Published in final edited form as:

Curr HIV/AIDS Rep. 2011 September ; 8(3): 133–141. doi:10.1007/s11904-011-0082-8.

Vitamin D in HIV-Infected Patients

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Abstract

Observational studies have noted very high rates of low 25(OH)D (vitamin D) levels in both the general and HIV-infected populations. In HIV-infected patients, low 25(OH)D levels are likely a combination of both traditional risk factors and HIV- and antiretroviral therapy-specific contributors. Because of this unique risk profile, HIV-infected persons may be at greater risk for low 25(OH)D levels and frank deficiency and/or may respond to standard repletion regimens differently than HIV-uninfected patients. Currently, the optimal repletion and maintenance dosing regimens for HIV-infected patients remain unknown, as do potential benefits of supplementation that may be unique to the HIV-infected population. This paper reviews data published on HIV infection and vitamin D health in adults over the last year.

Keywords

vitamin D; 25(OH)D; 1,25(OH)₂D; HIV; ART; efavirenz; tenofovir

Introduction

In recent years, startling rates of low serum levels of the major circulating metabolite of vitamin D (25-hydroxyvitamin D; 25(OH)D <30 ng/ml or 75 nmol/L) have been documented in the general population. Data from the U.S. National Health and Nutrition Examination Survey (NHANES) suggests >75% of persons living in the U.S. have suboptimal circulating levels of vitamin D (1). This degree of vitamin D insufficiency has been associated with cardiovascular disease (CVD), insulin resistance, osteoporosis, and all-cause mortality (2–6). As a result, routine screening for low 25(OH)D levels and supplementation of insufficient patients has become increasingly common. The safety of vitamin D supplementation at a wide range of doses has been demonstrated for most persons (7, 8), and the Institute of Medicine has endorsed the safety of daily oral doses of vitamin D up to 4000 international units (IU) (9).

Observational studies have also noted very high rates of low 25(OH)D levels in HIV-infected patients (10, 11), a finding that is likely a combination of both traditional risk factors and HIV- and antiretroviral therapy (ART)-specific contributors. Because of their unique risk profile, HIV-infected persons may be at greater risk for low 25(OH)D levels and frank vitamin D deficiency and/or may respond to standard repletion regimens differently

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than HIV-uninfected patients. Due to a lack of prospective, randomized controlled trials (RCTs), the optimal repletion and maintenance dosing regimens for HIV-infected patients remain unknown, as do potential benefits of supplementation that may be unique to the HIV-infected population. This review focuses on data published on HIV infection and vitamin D health in adults over the last year, as well as recent guidelines for vitamin D supplementation in the general population.

Background

Vitamin D Physiology

Detailed descriptions of vitamin D physiology and metabolism have been published elsewhere (4, 12). Vitamin D₃ (cholecalciferol) is photosynthesized in the skin upon exposure to ultraviolet B (UVB) radiation. Vitamin D₂ (ergocalciferol) can be ingested via foods or supplements (4, 12). Both forms of vitamin D are converted in the liver and other tissues to 25(OH)D (4, 13). 25(OH)D is further metabolized to its active form, 1,25-dihydroxyvitamin D [1,25(OH)₂D] by the 25-hydroxyvitamin D-1- α -hydroxylase, or CYP27B1 (14). This hydroxylation occurs primarily in the kidneys, but extra-renal tissues and immune cells are also capable of 1,25(OH)₂D production. This is important because extra-renal formation of 1,25(OH)₂D is dependent on local extracellular 25(OH)D concentrations, pro-inflammatory cytokine levels, and immune stimuli rather than the classic endocrine calcium-parathyroid hormone (PTH) regulatory axis (15, 16). Finally, the 25-hydroxyvitamin D-24-hydroxylase, or CYP24A1, is responsible for vitamin D catabolism (14). The interaction of vitamin D metabolites with the cytochrome P450 system is critical to the potential contribution of ART to vitamin D deficiency in HIV-infected patients.

Measurement of Vitamin D Stores

25(OH)D is the best measure of total body vitamin D stores. Levels <30ng/mL (75nmol/L) are generally considered insufficient, whereas levels <20ng/mL (50nmol/L) represent deficiency (17). Although it is the hormonal form of vitamin D, 1,25(OH)₂D is not used to monitor vitamin D status because: 1) it has a short serum half-life; 2) it is often converted from 25(OH)D outside the general circulation at the tissue level; and 3) circulating levels may be decreased, normal or elevated in patients with low 25(OH)D levels, making serum measurements unreliable (18, 19).

Immune Actions of Vitamin D

1,25(OH)₂D is active in virtually every organ system. In addition to interacting with PTH at the bone and kidney and stimulating intestinal calcium absorption for delivery to target organs, 1,25(OH)₂D plays a critical role in the human immune system. Notably, 1,25(OH)₂D: suppresses T cell activation and genes involved in cell proliferation and differentiation (16, 20); downregulates the production of pro-inflammatory cytokines such as TNF- α , IFN- γ , IL-2, and IL-12, shifting the activated T cell response from a Th1- to a Th2-like response (15, 21, 22); and plays multiple roles in anti-microbial defense and immune regulation, including monocyte chemotaxis and differentiation into macrophages, nitric oxide production by macrophages, and production of cathelicidin and β defensin 4, anti-microbial peptides whose functions include inhibition of viral replication (10, 15, 23–31). Because of vitamin D's critical anti-inflammatory and antimicrobial functions, vitamin D deficiency has been postulated to play a role in the immune reconstitution inflammatory syndrome (IRIS) (32).

Since HIV-infection is a chronic inflammatory state characterized by a Th1-like response, it is possible that the combination of HIV infection and insufficient local production of 1,25(OH)₂D could be additive in promoting pro-inflammatory cytokine generation and

action (with resultant resultant tissue dysfunction). It is also possible that restoration of extracellular 25(OH)D levels to normal could minimize both ongoing inflammation and the complications of HIV and ART associated with chronic inflammation. Lastly, low 25(OH)D levels could play a role in the severity of infections and malignancies commonly seen in HIV-infected patients.

Risk Factors for Low 25(OH)D Levels in HIV-Infected Patients

Published rates of vitamin D deficiency/insufficiency among HIV-infected persons vary from 12%–100% (33–38). The use of inconsistent definitions for deficiency/insufficiency, as well as variations in the populations studied, contributes to this discrepancy. Overall, rates of low 25(OH)D levels are high. This is partly due to traditional risk factors for low 25(OH)D levels such as lack of exposure to UVB radiation, age, and darker skin pigmentation (4). Interestingly, obesity is consistently a risk factor for vitamin D insufficiency in the general population (4, 39, 40) but not in HIV-infected patients (41–45). Additionally, data from several cohort studies suggest that HIV-infected patients overall have equal or lower-body mass indices (BMIs) than age-matched controls (46–48), highlighting the likelihood of HIV-specific risk factors for low 25(OH)D levels in this population. For example, elevated TNF- α levels in HIV infection may block PTH-stimulated conversion of 25(OH)D to 1,25(OH) $_2$ D in the kidney (49, 50).

Both vitamin D and many agents used in the treatment of HIV and opportunistic infections are metabolized via the cytochrome P450 system (10), creating the potential for interactions that could alter the effectiveness of standard vitamin D replacement strategies. For example, the protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes of antiretroviral agents have been linked to 1,25(OH) $_2$ D deficiency by accelerating the hydroxylation of vitamin D and its metabolites to non-biologically active compounds (51, 52). While PIs may inhibit the 24-hydroxylases (51), efavirenz is thought to increase both the 25-hydroxylation of vitamin D via CYP3A4 induction (53) and 24-hydroxylation of 25(OH)D and 1,25(OH) $_2$ D via CYP24A1-hydroxylase (54).

To date, the relationship between vitamin D sufficiency and CD4 T cell count remains unclear, although most studies have shown a positive association (10, 11, 49, 55, 56). Similarly, *in vitro* data supporting a direct effect of vitamin D metabolites on HIV-1 replication is conflicting (reviewed in Villamor, 2006).

Recent Developments

General Prevalence and Risk Factors

With increased awareness of low 25(OH)D levels as a potential health risk in HIV-infected persons, cross-sectional and observational data has continued to accumulate. In an analysis of baseline data from the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN), 70.3% of HIV-infected adults not on vitamin D supplementation had low 25(OH)D levels (<30ng/mL or 75nmol/L) compared with 79.1% of subjects enrolled in the NHANES 2003–2006 surveys. This difference was statistically significant after adjustment for age, race, and sex. In the SUN study, low 25(OH)D levels were significantly associated with traditional risk factors such as non-White race, higher BMI, decreased physical activity, and hypertension, but not age or sex. Findings unique to HIV-infected subjects included a 98% increased risk with efavirenz exposure and an observed protective effect of ritonavir exposure (44% risk reduction)(41). The increased rates of low 25(OH)D levels seen in HIV-infected SUN subjects is in contrast to most other published cohort data, where rates equal or exceed that of the general population. For example, in contrast to the prevalence of low 25(OH)D levels reported by NHANES for the general population (79.1%), 100% of HIV-infected NHANES subjects had low 25(OH)D

levels. Factors unique to HIV infection in that subset analysis included CD4 count <200 cells/ μ L in women only (38). Additionally, in the Swiss HIV Cohort study, rates of low 25(OH)D levels (<30ng/mL or 75nmol/L) and frank deficiency (<12ng/mL or 30nmol/L) following peak sun exposure were >76% and 14–18%, respectively, exceeding rates seen in the general Swiss population. Risk factors associated with low 25(OH)D levels in that cohort included NNRTI use, non-White race, and intravenous drug use (57).

In cohorts from two U.S. cities (Houston and New York City), similar rates of 25(OH)D <30ng/mL (75nmol/L) were seen (both 86%). Only African American race and BMI were associated with 25(OH)D <20ng/mL (50nmol/L) (58, 59). In a small study of primarily Black and Hispanic HIV-infected men on ART in New York, 75.8% of subjects met criteria for low 25(OH)D levels (<30ng/mL or 75nmol/L) or deficiency (<20ng/mL or 50nmol/L). In this cohort, NNRTI use (vs. PI) correlated with vitamin D deficiency ($p=0.0017$), while tobacco use was associated with severe deficiency (<10ng/mL or 25nmol/L). A similar cross-sectional study of African American and Hispanic post-menopausal women in New York reported 76% low 25(OH)D levels (<30ng/mL or 75nmol/L) and 36% deficiency (<20ng/mL or 50nmol/L). Prevalence rates did not vary by HIV status or ART use and were not associated with traditional risk factors other than African American race (60). In a study of HIV-infected patients in London, 91.3% had 25(OH)D <30ng/mL (75nmol/L). Black ethnicity, winter season, CD4 nadir <200 cells/ μ L and current ART use were associated with severe vitamin D deficiency (25(OH)D <10ng/mL or 25nmol/L) (61).

HIV-Specific Risk Factors

Due to the complex interactions of host response, chronic infection and inflammation, and metabolic consequences of ART, HIV-infected persons could be predicted to have unique risk factors for low 25(OH)D levels. For example, both obesity and lower body weight have been associated with vitamin D deficiency in the setting of HIV infection (41–45, 62, 63). In a study by Conesa-Botella et al, body weight <70kg was associated with a 4.7-fold risk of 25(OH)D <20ng/mL (50nmol/L) (42). Whether low body weight represents severity of chronic illness, is a surrogate for another factor unique to HIV infection or is an association seen in observational studies that lacks a causal relationship remains unknown. Other HIV-specific factors such as current or nadir CD4 count, HIV-1 viral load and stage of disease have also been inconsistently associated with low 25(OH)D levels to date (37, 42, 43, 45, 60–63).

In a prospective study of pregnant women enrolled in a multivitamin supplementation trial in Tanzania, Mehta et al found associations between low 25(OH)D levels (<32ng/mL or 80nmol/L) and: BMI <18kg/m² (RR 1.45, 95% CI 1.04–2.01), severe anemia (RR 1.46, 95% CI 1.09–1.96), progression to World Health Organization stage III or IV disease (RR 1.25, 95% CI 1.05–1.50), and all-cause mortality (RR 0.58, 95% CI 0.40–0.84). No association with CD4 T cell count was observed (43, 64). This association of 25(OH)D and all-cause mortality mirrors that seen in the general population (2).

Vitamin D Repletion in HIV-Infected Patients

The question of whether HIV-infected patients with low 25(OH)D levels can be successfully repleted with oral supplementation and maintain 25(OH)D levels in the normal range remains unknown. In a small study, only 40% of 20 men compliant with oral D3 supplementation successfully repleted to a 25(OH)D >30ng/mL (75nmol/L) after a median of 16 weeks follow-up (65). Interpretation of this data is complicated by low rates of compliance, small sample size, and variation in prescribed dosing regimens. Havens and colleagues demonstrated only a 46% decline in the prevalence of 25(OH)D <30ng/mL (75nmol/L) following administration of 50,000IU weekly for 12 weeks in their cohort of

HIV-infected subjects 18–24 years of age and on ART ($p < 0.001$ vs. placebo) (66). Lastly, in a RCT of the effects of 4000IU D3 daily vs. placebo, only subjects on non-efavirenz-containing regimens saw a statistically significant improvement in 25(OH)D levels after 12 weeks (efavirenz +3.6ng/mL or 9.0nmol/L, $p = 0.383$; non-efavirenz +5.0ng/mL or 12.5nmol/L, $p = 0.011$) (67). Additional RCTs are needed to establish whether or not oral repletion is successful in the setting of HIV infection, as well as optimal dosing regimens.

Association with ART

Data on the association of low 25(OH)D levels with ART is conflicting but overall suggests an association may be seen with agents such as efavirenz and tenofovir. Other agents may also contribute to low 25(OH)D levels, but data is lacking. To date, causal relationships between specific agents and vitamin D insufficiency cannot be inferred, as most studies have been retrospective or cross-sectional and were not designed to assess the direct effects of ART on vitamin D status.

Welz and colleagues found only efavirenz use was associated with severe vitamin D deficiency (25(OH)D < 10 ng/mL or 25nmol/L) in their analysis of subjects on combination ART (OR 2.0, 95% CI 1.5–2.7, $p < 0.001$). Additionally, efavirenz exposure was associated with an OR for severe vitamin D deficiency of 1.0003 (95% CI 1.0001–1.0004) per day of exposure ($p = 0.001$) (61). Brown and McComsey demonstrated a significant decline in 25(OH)D among patients initiating efavirenz- vs. non-efavirenz-based ART ($p = 0.001$). Similarly, the prevalence of vitamin D deficiency in that cohort (conservatively-defined as 25(OH)D < 15 ng/mL or 37.5nmol/L) was 80% higher for subjects on efavirenz-containing regimens ($p = 0.007$) (68). In the SUN Study, 25(OH)D < 30 ng/mL (75nmol/L) was associated with efavirenz exposure (OR 1.98, 95% CI 1.18–3.34). A significant protective effect of ritonavir exposure was also observed (OR 0.56, 95% CI 0.35–0.89) (41).

In the MONET study, subjects well-controlled on PI- or NNRTI-based regimens were randomized to switch to darunavir monotherapy vs. darunavir + 2 nucleoside reverse transcriptase inhibitors (NRTIs). In this predominantly white male population, lower 25(OH)D levels were associated with efavirenz ($p = 0.0062$) and zidovudine ($p = 0.015$) use. In a multivariable analysis of predictors of severe vitamin D deficiency (25(OH)D < 10 ng/mL or 25nmol/L) at screening, however, only zidovudine use was statistically significant (zidovudine OR 2.45, $p = 0.01$; efavirenz OR 1.5, $p = 0.27$). After 96 weeks on study, neither efavirenz nor zidovudine remained a predictor of vitamin D deficiency (25(OH)D < 20 ng/mL or 50nmol/L), but subjects discontinuing these medications demonstrated larger incremental increases in 25(OH)D levels than those discontinuing other agents [mean 25(OH)D increase for efavirenz and zidovudine = 3.2ng/mL (8nmol/L) or 27%, 95% CI 0.8–5.6ng/mL (2–14nmol/L), $p = 0.007$] (69). In the Dat' AIDS Cohort, both efavirenz and zidovudine use were statistically associated with lower 25(OH)D levels ($p < 0.0001$ and $p = 0.0008$, respectively). Interestingly, a positive association between 25(OH)D and tenofovir use was reported, an observation not seen in previous cohort studies (62).

It also remains unclear whether NNRTIs exhibit a class effect on 25(OH)D levels. While associations between efavirenz and vitamin D insufficiency have been demonstrated fairly consistently, an association with other NNRTIs has not clearly been established (36, 42, 70). Wasserman and colleagues observed 73.7% prevalent vitamin D deficiency in NNRTI users compared to 29.7% in PI users (OR for NNRTI 6.62, 95% CI 1.91–22.89, $p = 0.0017$). While efavirenz was the predominate NNRTI in that cohort, associations of efavirenz and nevirapine with 25(OH)D were not reported separately (36). In another study of 89 patients initiating ART, efavirenz and nevirapine ($p = 0.001$), but not tenofovir or PI use, were associated with 25(OH)D < 20 ng/mL (50nmol/L) (42). Lastly, efavirenz but not TMC278 (rilpivirine) was shown to affect 25(OH)D levels over 48 weeks in subjects initiating ART

(25(OH)D change: efavirenz -2.5ng/mL or -6.2nmol/L , $p<0.0001$; rilpivirine 0.2ng/mL or 0.6nmol/L , $p=0.57$; between group change $p=0.0002$) (71).

Investigators from the Swiss HIV Cohort study demonstrated increased rates of 1-hydroxylation only in tenofovir users with sufficient 25(OH)D levels. Although $1,25(\text{OH})_2\text{D}$ levels were lower overall in vitamin D deficient patients, an exponential increase in 1-hydroxylation occurred as 25(OH)D levels declined (57), highlighting the physiological need to maintain a $1,25(\text{OH})_2\text{D}$ threshold for normal tissue functioning. Since 1-hydroxylation of 25(OH)D is stimulated in response to low serum calcium or phosphate (72), this data may provide further evidence of tenofovir-induced proximal tubule dysfunction and phosphate wasting (73, 74).

Childs and colleagues observed a higher percentage of frank hyperparathyroidism (PTH $>87\text{pg/mL}$) and higher median PTH values among male tenofovir users (41% vs. 0% in non-users, $p=0.018$; 80pg/mL vs. 55pg/mL , $p=0.02$). 82% of subjects had a 25(OH)D $<30\text{ng/mL}$ (75nmol/L) irrespective of tenofovir use. Among tenofovir users, PTH was higher in subjects with 25(OH)D $<30\text{ng/mL}$ (75nmol/L , $p=0.045$). Regression analysis revealed an independent association of PTH with tenofovir use ($p=0.017$) (75). Independent associations between PTH, tenofovir use and low 25(OH)D levels have also been demonstrated by Pocaterra and colleagues (76). These observations are not unexpected, given tenofovir's known associations with secondary hyperparathyroidism (77) and loss of bone mineral density (BMD) (78–80). However, other attempts to confirm the association between PTH and tenofovir use have not been fruitful (81, 82). Labarga et al demonstrated an association between PTH elevations and tenofovir use only in subjects with suboptimal vitamin D levels (25(OH)D $15\text{--}25\text{ng/mL}$ or $37\text{--}62\text{nmol/L}$), suggesting 25(OH)D status was the driving force for hyperparathyroidism in these subjects (83). Still, published rates of hyperparathyroidism in HIV-infected patients on ART range from 17–40% (33, 35). If vitamin D deficiency compounds the severity of hyperparathyroidism in patients on ART, vitamin D supplementation could be an easy and inexpensive way to minimize bone loss in these patients.

Some data exists correlating low 25(OH)D levels with non-efavirenz-, non-tenofovir-containing regimens, as well as with ART in general. In a study of HIV-infected Indian men, Paul et al demonstrated a 10-fold increase in vitamin D insufficiency among patients on ART regimens not containing efavirenz or tenofovir (84). The Italian ICONA Cohort demonstrated an association of hypovitaminosis D with duration of ART (OR 1.33 per year, 95% CI 1.1–1.5, $p=0.0001$) but not individual agents in their large, retrospective analysis of patients initiating ART (85). Lastly, other studies have failed to find any association between ART and low 25(OH)D levels (37, 60, 86).

Immunologic

Campbell and Spector demonstrated inhibition of HIV-1 viral replication in human macrophages incubated with $1,25(\text{OH})_2\text{D}_3$, a process that was partially mediated via autophagy (87). Similar benefits were seen for cells infected with *Mycobacterium tuberculosis* (Mtb) and co-infected with HIV-1 and Mtb (88). These findings provide further support for the role of vitamin D as a modulator of human antiviral and antibacterial responses.

Metabolic

In a cross-sectional study of 1811 HIV-infected patients from Modena, Italy, Szep and colleagues demonstrated an independent association of vitamin D deficiency (25(OH)D $<20\text{ng/mL}$ or 50nmol/L) with type 2 diabetes after controlling for other factors (OR 1.85,

95% CI 1.03–3.32, $p=0.038$) (89). In a retrospective subset analysis of non-diabetic Modena cohort participants ($n=1574$), 30,000IU of D3 weekly was associated with an 83% decline in diabetes incidence (HR 0.17, 95% CI 0.04–0.72) (90). These findings support those of previous studies (5, 6, 91), and are not surprising given the known role of vitamin D in promoting insulin secretion and insulin-mediated glucose transport (92–95).

Rates of osteopenia and osteoporosis are estimated to be 52% and 15%, respectively, in HIV-infected patients both on and off ART (96). Welz and colleagues demonstrated an additive effect of efavirenz and tenofovir on alkaline phosphatase, a marker of bone turnover, in the setting of severe vitamin D deficiency (61). In the Women's Interagency Health Study study, loss of femoral neck BMD in premenopausal, HIV-infected women was associated with vitamin D deficiency ($25(\text{OH})\text{D} < 20\text{ng/mL}$ or 50nmol/L , $p=0.01$) but not ART. Specifically, there was no association between efavirenz use or cumulative tenofovir exposure and bone loss (97). In a cohort of HIV-infected Israeli women, women of Ethiopian descent had significantly: higher rates of severe vitamin D deficiency ($25(\text{OH})\text{D} < 10\text{ng/mL}$ or 25nmol/L , $p=0.001$), higher PTH levels ($p<0.001$), and lower BMD ($p=0.001$ at lumbar spine) vs. Caucasian women (98). Other descriptive studies have not demonstrated an association between BMD and low $25(\text{OH})\text{D}$ levels (86). While decreased BMD in the setting of HIV infection is likely multi-factorial, normalization of vitamin D levels in these patients could prevent the additional contribution of low $25(\text{OH})\text{D}$ levels to metabolic bone disease.

Important data linking low $25(\text{OH})\text{D}$ levels to atherosclerotic disease in HIV-infected patients has come to light this year. Choi et al demonstrated a graded, inverse, independent relationship between $25(\text{OH})\text{D}$ levels and carotid artery intima-media thickness (IMT) in their cross-sectional analysis of patients (99). Similarly, in a study of HIV-infected subjects on ART, Ross and colleagues reported a 10.6-fold increase in the odds of having common carotid artery IMT above the median value in subjects with $25(\text{OH})\text{D} < 30\text{ng/mL}$ (75nmol/L) (63). While these findings mirror the cardio-protective effects of vitamin D observed in the general population, future studies are needed to verify the role of vitamin D supplementation in atherosclerotic disease in HIV infection. If this relationship is validated, low $25(\text{OH})\text{D}$ levels would be an easily modifiable CVD risk factor in HIV-infected patients.

Recent Guidelines

In 2010, both the Institute of Medicine (IOM) and Osteoporosis Canada issued recommendations for vitamin D supplementation. The IOM report stated data supporting vitamin D supplementation on outcomes other than bone health were inconclusive, and suggested that the frequency of vitamin D deficiency in the U.S. and Canada are overestimated. However, an increase in the recommended daily intake of vitamin D from 400IU to 600IU for most adults was made, with a recommended upper supplementation limit of 4000IU per day (9). Given the unique risk for low $25(\text{OH})\text{D}$ levels contributed by HIV infection and ART, it is unreasonable to assume that these guidelines are adequate for HIV-infected patients.

The Osteoporosis Canada guidelines promote more liberal vitamin D supplementation for patients at risk for insufficiency. Their guidelines divide patients into 3 categories: low risk patients that should receive 400–1000IU daily without $25(\text{OH})\text{D}$ monitoring, moderate risk patients that should receive 800–2000IU daily without monitoring, and high-risk subjects that should receive enough vitamin D supplementation to maintain $25(\text{OH})\text{D}$ levels $> 30\text{ng/mL}$ (75nmol/L). While these practice guidelines also admit data demonstrating benefits beyond bone health is currently insufficient, the panel concluded that the safety, tolerability, and potential benefits of vitamin D supplementation outweigh the risks of long-term insufficiency (100).

Given the prevalence of low 25(OH)D levels in HIV-infected patients and the potential for added risk of low 25(OH)D due to chronic comorbidities and/or ART, most patients would be considered medium-to-high risk under Canadian guidelines and should receive a minimum of 800IU daily. However, the authors of this article argue that all HIV-infected subjects should be screened for low 25(OH)D levels, monitored while on supplementation, and given sufficient supplementation to maintain 25(OH)D levels >30ng/mL (75nmol/L). This recommendation seems reasonable given the high rates of osteoporosis and osteopenia in HIV-infected persons (96), the low risk of supplementation, and the potential for benefits beyond bone health in this population. The controversy over supplementation and the lack of consensus guidelines specific to HIV infection underlie the need for RCTs to critically assess repletion and maintenance regimens, as well as the potential immunologic and physiologic benefits of vitamin D supplementation in HIV-infected patients.

Limitations

To date, only associations between vitamin D insufficiency and HIV infection, ART, and HIV-specific risk factors have been made. This is due in large part to the cross-sectional or observational nature of the studies involved, from which causation cannot be demonstrated. The lack of consistency in defining low 25(OH)D levels and frank deficiency, clinical and laboratory endpoints, and supplementation regimens also complicates data interpretation. Prospective, RCT will help elucidate the true role of vitamin D in the setting of HIV, and will better inform clinical decision-making.

Conclusions and Future Directions

As in the general population, data on low 25(OH)D levels in the setting of HIV infection are emerging. To date, low 25(OH)D levels have been associated with both traditional and HIV-specific risk factors. Of note, the growing body of evidence supporting an association between low 25(OH)D levels and efavirenz and tenofovir use warrants further attention. Low 25(OH)D levels have also been associated with severity of disease in HIV infection and all-cause mortality.

Sufficient observational data is available to support RCTs for vitamin D supplementation in HIV-infected patients, and their importance cannot be over-emphasized. Repletion and maintenance regimens, as well as the benefits of supplementation in HIV-infected persons, must be critically evaluated before evidence-based practice guidelines can be made.

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