Published in final edited form as:

Curr HIV/AIDS Rep. 2018 June ; 15(3): 199–211. doi:10.1007/s11904-018-0401-4.

Continued Interest and Controversy: Vitamin D in HIV

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Abstract

Purpose of Review—Vitamin D (VitD) deficiency is highly prevalent among HIV-infected individuals. Given the overlapping risk for several chronic disease and immunomodulatory outcomes from both long-standing HIV and VitD deficiency, there is great interest in clarifying the clinical role of VitD for this population.

Recent Findings—Recent studies have expanded our knowledge regarding the epidemiology and mechanisms of VitD deficiency-associated outcomes in the setting of HIV. Clinical trials focusing on VitD supplementation have demonstrated a positive impact on bone mineral density in subgroups of HIV-infected individuals initiating ART or on suppressive ART regimens; however significant heterogeneity exists between studies and data are less consistent with other clinical outcomes.

Summary—Further research is needed to clarify uncertainly in several domains, including identifying patients at greatest risk for poor outcomes from VitD deficiency, standardizing definitions and measurement techniques, and better quantifying the benefits and risks of VitD supplementation across different demographic strata for skeletal and extra-skeletal outcomes.

Keywords

Vitamin D; HIV/AIDS; Vitamin D Supplementation; Antiretroviral Therapy; Musculoskeletal Health; Immune Function; Cardiovascular Disease

Introduction

Vitamin D (VitD) plays an essential role in calcium homeostasis and has historically been linked to disorders of bone mineralization [1, 2]. In recent decades, the potential role of VitD in a multitude of extra-skeletal health outcomes—including muscle function and falls,

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Compliance with Ethics Guidelines

Conflict of Interest

Dr. Hsieh is supported by NIH/Fogarty International Center K01TW009995, the Yale Center for Clinical Investigation/Doris Duke Charitable Trust Foundation Fund to Retain Clinical Scientists and has received honoraria from Gilead. Dr. Yin is supported by NIH/NIAID R01 AI-095089 and has served as a consultant for Gilead and Viiv.

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.

immune function and autoimmunity, cardiovascular disease, diabetes, and cancer—has also been illuminated [3, 4]. This, compounded by data demonstrating high prevalence of VitD deficiency worldwide, has prompted an explosion of interest in VitD and the potential benefits of VitD supplementation.

Similar to the general population, studies have shown VitD deficiency is highly prevalent among individuals with HIV [5–7]. Chronic HIV infection is associated with increased risk for comorbidities including cardiovascular disease (CVD), osteoporosis and fractures, cancer, and other conditions classically associated with aging. Given the overlapping risk for chronic disease outcomes with those observed in VitD deficiency, and importance of immune function in HIV disease progression and susceptibility to opportunistic infection, there has been acute interest in clarifying the clinical importance of VitD in this population.

In the present review, we summarize the epidemiology of and risk factors for VitD deficiency among individuals with HIV, discuss findings from recent vitamin D supplementation studies, and highlight new areas of interest and debate.

Vitamin D Physiology and Metabolism

VitD is available to humans through three principal routes: (1) the majority of VitD is synthesized in the skin upon exposure ultraviolet B radiation and subsequent conversion of 7-dehydrocholesterol to pre-Vitamin D_3, which is then rapidly converted to $VitD_3$ (2) a smaller proportion of VitD derives from dietary intake of foods naturally containing or fortified with $VitD_2$ (ergocalciferol) or D_3 (cholecalciferol); and (3) VitD can be obtained from dietary supplementation in the form of $VitD_2$ or D_3 [3].

In the liver, VitD is converted to 25-hydroxy VitD (25OHD), which has a long serum half-life (3 weeks); therefore, it is the metabolite upon which clinical evaluation of VitD status is based. In the kidney, 25OHD undergoes further hydroxylation by the renal enzyme 1-α-hydroxylase to the active form of VitD, $1,25(OH)_2D$, which acts upon target cells by binding to the VitD receptor (VDR). During each step of this process, 85–90% of the body's VitD metabolites circulate tightly bound to the carrier protein, VitD binding protein (DBP). The non DBP-bound portion, known as bioavailable VitD, circulates less tightly bound to albumin, with <1% in the free form [8, 9]. The free form acts upon VDR in target cells in the intestine, kidney and bone to maintain calcium homeostasis. It is now appreciated that $1,25(OH)_2D$ binds to the VDR in a wide range of cell types and non-renal cells are also capable of converting 25OHD to $1,25(OH)_2D$.

The specific terminology and thresholds for defining VitD deficiency and insufficiency remain a subject of debate [10, 11]. In the setting of VitD deficiency, decreased calcium absorption leads to secondary elevations in parathyroid hormone (PTH) levels, which in turn lead to excessive bone resorption [12]. Clinical studies have shown that VitD deficiency is linked to decreased bone mineral density (BMD), increased falls, and increased fracture rates [13–18, 11]. The Institute of Medicine (IOM) classifies insufficiency as 25OHD levels between 12–20ng/mL (30–50nmol/L) and deficiency as levels <12ng/mL (30nmol/L) based upon studies of skeletal health outcomes [19]. However, the most commonly accepted

definitions—endorsed by the Endocrine Society, International Osteoporosis Foundation, among others—defines insufficiency as a 25OHD level between 20–29ng/mL (50–74 nmol/L), and deficiency at levels <20ng/mL (50nmmol/L), based upon observations that the inflection point above which PTH levels nadir and fall risk is reduced lies near 30ng/mL [20–22]. Some further define severe deficiency as 25OHD levels <10ng/mL (25 nmol/L) because risk for poor bone mineralization and osteomalacia/rickets rise sharply below this point.

HIV and Risk for Vitamin D Deficiency

The prevalence of low VitD (insufficiency or deficiency) among HIV-infected patients across different geographic regions, climates/latitudes, and age groups ranges from 24% to 72% [23–26, 5, 7, 27]. Variability in definitions employed and heterogeneity of study populations complicate the ability to aggregate data. Risk factors for VitD deficiency among individuals with HIV include traditional risk factors such as age, poor dietary VitD intake and malabsorption, decreased sun exposure, darker skin pigmentation, obesity, smoking and intravenous drug use, and liver or kidney disease. Several HIV-associated risk factors have also been identified, including exposure to specific antiretrovirals, chronic inflammation and immune activation, and direct effects of HIV proteins on the enzymes involved in $1,25(OH)_2D$ production [1, 28].

Studies comparing patients with HIV to healthy control populations have not consistently found lower prevalence of VitD insufficiency and deficiency among those with HIV [29, 30]. However, there may be reason to believe sustained low VitD levels poses unique risks to the health of patients with HIV, including faster HIV progression and severity, lower CD4+ counts, increased risk of mortality, and increased vulnerability to mycobacterium tuberculosis [31–39].

Vitamin D and Musculoskeletal Outcomes in HIV

Chronic HIV infection and long-term exposure to ART leads to decreased bone mineral density (BMD), and increased risk for fracture [40–42]. Data from randomized clinical trials have demonstrated that BMD declines 2–6% in the first year of ART [43–45]. Longer-term studies have shown that rates of bone loss stabilize thereafter compared with healthy controls, however, absolute BMD of those on continuous ART remain lower compared with their healthy counterparts [46]. Vulnerable periods for fracture include the first two years after ART initiation and after reaching middle age (approximately 50 years), even among men [47–49].

Low 25OHD levels have been shown in some but not all studies to be independently associated with low BMD [26, 42, 50, 51]. In a cross-sectional evaluation of 444 South African HIV-infected adults, higher 25OHD levels were associated with higher BMD at the total hip, but not at the lumbar spine. Erlandson et al. found that VitD insufficiency was independently associated with lower BMD at the femoral neck in a large Italian cohort of men and women with HIV [50]. Atteritano et al. found that among 16 HIV+ patients with vertebral fractures, 87% had insufficient VitD levels [26]. Given peak bone mass is built in

the first two decades of life and has a significant impact on lifelong risk for fracture, recent attention has turned to understanding the relationship between VitD and bone outcomes for children and adolescents. Jacobson at al. found that prevalence of low 25OHD (≤ 20ng/ml) was 42% among perinatally-infected children with HIV (PHIV), and that children with low 25OHD had lower total body BMD z-scores and bone mineral content [52].

Several recent trials have explored the ability of VitD supplementation to improve bone-related outcomes among HIV-infected individuals. Dosing approaches have ranged from daily supplements (4000–7000IU) to intermittent high dose boluses (16,000IU weekly to 200,000 x one time) [53–56]. Most studies have utilized cholecalciferol ($VitD_3$) supplements, however protocols employing ergocalciferol ($VitD_2$) and one using calcidiol have also been reported. By and large, they have successfully repleted VitD levels at a rate and magnitude consistent with healthy individuals. Furthermore, VitD supplementation has been shown to decrease BTMs and improve secondary hyperparathyroidism [57, 58]. Several VitD supplementation trials evaluating BMD as a primary outcome among adult and pediatric populations have also now been published. Havens et al. evaluated the impact of 50,000IU ergocalciferol monthly plus a multivitamin compared with a multivitamin alone among a group of 214 HIV-infected adolescents on stable continuous tenofovir (TDF)-based ART, and observed an increase in lumbar spine BMD in the intervention but not placebo group [59]. Rovner and colleagues evaluated the impact of 7000IU $VitD_3$ daily vs. placebo for 12 months among 58 children and adolescents with HIV on BMD and body composition parameters. Despite improvement of 25OHD levels, no change in BMD or body composition was observed, however there was notable heterogeneity of duration of HIV treatment and cART regimen used, and subjects only achieved mean 25OHD levels of 26.7 ng/dL [60]. The placebo arms of randomized trials of biosphosphate use in HIV-infected individuals have generally included calcium and VitD, and a small beneficial effect in BMD has been observed on the order of 1–3.5% [61–67].

In addition, low VitD, particularly <20ng/mL, has been associated impaired muscle strength, function, and balance in the general population, which have important implications for falls and fracture risk [22, 68, 69]. To our knowledge, only one study has evaluated the potential impact of VitD supplementation on neuromuscular outcomes among patients with HIV [70]. This study randomized 56 HIV-infected children and young adults to receive 7000IU of VitD daily versus placebo over 12 months and measured a battery of neuromuscular motor skills including the Bruininks-Oseretsky test of motor performance, jump power and energy, and muscular force and strength. The authors observed a mild increase in Bruininks-Oseretsky test score (β=1.14; P=0.041), but no change in other parameters. Given the small size of this sample, further studies are necessary to corroborate these findings and determine whether the increase observed yields clinically significant improvements.

Vitamin D Deficiency and ART

With regards to ARTs, studies have focused on whether the increased risk for low BMD and fractures observed clinically with certain ARTs may be mediated in part through alterations in VitD metabolism.

Protease inhibitors (PIs), and in particular ritonavir, have been shown to *in vivo* to strongly suppress 25-hydroxylase and 1-a-hydroxylase in a dose-dependent and reversible manner, while exerting a milder inhibition of 24-hydroxylase, the enzyme responsible for catabolism of $1,25(OH)_2D$, resulting in a net decrease in overall levels of $1,25(OH)_2D$ [71–73]. Human studies have been less consistent. Cervero et al. conducted a cross-sectional study of 352 Spanish HIV-infected adults, and found risk for VitD deficiency or insufficiency (defined as 25OHD <30ng/mL) was lower among patients on boosted PIs [23]. Klassen and colleagues found that among Austrialian HIV-infected patients with 25OHD <50ng/mL, PI use was associated with lower $1,25(OH)_2D$ levels, however not among those with 25OHD >50ng/mL [24]. Lerma-Chippirraz et al. conducted an observational study of 300 HIV-infected patients who received VitD supplementation, and found that while over 80% of individuals achieved replete levels of 25OHD, PI use was associated with not achieving normalization of PTH levels [54].

Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), has been associated with low plasma 25OHD levels in cross sectional studies, and with decreases in 25OHD in longitudinal studies [30, 37, 39, 74]. Nylen et al. showed that the prevalence of VitD deficiency (<25nmol/L) increased from 27% to 43% at 48 weeks in patients initiating EFV-based ART [37]. In vivo studies suggest that concentration-dependent induction of cytochromes P450 (CYP) 24 and 3A4 by efavirenz results in increased breakdown of $1,25(OH)_2D$ and 25OHD to their inactive forms [75, 76]. The influence of EFV on VitD may also be modulated by genetic factors [77]. For example, single nucleotide polymorphisms of CYP 2B6, such as the G516T allele, have been associated with higher plasma EFV concentrations [78–81]. Among HIV-infected patients in Botswana supplemented with either 4000IU versus 7000IU VitD3 daily, patients on NNRTI therapy (EFV or NVP) sustained a more robust increase in 25OHD levels compared with those on a protease inhibitor (22±12, 27±17, vs. 13±10, respectively, $p \leq 0.03$) [82]. Other NNRTIs have not been similarly singled out as having a deleterious impact on vitamin D levels or bone health, although the literature remains limited in this regard. In 2014, Wohl and colleagues observed that among 690 patients randomized to receive rilpivirine versus efavirenz once daily plus TDF/emtricitabine for 48 weeks, 25OHD levels remained stable among those in the rilpivirine group over time, but declined significantly in the EFV-treated group [83].

Finally, tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor, has received significant attention compared with other ARTs for its independent and slightly more pronounced association with alterations in markers of bone and VitD metabolism, BMD and in some studies, fractures [44, 84]. The mechanism for bone loss is still uncertain, and proposed etiologies have included proximal renal tubulopathy (leading to urinary phosphate wasting, alterations of calcium and phosphate homeostasis, and osteomalacia), secondary hyperparathyroidism (leading to increased stimulation of bone turnover), and potential direct effects of TDF on gene transcription in bone cells. [85–90].

Interestingly, secondary hyperparathyroidism has been observed after initiation of TDF-containing regimens, independent of renal impairment or VitD deficiency. In HIV-infected youths receiving TDF-based ART, $VitD_3$ supplementation led to decreases in PTH levels at 12 weeks, regardless of baseline 25OHD levels [91]. Several groups have started to

investigate potential unique mechanisms behind these findings. One hypothesis suggests that increased DBP levels upon TDF exposure decreases bioavailable VitD, thereby leading to a functional VitD deficiency and secondary hyperparathyroidism. DBP levels may be increased (pregnancy, exposure to exogenous estrogen) or decreased (chronic liver or kidney disease, sepsis) in a variety of physiologic and pathophysiologic conditions [92–98]. Havens et al. showed that DBP levels increased with successive quintiles of plasma TDF concentration among HIV-infected youth stably treated with TDF [99]. A longitudinal study among 134 Chinese HIV-infected individuals found that levels of DBP increased steadily over 48 weeks after initiation of TDF-lamivudine-EFV, concurrent with a steady increase in proportion of patients with secondary hyperparathyroidism (2.2% to 20.1%, $p<0.001$), despite stable creatinine and 25OHD levels [100]. The AIDS Clinical Trials Group (ACTG) A5280 Trial randomized 165 HIV-infected individuals initiating TDF-emtricitabine(FTC)-EFV to receive 4000IU $VitD_3$ and 1000mg calcium daily versus placebo. In both arms, DBP increased from baseline, but total 25OHD and bioavailable 25OHD increased only in the supplementation group [56]. PTH levels increased significantly in the placebo group but not the supplementation group, supporting the concept of a functional VitD deficiency; however, BMD changes were not consistently associated with bioavailable VitD [101]. In a small study of patients on TDF-FTC-EFV switched to darunavir(DRV)/r, a significant increase in BMD and 25OHD levels were observed compared with those continuing TDF-FTC-EFV, but no significant change was observed in DBP, PTH, or renal function [102]. No studies to date have examined whether TDF exposure impacts hepatocyte production or renal excretion of DBP.

Finally, Mingione et al. examined the potential effect of TDF on the calcium sensing receptor (CaSR) in the kidney, and found that stimulation of human embryonic kidney cells *in vitro* by CaCl2 with and without TDF revealed a dose-dependent inhibition of CaSR activity by TDF, comparable to that observed from known CaSR gene inactivating mutations [103]. The authors concluded that the hyperparathyroidism observed with TDF treatment may be explained in part by the direct effect of TDF on CaSR.

Immunomodulatory Effects of Vitamin D in HIV

VitD plays a role in both the innate and adaptive immune responses and VDR is expressed almost all cells of the immune system; in greatest quantity in $CD8^+$ T lymphocytes, but also in $CD4^+$ T lymphocytes, and to a lesser extent, B lymphocytes and cells of the monocyte/macrophage lineage [104, 105]. Therefore, not only does VitD play a role in response to infection, but also in preventing development of autoimmune conditions such as type 1 diabetes, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease [31, 106].

Several mechanisms have been elucidated and are reviewed in greater detail elsewhere [31, 106]. In brief, $1,25(OH)_2D$ influences innate immune cell differentiation promoting a tolerogenic state and T regulatory lymphocyte development with suppressive activity. In addition, pathogen elimination is promoted via increased intracrine $1,25(OH)_2D$ production by monocytes and macrophages leading to increased phagocytosis and expression of pathogen-recognition receptors. This signaling appears to increase transcription of

cathelicidin, which has antimicrobial properties, and defensins, which play a role in both antimicrobial and antiviral activities [107–109]. *In vitro* studies also demonstrate that cathelicidin inhibits replication of HIV in $CD4^+$ T cells and macrophages [110]. Finally, $1,25(OH)_2D$ appears to control transcription of inflammatory cytokines and chemokines through actions on NFkB, and via shifts of the T helper response from Th1 to Th2, thereby reducing Th1-mediated tissue damage.

In the setting of HIV, key areas of interest have included the role of VitD in disease progression and all-cause mortality, response to ART, and co-infection with tuberculosis and hepatitis C [38, 111–113, 36, 114, 115]. In two recent cross-sectional studies among HIV-infected populations, patients with VitD deficiency had greater levels of inflammation (IL-6 levels) and activated monocyte phenotypes (CX3CR1+ and CCR2+), and higher hydroperoxide levels indicating oxidative stress [116, 117].

Several studies examined the effect of VitD supplementation on immune parameters. Fabre-Mersseman et al found that VitD deficient patients had a slightly increased expression of $CD38^+$ among memory $CD8^+$ T cells, which deceased after VitD supplementation [118]. Lachmann et al. evaluated the effect of a one-time dose of 200,000IU VitD3 on $CD4^+$ T-cell function and found an increase in frequency of antigen-specific T cells producing the anti-HIV chemokine macrophage inflammatory protein (MIP)-1β, concurrent with a rise in actual (MIP)-1β levels and increase in median plasma levels of cathelicidin [119]. Stallings et al. randomized 50 HIV-infected children to receive 7000IU VitD3 daily versus placebo, and found that after 12 months, the percentage of naïve T cells were significantly higher and HIV RNA levels lower. Change in 25OHD levels predicted HIV RNA levels at 3 and 12 months, and $CD4^+$ T cell percentage at 3 months [120]. Finally, Eckard et al. found that among 51 HIV-infected youth receiving 18,000IU, 60,000IU, or 120,000 IU VitD3 monthly, $CD4^+$ and $CD8^+$ activation and monocytes decreased significantly in the high dose supplementation group [121]. In all protocols, patients tolerated VitD supplementation well without adverse outcomes.

Vitamin D and Cardiometabolic Outcomes

HIV-infected individuals are at increased risk for cardiovascular morbidity and mortality, as well as cardiovascular risk factors such as hypertension, dyslipidemia, smoking, and diabetes [122–129]. HIV-specific factors such as dyslipidemia from PIs or other ARTs, chronic inflammation, immune activation, and endothelial dysfunction have been found to play a role in enhanced atherogenesis [130–137].

In the general population, several observational studies have demonstrated associations between low VitD levels (25OHD <30 nmol/l) and CVD mortality risk [138–140]. While associations between low 25OHD levels and carotid intima medial thickness, carotid atherosclerosis, and coronary artery calcification scores have been shown in observational studies, randomized trials of VitD supplementation have not confirmed these findings consistently [138, 141–148]. Furthermore, recent concerns have arisen about a biphasic, or U-shaped, effect of VitD on cardiovascular health, suggesting that while deficient VitD

carries adverse consequences, high levels of VitD may also be associated with adverse cardiovascular outcomes [139].

Among HIV-infected individuals, cross sectional studies have shown vitamin D levels to be inversely correlated with carotid IMT, however there is little data on the impact of VitD supplementation on cardiac outcomes [130, 131]. Longenecker et al. performed a 12-week trial of 4000IU vitamin D_3 daily versus placebo among 45 vitamin D-deficient HIV patients and found no change in endothelial function as assessed by flow-mediated brachial artery dilation [149]. Recently, Eckard et al. investigated the impact of 24 months of standard vs high dose $VitD_3$ supplementation in HIV-infected and uninfected youth, and found that standard dose $VitD_3$ (18,000 IU monthly) supplementation resulted in a statistically significant decrease in carotid bulb IMT among HIV-infected participants (p=0.03) compared with higher $VitD_3$ [150].

Both HIV infection and ART initiation have also been associated with altered glycemic control, insulin resistance and diabetes [151, 152]. Observational studies have suggested that these indices may be associated with vitamin D deficiency, however the degree of association has not been consistently robust across studies [153–155]. Furthermore, in the small vitamin D_3 supplementation trial described above by Longenecker et al., supplementation led to increased insulin resistance over 12 weeks among vitamin D deficient patients on stable ART [149]. The more recent ACTG A5280 study found that supplementation with vitamin D_3 plus calcium did not alter insulin resistance (as estimated by the homeostatic model assessment) over 48 weeks compared with placebo among treatment naïve patients initiating ART [156].

Controversy Regarding Risks of Vitamin D Supplementation

Frank VitD toxicity in the form of hypercalcemia is exceedingly rare and cases have occurred only in the setting of ingestion of extremely high doses of VitD supplements for extended periods. Concerns regarding a U-shaped risk curve for VitD have arisen, not only in the context of cardiovascular disease risk, but also in the context of other important outcomes including falls and fracture, mortality and cancer. In the case of falls and fractures, this was first illuminated in a few trials utilizing bolus dosing regimens for the prevention of falls and fracture among elderly populations (>70 years) with known risk factors for falls or fracture, which tested regimens ranging from monthly to annual doses of VitD. Unexpectedly, not only was risk for falls and fractures not improved in the high dose groups, in one study risk was higher, and appeared to correlate with periods of high 25OHD levels during the first 3 months after supplementation [157, 158]. Two recent studies have also found that compared with lower dose regimens or daily regimens (equivalent of 400–1000IU daily), higher dose regimens (equivalent 2000–3300IU daily) were associated with a higher risk for falls [159, 160]. Lower extremity function and fractures were not significantly different.

In studies of community-dwelling older individuals without pre-specified risk for fall or fracture, the findings have been less conclusive. Trivedi et al. found a reduction in fracture rates in adults (age 65–85) from the community treated with 100,000 IU cholecalciferol

every 4 months [161]. Smith et al. conducted a randomized trial among postmenopausal women with baseline 25OHD<20ng/ml, and evaluated the impact of seven different daily doses of VitD compared with placebo. Compared with placebo, no decrease in falls was observed with <800 IU daily of VitD. At 1600IU–3200IU daily a significant decrease in falls was observed (p=0.02), however this effect was no longer seen at the highest doses 4000–4800IU daily (p=0.55). While elegant in design, the major weakness of the study was the small sample size with only 17–19 patients per group [162]. Zhao et al. recently published a meta-analysis of 33 randomized clinical trials involving 51,145 community-dwelling participants and did not find evidence for reduction in fracture risk with VitD and/or calcium supplementation but also did not note increase in risk based upon dose or frequency [163]. It has been posited by Grant and colleagues that potential artefactual explanations may exist for the observed U-shaped associations. For example, in some studies, elevated 25OHD levels >50ng/mL may actually reflect self-administration of $VitD_2$ supplements to correct a prior VitD deficiency that is actually responsible for the poor outcome in question [164].

A range of VitD dosages have been utilized to study skeletal and non-skeletal outcomes in HIV participants, and to our knowledge, there have not been reports of increased risk with high dose or intermittent bolus dosing regimens; however, HIV-infected patients enrolled in such studies are generally younger than the studies in the general population and therefore are not at the clinical threshold necessary to observe this increased risk.

Considerations for Clinical Management

The latest version of the European AIDS Clinical Society (EACS) Guidelines (version 9.0) recommends VitD screening in patients with history of low BMD, actual or high risk for fracture, or one of the following risk factors for VitD deficiency: dark skin, dietary deficiency, avoidance of sun exposure, malabsorption, obesity, chronic kidney disease, and ARVs associated with low VitD levels as discussed above. VitD deficiency is defined by the EACS as 25OHD <10ng/mL, and insufficiency as <20ng/mL. An upper threshold for 25OHD is not defined as it has not been studied in this population. Those with low VitD should have further workup with PTH, calcium, phosphate and alkaline phosphatase to identify secondary hyperparathyroidism and osteomalacia. Supplementation is recommended for individuals with VitD deficiency or those with insufficiency plus osteoporosis, osteomalacia, or secondary hyperparathyroidism to reach the goal of 25OHD >20ng/mL [165]. Another guideline, authored by The Osteo Renal Exchange, recommended that supplementation be titrated to achieve a goal 25OHD level of approximately 30ng/ml using varying doses based upon baseline 25OHD levels, followed by maintenance thereafter [166].

These guidelines represent a starting point for HIV providers. Referring to the guidelines from the IOM and Endocrine Society, or regional/national specialty societies that may better take into account ethnic/regional considerations, can offer additional direction to providers in managing specific cases. While many studies are focused on the ability of VitD monotherapy to counteract specific VitD-mediated mechanisms of skeletal and extra-skeletal outcomes, in practice, it is reasonable to combine VitD supplementation with calcium

according to the aforementioned guidelines. Finally, encouraging VitD repletion via non-pharmacologic approaches remains an important means of preventing VitD deficiency. In particular, as sun exposure cannot lead to over-production of VitD, appropriate guidance on sun exposure can be an effective intervention in the right patient. Increased intake of VitD rich (oily fish, cod liver oil, certain mushrooms) or fortified foods (availability depends on country) is also prudent to suggest, although access to such foods may be a challenge for many patients.

Conclusions

As with the field of VitD research in the general population, challenges remain in adequately quantifying the impact of VitD on HIV and its associated outcomes. These include challenges with isolating the impact of VitD versus VitD plus calcium, standardizing definitions across studies for deficiency and insufficiency, standardizing assay techniques for both VitD and other components of the metabolic pathway, and elucidating the relationship between VitD dose and timing on outcomes. Furthermore, the role of genetic variation/race and ethnicity on outcomes remains to be elucidated. Finally, the benefits and risk of VitD supplementation across different age strata for different skeletal and extra-skeletal outcomes remains uncertain and requires further study.

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