Perspective

Vitamin D, Bone, and HIV Infection

Vitamin D deficiency has been associated with increased risk for falls and fractures, diabetes and obesity, cardiovascular disease, some malignancies, and tuberculosis. Observational data have suggested benefit of higher vitamin D levels in many of these settings. However, data from randomized trials supporting the benefit of vitamin D supplementation are generally lacking, apart from data showing benefit in preventing falls and fractures in the elderly. HIV-infected persons have a high prevalence of vitamin D deficiency and insufficiency, and some antiretroviral drugs are known to interfere with vitamin D metabolism. However, as in the general population, there are currently few data from clinical trials to identify benefits of vitamin D screening and supplementation in the HIV-infected population. A rational approach is to screen at-risk patients (eg, those aged 50 years and older and those with osteoporosis, prior fracture, or high risk for falls); supplementation may be considered in specific subgroups of patients. This article summarizes a presentation by Michael Yin, MD, MS, at the IAS–USA live Improving the Management of HIV DIsease continuing medical education program held in New York, New York, in October 2012.

Vitamin D is synthesized in the form of cholecalciferol (vitamin D_3) in the epidermis upon exposure to ultraviolet light. Cholecalciferol is also available through diet via animal sources; plant sources provide ergocalciferol (vitamin D_2). These forms of vitamin D, which are inert and have a short half-life, are converted in the liver via 25 hydroxylase to $25(OH)D_3$, or calcidiol. This inert form is converted by 1-α hydroxylase, which is predominantly found in the kidney, to $1,25(OH)_2D_3$, or calcitriol, which is the active form of vitamin D. Calcitriol synthesized in the kidney resides in the circulation for a brief period and is active in endocrine signaling. 1-α hydroxylase is also found in macrophages and monocytes, with vitamin D synthesized in these cells participating in autocrine and paracrine signaling.

Vitamin D regulates calcium and phosphate homeostasis, interacting with parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) in increasing intestinal absorption of calcium and exerting direct effects on bone cells. Vitamin D also has immunomodulatory effects. In innate immunity, it increases cathelicidin gene expression in macrophages, which is associated with bactericidal activity, including antimycobacterial effects. In adaptive immunity, it predominantly targets T cells, acting to downregulate activation and recruitment of helper T cell (T_H) subtypes 1 (T_H1) and 17 (T_H17) and polarize phentoypes towards T_H2 and regulatory T cells (T_{reg}).

Numerous effects of vitamin D and vitamin D deficiency have been reported for specific disease states (Table 1). Vitamin D deficiency has been associated with increased risk for fractures and falls in the elderly, metabolic disorders (obesity, diabetes, metabolic syndrome) and cardiovascular disease, some cancers, tuberculosis (TB), and reduced likelihood of sustained virologic response (SVR) in patients receiving treatment for hepatitis C virus (HCV) infection. The potential effects by which vitamin D may act to reduce risk of such diseases include improvement of bone strength and muscle function; reduced lipogenesis and increased lipolysis; antiinflammatory, antiangiogenic, and proapoptotic effects; improvement of vascular compliance; increased cathelicidin gene expression; and a synergistic interaction with interferon alfa in reducing HCV replication. Results of randomized controlled trials of vitamin D supplementation in most of these settings with the exception of reduction of fall and fracture risk in the elderly,[1,2] have yielded negative or inconsistent results to date.

Vitamin D deficiency currently is defined as a 25-hydroxyvitamin D (25[OH]D) level below 20 ng/mL, with levels below 10 ng/mL, levels between 20 ng/mL and 30 ng/mL, and levels above 30 ng/mL constituting severe deficiency, insufficiency, and normal levels, respectively. Most of the data supporting this classification come from 2 studies. One was an observational study in approximately 1300 postmenopausal women, predominantly white, in the Northeast United States who had a median age of 70 years.[3] When PTH level was plotted against serum vitamin D levels, the inflection point at which increasing concentrations of vitamin D did not produce lower PTH levels was around 30 ng/mL, suggesting absence of physiologic response of PTH to vitamin D beyond this concentration. The second study was a meta-analysis examining relative risks according to vitamin D level using clinical trial data for falls and fractures and observational data for other disease endpoints, including cardiovascular mortality, colorectal cancer, hypertension, and all-cause mortality. Relative risks decreased to about 1 as vitamin D level increased to the range of 30 ng/mL to 44 ng/mL, suggesting that benefit in preventing such outcomes becomes apparent when the vitamin D level is above 30 ng/mL.[4]

Vitamin D in HIV-Infected Persons

Based on current knowledge, there are numerous potential benefits of optimizing vitamin D levels in HIV-infected persons, including improvements

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Table 1. Immune Effects of Vitamin D and Effects of Vitamin D on Disease

Disease or Condition	Mechanism	Observational Trial Data	Randomized Controlled Trial (RCT) Data
Effects of Vitamin D on Disease			
Fractures and falls	Increase bone strength, improve muscle function	VDD associated with fractures and falls in elderly	Meta-analysis of RCTs found benefit with vitamin D and calcium
Diabetes and obesity	Decrease lipogenesis, increase lipolysis in adipocytes	VDD associated with obesity, diabetes, metabolic syndrome	WHI: no effect on diabetes with 400 IU vitamin D_3
Cancer	Antiinflammatory, proapoptotic, antiangiogenic effects	VDD associated with colorectal cancer; inconsistent for breast and prostate	Limited RCT data: no benefit seen
Immune Effects of Vitamin D			
Cardiovascular disease (CVD)	Improve vascular compliance, antiinflammatory effects	VDD associated with increased CVD	Limited RCTs, no consistent benefit
Tuberculosis (TB)	Stimulate cathelicidin gene expression	VDD associated with increased TB incidence	Adjunct to TB treatment, decreased time to sputum negativity in 1 but not others
Hepatitis C virus (HCV)	Synergize with interferon alfa to inhibit HCV replication; decrease fibrosis	Correlation between 25(OH)D and SVR	2000 IU/day improves SVR in HCV monoinfection

25(OH)D indicates 25-hydroxyvitamin D; SVR, sustained virologic response; VDD, vitamin D deficiency; WHI, Women's Health Initiative. Data drawn from Rosen et al,[19] Murad et al,[20] de Boer et al,[21] Nursyam et al,[22] Martineau et al,[23] Wejse et al,[24] Rahman et al,[25] Abu-Mouch et al,[26] and Nimer et al.[27]

in innate immunity, modulation of such coinfections as HCV and TB, modulation of immune response (eg, in immune reconstitution inflammatory syndrome [IRIS]), modulation of chronic inflammatory response, and reduction in risk for non-AIDS-related events, eg, osteoporosis, fractures, falls and frailty, cardiovascular disease, diabetes, and malignancies.

Results from studies in 4 large New York City health-care centers indicate that approximately 80% of HIV-infected persons have vitamin D insufficiency or deficiency (< 30 ng/mL). This problem is not exclusive to the HIV-infected population; a similar proportion of HIV-uninfected persons have vitamin D deficiency or insufficiency.[5-7] It has been found that some antiretroviral drugs affect vitamin D metabolism, with this effect becoming increasingly clear for efavirenz. A recent study showed that initiation of antiretroviral therapy with efavirenz resulted in a mean decrease in vitamin D levels of approximately 5 ng/mL after 6-12 months of therapy, compared with an increase in vitamin D levels of 1 ng/mL to 2 ng/mL with antiretroviral therapy without efavirenz.[8] The putative mechanism of this effect of efavirenz is induction of 24-hydroxylase, a cytochrome P450 (CYP450) enzyme that inactivates 25(OH)D and $1,25(OH)_2D$ similar to the effects of antiepileptics,[8] but the exact mechanisms and long-term impact are uncertain.

Other studies have shown an increase in vitamin D level with switching from efavirenz to ritonavir-boosted (/r) atazanavir, a greater decrease with efavirenz than with rilpivirine (-6.2 ng/mL vs -0.6 ng/mL), and no change in vitamin D level over 3 years in patients receiving nevirapine.[9,10] In vitro studies indicate that protease inhibitors (PIs) can lower levels of active vitamin D by inhibiting 1-α hydroxylase, which converts calcidiol to calcitriol, although reduction in vitamin D has not been consistently observed in clinical studies. Although tenofovir does not have a direct effect on vitamin D metabolism, hypophosphatemia resulting from tenofovir-related proximal renal tubular dysfunction induces an increase in 1-α hydroxylase that increases gut absorption of phosphate as a compensatory mechanism. It is thus possible that patients with very low stores of vitamin D on tenofovir will be more likely to exhibit clinical manifestations of osteomalacia.

Vitamin D Deficiency and Outcomes in HIV

Observational Data

Bone mineral density (BMD) has been found to be lower in HIV-infected persons than in HIV-uninfected persons, but observational data do not point to a consistent role of low vitamin D levels in explaining this difference. The etiology of bone loss and fracture in HIV infection is multifactorial. In addition to vitamin D deficiency, host factors include weight loss, hypogonadism, decreased physical activity, smoking, alcohol use, glucocorticoid use, HCV infection, lipodystrophy, and chronic kidney disease. Viral factors include direct effects of HIV proteins on bone cells and persistent immune activation. Effects of antiretroviral therapy include direct effects on bone cells, inadequate mineralization, and immune reconstitution.

With regard to potential risk for cardiovascular disease, a cross-sectional observational study in HIV-infected patients has shown that mean carotid intima media thickness (CIMT) is higher in patients with 25(OH)D levels below 15 ng/mL than in patients with 25(OH)D levels above 30 ng/mL.[11]

With regard to overall mortality, a recent study in more than 1100 Tanzanian adults starting antiretroviral therapy showed that 44% had vitamin D levels below 20 ng/mL. The hazard ratio (HR) for mortality was 2.0 for those with levels below 20 ng/mL versus those with levels above 30 ng/mL

over 24 months.[12] Similar findings were made in a recent analysis in the larger EuroSIDA cohort. This analysis, which compared outcomes according to vitamin D tertiles of less than 12 ng/mL, 12.1 ng/mL to 20 ng/mL, and greater than 20 ng/mL, showed that patients in the lowest tertile had a statistically significant increased risk for progression to AIDS and to death and a nonstatistically significant increased risk for progression to non-AIDS-related events, compared with patients in higher tertiles (Figure).[13]

Randomized Clinical Trials

A number of study results have shown the ability of vitamin D plus calcium to increase BMD in HIV-infected patients with low BMD. For example, a study in adults with lumbar spine T-score of less than −1.5 showed that vitamin D (400 IU-600 IU) plus calcium produced a statistically significant increase of approximately 1.5% in lumbar spine BMD at 24 weeks, with a 1% increase persisting at 48 weeks; the addition of alendronate resulted in increases of 2.5% and greater than 3% in BMD at these time points.[14]

However, a study in 59 children infected with HIV perinatally, aged 6 years to 16 years, and without low BMD at baseline, showed no increase in BMD with vitamin D 100,000 IU every 2 months for 2 years plus calcium 1000 g/d per day compared with placebo. Patients with vitamin D levels below 12 ng/mL were not included in the study. Vitamin D levels did increase in the treatment group, suggesting that increased vitamin D levels in HIV-infected patients may increase BMD only in those with preexisting low BMD.

The Adolescent Medicine Trials Network (ATN) for HIV/AIDS Intervention 063 study results showed that over 3 months, patients on tenofovir-containing regimens had a decrease in PTH levels with vitamin D supplementation irrespective of whether they were vitamin D insufficient or sufficient. No change in PTH levels was observed in patients not receiving tenofovir. These findings suggest that vitamin D supplementation corrected a dysfunction in calcium homeostasis that included PTH in patients receiving tenofovir. The mechanism of this dysfunction is unclear, particularly because the effect was observed in both vitamin D insufficient and sufficient patients. Although vitamin D supplementation lowered PTH levels in tenofovir recipients, no effect on bone turnover markers was observed, suggesting that the potentially beneficial effect on calcium homeostasis did not necessarily translate into an impact on bone.

With regard to potential cardiovascular effects, a 12-week study in 45 adults on stable antiretroviral therapy showed that vitamin D 4000 IU produced an increase of approximately 5 ng/mL in vitamin D level compared with placebo, but had no effect on brachial artery flow-mediated dilation (FMD).[15] There was also no difference between groups with regard to changes in levels of cardiovascular disease markers including intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), soluble tumor necrosis factor receptors (sTNFR) I and II, c-reactive protein (CRP), interleukin 6 (IL-6), D-dimer, and fibrinogen.

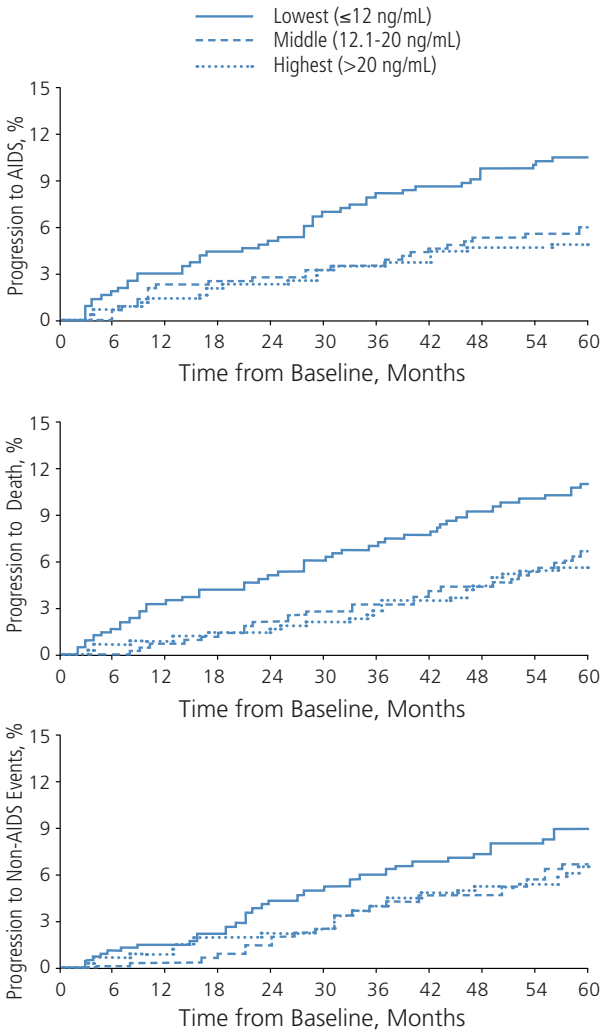

Figure. Progression to AIDS (top), death (middle), and non-AIDS-related events (bottom) according to 25-hydroxyvitamin D tertile (lowest, ≤12 ng/mL; middle, 12.1-20 ng/mL; highest, > 20 ng/mL) in EuroSIDA analysis. Adapted from Viard et al.[13]

Should Clinicians Routinely Screen for Vitamin D Deficiency?

The arguments in favor of routine screening of vitamin D in HIV-infected patients include the potential optimization of skeletal, metabolic, and immunologic parameters with vitamin D supplementation, as well as the low toxicity of supplementation. The arguments against routine screening include absence of proven benefit of supplementation apart from preventing falls and fractures in the elderly general population, limited randomized clinical trial data in the HIV-infected population, potential harm from some supplementation approaches, lack of a clear target range, inability to distinguish the effects of calcium and vitamin D supplementation on bone, assay variability and costs; and increased pill regimen.

Among the issues to be confronted when considering screening and supplementation is that vitamin D physiology in black patients appears to differ from that suggested by studies in predominantly postmenopausal white women. In black patients, PTH may be maximally suppressed at a lower

vitamin D level (16 ng/mL-20 ng/mL). Vitamin D levels are not correlated with BMD in elderly black men, and no improvement in BMD was observed in a clinical trial of vitamin D supplementation in postmenopausal black women despite increased serum vitamin D levels.[16,17]

As noted, some supplementation regimens can be harmful. A study comparing yearly doses of vitamin D 500,000 IU with placebo in 2256 postmenopausal women aged older than 70 years found that vitamin D supplementation produced a statistically significant 16% increase in risk of falls (P = .003) and was associated with a borderline statistically significant 26% increase in risk of fracture (P = .06) over 4 years.[18]

Current recommendations of the Institute of Medicine, Endocrine Society, and European AIDS Clinical Society for vitamin D screening and supplementation are shown in Table 2. The Institute of Medicine does not recommend routine screening in the general population and makes no specific recommendations with regard to HIV-infected persons. The Endocrine Society recommends that at-risk persons be screened, including all persons receiving AIDS medications, although individual medications are not specified. The European AIDS Clinical Society recommends screening in HIV-infected persons receiving some antiretroviral drugs, including efavirenz. The Institute of Medicine recommends a target vitamin D level of 20 ng/mL or higher, as does the European AIDS Clinical Society. The Endocrine Society recommendations are intended more for at-risk persons, and include target levels above 30 ng/mL, a minimum daily dose of 1500 IU in patients receiving antiretroviral therapy, and a loading dose in persons with initial vitamin D levels below 20 ng/mL.

Dr Yin's approach is not to screen all HIV-infected persons, since data to justify such routine screening are not yet available. Such screening would be costly and, as yet, there is no clear idea of the specific benefits of increasing vitamin D to target levels in most settings. Instead, he recommends screening in high-risk populations and aiming for a target vitamin D level above 30 ng/mL. High-risk populations consist of individuals aged older than 50 years (due to increased risk of bone loss and fracture) and those with osteoporosis, prior fracture, or high risk for falls. Screening and supplementation could also be considered at initiation of TB treatment, at initiation of antiretroviral treatment with efavirenz or tenofovir, in HCV coinfection, and in adolescence. Studies in each of these settings are needed to strengthen the recommendations. Currently, an ACTG (AIDS Clinical Trials Group) study is examining whether a strategy of vitamin D and calcium supplementation with initiation of tenofovir/emtricitabine/efavirenz can mitigate bone loss.

Table 2. Current Vitamin D Screening and Supplementation Recommendations from Major Institutions

	Institute of Medicine, 2010[28]	Endocrine Society, 2011[29]	European AIDS Clinical Society, 2011[30]
Screening Recommendations			
Screen	No screening	At-risk patients	At-risk patients
HIV-specific criteria	NA	HIV medication	Some antiretroviral drugs
General criteria		• African American or Hispanic • Chronic kidney disease • Malabsorption • Fracture/fall risk • Osteoporosis • Obesity • Hepatic failure	• Dark skin • Chronic kidney disease • Malabsorption • Fracture risk • Low BMD
Supplementation Recommendations			
25(OH)D target level	≥ 20 ng/mL (50 nmol/L)	30 ng/mL (75 nmol/L)	20 ng/mL (50 nmol/L)
RDA (age 18-70 years)	600 IU	600 IU	800-2000 IU
RDA (age > 70 years)	800 IU	800 IU	
Daily requirement with antiretroviral therapy	NA	1500-2000 IU	
Daily upper limit	4000 IU	10,000 IU	
Loading dose for 25(OH)D < 30 ng/mL		50,000 IU vitamin D_2 weekly or 6000 IU daily for 8 weeks	

25(OH)D indicates 25-hydroxyvitamin D; BMD, bone mineral density; NA, not available; RDA, recommended daily allowance. Data from Institute of Medicine,[28] Holick et al,[29] and European AIDS Clinical Society.[30]

For everyone else, irrespective of age, the current National Osteoporosis Guidelines for age older than 65 years should be implemented. These include adequate intake of calcium and vitamin D from food, with supplementation of vitamin D 800 IU to 1000 IU daily and calcium 1000 mg to 1200 mg daily if necessary; regular weight-bearing exercise; avoidance of tobacco use; and avoidance of excessive alcohol intake (> 3 drinks/day). Some dietary sources of vitamin D are shown in Table 3.

Summary

Vitamin D deficiency is highly prevalent in HIV-infected persons and in the general population. There are associations

Table 3. Dietary Sources of Vitamin D

Food (Serving Size)	IU per serving
Salmon (3.5 oz)	360
Mackerel (3.5 oz)	345
Tuna (3.5 oz)	200
Milk, fortified (1 cup)	98
Orange juice, fortified (1 cup)	100
Breakfast cereal, fortified (.75-1 cup)	40-100
Margarine, fortified (1 tbsp)	60
Liver, beef (3.5 oz)	30
Egg (1 whole)	25
Multivitamin	400

Data from Office of Dietary Supplements.[31]

of vitamin D deficiency with many extraskeletal outcomes in observational studies. However, there are limited data from randomized clinical trials supporting vitamin D supplementation, with a benefit of vitamin D and calcium supplementation being most clear in preventing fractures and falls in the elderly. Studies of supplementation are ongoing in HIV-infected populations. For now, universal screening of HIV-infected persons should be avoided, with screening being reserved for persons at higher risk of fracture. Although optimal supplement doses and vitamin D target levels are uncertain, a target vitamin D level above 30 ng/mL appears reasonable in at-risk persons.

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