suppression of 25-OHase, the enzyme which converts vitamin D₂ and D₃ to 25(OH)D [18]. For example, EFV initiation is associated with a 70-80% increase in the risk of severe vitamin D deficiency, compared to non-EFV regimens [3]. However, with a high supplementation dose, EFV's effect on 25(OH)D levels may be overcome. For example, in a randomized-controlled trial of 4,000 IU vitamin D₃ daily versus placebo for 12 weeks in 45 HIV-infected adults on stable ART with baseline 25(OH)D = 20 ng/mL, participants in the vitamin D arm who were on EFV (N = 9) did not have a significantly different change in serum 25(OH)D concentrations compared to those who were not on EFV (N = 20) (P = 0.54) [16]. Similarly, in the recent AIDS Clinical Trials Group (ACTG) A5280 study, a prospective, randomized, double-blind, placebo-controlled study evaluating the effect of high-dose vitamin D plus calcium supplementation on bone mineral density (BMD) in HIV-infected subjects starting ARVs with EFV, emtricitabine, and tenofovir (TDF), 4,000 IU daily of vitamin D₃ increased the median 25(OH)D concentration from 26.7 ng/mL at baseline to a median of 56.4 ng/mL at 48 weeks [••19].

Studies evaluating changing antiretrovirals, however, are conflicting. In a recent randomized-controlled study of 30 HIV-infected subjects, who were either continued on TDF/emtricitabine/EFV or switched to TDF/emtricitabine/raltegravir for 24 weeks, there were no significant differences in changes in 25(OH)D concentrations [20]. In contrast, 25(OH)D concentrations were measured at screening and after 96 weeks in a subset of subjects (N=178) from the MONET trial, which evaluated a switch from a non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based ART regimen to darunavir/ritonavir (with or without 2 nucleoside reverse transcriptase inhibitors). Increases in vitamin D between screening and week 96 were significantly greater for patients who discontinued EFV versus those who stopped other antiretrovirals (except zidovudine). In multivariate analysis, stopping EFV was significantly associated with increases in 25(OH)D level (P=0.0074) [21].

Thus, it is not clear at this time that avoiding or stopping the use of EFV is warranted. Instead, the Endocrine Society has endorsed screening for vitamin D deficiency in patients at high risk, which now includes those taking antiretrovirals [7]. In addition, patients on EFV may require higher repletion or maintenance doses of vitamin D than patients on other antiretrovirals, although precise dosing data are not yet available. Screening 25(OH)D concentrations and close monitoring of HIV-infected patients on ART, especially at ART initiation, should be considered.

ALTERED BONE METABOLISM IN HIV

The Role of Vitamin D—In the HIV population, the pathophysiologic mechanisms underlying bone changes are poorly understood. The extent to which vitamin D deficiency

contributes to osteopenia and osteoporosis in the HIV population is largely unknown, unlike in the general population where there are data from randomized, placebo-controlled trials that vitamin D and calcium supplementation modestly but significantly decrease the risk of fractures and improve BMD [22-24]. Even in healthy children, vitamin D supplementation, particularly among those with vitamin D deficiency, shows promise in improving BMD [25, 26]. However, there are only a few randomized, placebo-controlled supplementation trials in the HIV population, and results have been conflicting.

Two studies were designed to compare alendronate with vitamin D and calcium versus vitamin D and calcium alone for the treatment of osteopenia/osteoporosis in HIV-infected individuals [27, 28]. For example, in McComsey, *et al*, the authors demonstrated that alendronate in combination with vitamin D and calcium increased lumbar spine and hip BMD by 3.5-5% at 48 weeks compared with an increase of ~1.5% in subjects receiving vitamin D and calcium alone. However, as this study was not designed primarily to evaluate vitamin D supplementation as a treatment for osteoporosis, the authors did not evaluate 25(OH)D concentrations at baseline or changes over time, only administered a very low-dose of vitamin D (400 IU/day), and excluded subjects with 25(OH)D <15 ng/mL at the study screening visit.

The recent ACTG A5280 study is the only study to date that has used vitamin D and calcium as a strategy to prevent bone loss associated with ART initiation [19]. Overton, *et al* included 142 subjects in the analysis that investigated giving 4,000 IU of vitamin D and 1,000 mg of calcium carbonate daily for 48 weeks starting at ART initiation with EFV/emtricitabine/TDF. Results showed that vitamin D/calcium supplementation led to about half the extent of bone loss normally seen after initiation of ART (median total hip BMD) change in treatment arm: -1.46% vs. placebo: -3.16%; $P = 0.001$). However, it is important to note that it is unclear if this finding can be generalized to all ART regimens and whether it was the calcium or vitamin D that contributed to the preventive effect of bone loss.

Only one study has been specifically designed to evaluate the bone effects of vitamin D supplementation in HIV-infected children and adolescents [29]. Arpadi, *et al* evaluated the bone mass accrual in 64 perinatally-infected individuals, aged 6-16 years, after 2 years of 100,000 IU of vitamin D₃ every other month plus daily calcium compared to placebo. They did not find any difference in bone mass parameters between the two groups after adjusting for confounding variables. However, while the intervention group increased their mean 25(OH)D concentrations after two years compared to the placebo group, 75% in the treatment group had at least 1 month with 25(OH)D <30 ng/mL. In addition, individuals screened who were found to have severe vitamin D deficiency (<12 ng/mL) were ineligible for the study, the group where one would be most likely to see a change in BMD with vitamin D supplementation. In another recent study, investigators examined change in bone markers in HIV-infected subjects on EFV after a single dose of 300,000 IU of vitamin D. Serum levels of both osteocalcin and collagen telopeptidase increased significantly ($P < 0.001$), but obviously this study was short and did not include BMD measurements [30].

Collectively, these studies demonstrate the need for further studies, especially randomized, placebo-controlled trials evaluating long-term changes in BMD after administering adequate

doses of vitamin D in HIV-infected individuals. In particular, patients with baseline vitamin D deficiency might benefit the most from supplementation. Since it is unclear to what extent vitamin D deficiency contributes to decreased BMD in HIV, randomized studies in subjects on stable ART that optimize 25(OH)D concentrations will be necessary to clarify such relationship in HIV.

The Role of Tenofovir—While TDF has been associated with higher PTH levels, renal calcium and phosphate wasting, and lower BMD in HIV-infected subjects [31-36], there are no data that suggest it directly interferes with vitamin D metabolism. In fact, some studies show no difference between 25(OH)D in those on current TDF or not [37]. It appears that TDF-induced proximal renal tubular dysfunction, which can result in excessive urinary losses of phosphate and/or calcium, may stimulate PTH as a compensatory mechanism. The increased PTH stimulates the kidney to produce more 1,25(OH)₂D through 1 α -OH activity, in order to maintain normal blood homeostasis. In support of this, one study found that TDF use was correlated with increased serum concentrations of 1,25(OH)₂D [38]. Similarly, several studies have demonstrated higher PTH levels among TDF-users [39-41], especially among TDF-users with vitamin D deficiency. Perhaps the most convincing evidence is the study by Havens, *et al*, which was a randomized, placebo-controlled trial investigating 50,000 IU of vitamin D₃ monthly for 12 weeks in HIV-infected youth ages 18-24 years old [42]. All 203 subjects were on stable ART (118 TDF-users), and were randomized 1:1 to either receive vitamin D supplementation or placebo. At baseline, TDF-users, regardless of vitamin D status, had higher levels of PTH, which decreased within the study period among the TDF-users who received vitamin D, but not in the non-TDF-users who received vitamin D or in placebo group. However, vitamin D supplementation did not change the amount of tubular reabsorption of phosphate or the serum levels of the bone markers, C-telopeptide and bone alkaline phosphatase. Thus, while TDF may predispose HIV-infected individuals to elevated PTH, its effect on 25(OH)D concentrations remain unclear. Similarly, it is unclear how much of the bone effects of TDF are related to changes in PTH or 25(OH)D levels.

NONSKELETAL FUNCTIONS OF VITAMIN D IN HIV

Vitamin D and the Immune System

Vitamin D Status and HIV Disease Progression and Mortality: Vitamin D is a steroid hormone which has long been known to play a critical role in the immune system, including effects on innate immunity, adaptive immunity, and levels of inflammatory cytokines [15, 43-45]. In non-HIV populations, an individual's vitamin D status affects their susceptibility to tuberculosis, the disease severity, and their response to treatment [46, 47]. Clinical studies have also shown that children with vitamin D deficiency and rickets are predisposed to respiratory infections and pneumonia, and vitamin D supplementation reduces this risk [48-51]. The extensive effects of vitamin D on the immune system in the general population are discussed in detail elsewhere [15, 44, 45]. This section will focus on recent studies investigating the impact of vitamin D status on immunologic and virologic aspects of HIV infection.

Recent observational cohort studies suggested that vitamin D status affects HIV infection, disease progression and mortality. Vitamin D deficiency has not only been shown to

contribute to HIV disease progression and mortality in HIV-infected pregnant women in resource-limited settings [52], but also increases the overall risk of mother-to-child transmission (MTCT) by 46% [53]. The HIV-infected children born from these HIV-infected women with vitamin D deficiency also have a 61% higher risk of death during follow-up.

Low vitamin D status also appears to negatively affect HIV progression and mortality in non-pregnant populations [54-57]. Within the EuroSIDA study, 2000 subjects were randomly selected to examine the association between 25(OH)D measured from stored plasma samples and HIV disease progression [55]. Compared to those in the lowest 25(OH)D tertile (<12 ng/ml), those in the middle (12-20) and higher (>20) tertiles had a significantly lower risk of clinical progression during subsequent follow-up. Adjusted incidence rate ratios for all-cause mortality were 0.68 (95% CI 0.47-0.99, $P = 0.045$) and 0.56 (95% CI 0.37-0.83, $P = 0.0039$), and for AIDS events were 0.58 (95% CI 0.39-0.87, $P = 0.0086$) and 0.61 (95% CI 0.40-0.93, $P = 0.020$), for the middle and higher tertiles, respectively. In a recent follow-up study, the authors performed a prospective 1-1 case-control study nested with the EuroSIDA cohort [57]. Matched cases and controls for AIDS, non-AIDS-defining events and death with plasma samples during follow-up were selected. Among 250 subjects, odds of death decreased by 46.0% (95% confidence interval [CI], 2.0-70.0, $P = .04$) for a 2-fold increase in most recent 25(OH)D level. There was no association between 25(OH)D and the occurrence of AIDS or non-AIDS-defining events ($P > .05$). In patients with current 25(OH)D <10 ng/mL, interleukin-6 concentration increased by 4.7% (95% CI, 0.2,9.4, $P = 0.04$) annually after adjustment for immunological/inflammatory markers, but no change in high-sensitivity C-reactive protein rates were observed ($P = 0.76$).

While the aforementioned observational studies examined 25(OH)D levels and AIDS progression in subjects regardless of ART status, there have been several recent studies that have evaluated similar outcomes in ART-naïve subjects initiating ART. In a nested case-cohort study, 411 subjects within a randomized ART trial in eight low and middle-income countries and the United States were prospectively examined for 96 weeks from ART initiation. Baseline low 25(OH)D was associated with increased risk of HIV progression and death (adjusted hazard ratio (aHR) 2.13; 95% confidence interval (CI), 1.09,4.18). They also demonstrated, for the first time, that low 25(OH)D levels were independently associated with virologic failure (aHR 2.42; 95% CI, 1.33,4.41). In another study of ART initiation, Sudfeld, *et al* showed that vitamin D deficiency (25(OH)D <20 ng/mL) had a significantly greater association with incident pulmonary tuberculosis, compared with vitamin D sufficiency (hazard ratio 2.89; 95% CI, 1.31, 7.41; $P = .027$) [58]. A cross-sectional study of 149 HIV-infected subjects that showed that 25(OH)D levels were associated with CD4 recovery after starting ART support these findings [1].

Taken together, these studies demonstrate the possible role that vitamin D plays in HIV disease progression and possibly immune restoration in HIV infection. Randomized-controlled trials are needed to properly investigate if vitamin D supplementation, particularly at the time of ART initiation, offers a safe and effective means of improving the immune system and inflammation. In addition, more molecular-based studies may be

necessary, as studies have demonstrated that polymorphisms of the VDR may also influence HIV disease progression and susceptibility to infections such as tuberculosis in certain populations [59, 60].

Vitamin D Supplementation and Effects on CD4+ T-cell Count: Data evaluating vitamin D status and CD4+ cell count, on the other hand, have been conflicting. De Luis, *et al* found a positive association between vitamin D intake by questionnaires and CD4+ cell count after adjustment for age, sex, energy and protein intake, and ART [61]. No measurements of 25(OH)D were performed in this study. Another study showed that 25(OH)D concentrations were associated with current CD4+ cell counts in HIV-infected woman on ART [5], but several other cross-sectional studies with other HIV populations did not find the same association [1, 2, 62, 63]. Two randomized, placebo-controlled trials reported that 6-12 months of vitamin D supplementation in HIV-infected children did not change CD4+ cell counts [64, 65]. Notably, these two latter studies were small, supplementation doses were low, and baseline 25(OH)D were relatively high. Moreover, in Arpadi, *et al*, at study completion, more than half of the subjects receiving vitamin D still had 25(OH)D concentrations <30 ng/mL. Interestingly, in one study of 149 ART-treated adults, we showed an independent association between vitamin D status and immune reconstitution, where subjects with higher plasma 25(OH)D concentrations exhibited a more robust increase in CD4+ cell counts after starting ART [1]. This finding, however, has not been consistent in other studies [63].

Ultimately, it is not clear from these studies if increasing an individual's 25(OH)D improves CD4+ cell counts, or if the positive findings seen in these few studies are merely a marker of better health, resulting in increased time spent outdoors and/or improved nutrition among individuals with better immunological status. For example, Rutstein, *et al*, showed that among 81 perinatally-infected children, those with current CDC immunological stage 2 or 3 had an increased odds of vitamin D deficiency (odds ratio (OR) 14.3; 95% CI, 2.7, 76.1; P = 0.002) [4], and in Welz, *et al*, nadir CD4+ cell count <200 cells/ L was associated with severe vitamin D deficiency [6].

Together, the studies investigating vitamin D and its relationship to HIV infection, CD4+ cell counts, and disease progression demonstrate the need for further research. It is currently not clear if optimizing 25(OH)D concentrations could improve CD4 restoration in subjects with baseline low or even normal 25(OH)D, and whether attaining optimal vitamin D status would decrease the deleterious long-term consequences of HIV infection, including immune activation and enhanced inflammation. Only large, well-designed, randomized, placebo-controlled vitamin D supplementation studies in subjects with a range of CD4+ cell counts are needed to answer some of these critical questions.

Vitamin D and Modulation of the Immune System: Recently, studies have shown that vitamin D's effects on the immune system derive from its upregulation of the anti-microbial peptide cathelicidin, or LL-37 [58, 66-69]. In response to endogenously-produced 1,25(OH)₂D, cells produce LL-37, which in turn inhibits bacteria through the disruption of the cellular membrane, but also has broad anti microbial activity against gram-positive and – negative bacteria, as well as certain viruses and fungi. LL-37 also exerts chemotactic,

immunomodulatory, and angiogenic effects, and affects serum levels of pro-inflammatory cytokines. Moreover, LL-37 has been shown to increase autophagy in macrophages to enhance innate immunity against viral infections [67], and *in vitro* LL-37 inhibits HIV replication in peripheral blood mononuclear cells including in CD4+ T-cells [68, 69]. LL-37 is produced by various epithelial cell types, including oral, genital and gut mucosa [70], critical tissues for HIV entry. Concentrations of LL-37 elicited by macrophages in response to 1,25(OH)₂D are similar to what is found in cervicovaginal secretions, where higher baseline genital levels are independently associated with increased acquisition of HIV-1 [71]. Thus, more studies are needed in order to determine the full effect of 1,25(OH)₂D and LL-37 on HIV entry and replication.

In addition to vitamin D's effect on innate immunity, evidence shows that 1,25(OH)₂D modulates the adaptive immune system as well, through direct effects on T-cell activation and on the phenotype and function of antigen-presenting cells [15]. Activation of CD4+ T cells results in a 5-fold increase in VDR expression, enabling regulation of at least 102 identified genes responsive to 1,25(OH)₂D [72]. In addition, 1,25(OH)₂D suppresses T-cell receptor-induced T-cell proliferation and alters their cytokine expression profile, so that the activated T-cell response is more a Th2-like response instead of Th1-like [73-75]. Vitamin D also plays a role in systemic inflammation, as it affects various levels of inflammatory cytokines, including interleukin-6 [43].

Vitamin D and Risk of Diabetes—Vitamin D deficiency is also associated with Type-1 and Type-2 diabetes in the general population, as it affects insulin sensitivity and pancreatic cell function. Vitamin D repletion improves both insulin sensitivity and insulin secretion in animal and human studies, thus lowering the risk of future diabetes [76]. An association between vitamin D deficiency and β -cell dysfunction has also been reported in healthy and glucose-tolerant subjects, non-diabetics, and patients with Type-2 diabetes [77-79]. One large cohort study found that HIV-infected subjects with vitamin D deficiency had an 80% higher prevalence of diabetes compared to those with normal 25(OH)D concentrations [80]. However, in a placebo-controlled vitamin D supplementation trial, we showed that vitamin D supplementation worsened insulin resistance, as measured by homeostasis model assessment of insulin resistance (HOMA-IR) [16]. Thus, given that the HIV-infected population is at an increased risk of insulin resistance and diabetes, vitamin D status and optimization of deficient patients and the effects on glucose metabolism deserves further research.

Vitamin D Deficiency and Risk of Cardiovascular Disease—In the general population, vitamin D insufficiency is associated with a 2-fold increased risk of developing an initial cardiovascular event in previously healthy asymptomatic individuals [11]. This association between vitamin D and incident CVD remained significant after adjustment for several confounders associated with CVD including age, sex, systolic blood pressure, diabetes, total to high-density lipoprotein (HDL) cholesterol ratio, body mass index, and tobacco use. Proposed mechanisms of vitamin D's role in CVD include its effects on the renin-angiotensin system [45], on glycemic control [81], and on inflammatory cytokines

[82], and/or its direct effects on the vasculature by affecting proliferation of myocardial and vascular smooth muscle cells [83-87].

Few studies have investigated the association between CVD and vitamin D deficiency in the HIV population. In a cross-sectional study, we showed a significant association between vitamin D status and common carotid artery intima-media thickness (CCA IMT), a marker of subclinical vascular disease, in a group of HIV-infected subjects on stable ART [1]. Subjects with CCA IMT levels below the median were >10 times more likely to have the highest levels of 25(OH)D (i.e. lower IMT values = lower CVD risk) (OR 10.62; 95% CI, 1.37,82.34, $P < 0.01$). Another cross-sectional study found similar results [88]. Likewise, in Lai, *et al*, vitamin D deficiency was independently associated with development of subclinical coronary artery disease, as assessed by coronary calcifications detected by computed tomography scan in 169 HIV-infected African-American cocaine users with low Framingham risk score [89]. These data suggest that a high 25(OH)D concentration may be protective against CVD development in HIV-infected patients, but randomized, placebo-controlled trials are needed to further examine this association.

CONCLUSIONS

Chronic HIV infection causes an increased risk of osteoporosis, immune system dysfunction, and increased systemic inflammation— all pathophysiologic mechanisms where vitamin D is known to play an important role. Vitamin D deficiency is widespread among HIV-infected individuals, and supplementation to achieve adequate circulating concentrations of 25(OH)D may help minimize the risk of HIV-related complications. However, much of the current knowledge is based on observational studies which do not establish causation. More research is needed to better characterize the implications of vitamin D deficiency in the HIV population.

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