Effects of vitamin D deficiency and combination antiretroviral therapy on bone in HIV-positive patients

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Objectives: In the era of combination antiretroviral therapy (cART), vitamin D deficiency, low bone mineral density (BMD) and fractures have emerged as subjects of concern in HIV-positive patients. Testing for vitamin D deficiency has been widely adopted in clinical practice even though the benefits of vitamin D supplementation in this population remain uncertain. The objective of this review was to evaluate the evidence for such a strategy.

Design: Systematic review of the literature on vitamin D deficiency in HIV infection, the effects of cART on vitamin D status, and the effects of vitamin D deficiency and cART on parathyroid hormone (PTH), bone turnover, BMD and the incidence of fractures in HIV-positive patients.

Methods: PubMed was used to identify relevant articles up to September 2011.

Results: Vitamin D deficiency, secondary hyperparathyroidism and low BMD are common in HIV-positive patients. Efavirenz is associated with a reduction in 25-hydroxy vitamin D levels, tenofovir with secondary hyperparathyroidism, and cART with increased bone turnover and low BMD. The clinical significance of low BMD, however, remains unclear, especially in younger patients. Although the incidence of fractures may be increased in HIV-positive patients, the contribution of low BMD and vitamin D deficiency to these fractures is uncertain. Limited data on vitamin D supplementation in HIV-positive patients have shown transient, beneficial effects on PTH, but no effects on BMD.

Conclusion: The benefits of vitamin D supplementation in this population need to be demonstrated before widespread 'test and treat' policies can be recommended as part of routine clinical practice.

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Keywords: vitamin D, parathyroid hormone, antiretroviral therapy, bone turnover, bone mineral density, fractures, HIV

Introduction

With the decline of opportunistic infections [1], comorbidities affecting the liver, kidney, bone, cardiovascular and central nervous system have become increasingly prevalent and emerged as important causes of death in the era of combination antiretroviral therapy (cART) [2]. Low bone mineral density (BMD) and vitamin D deficiency are both

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common in HIV-positive patients [3–6] and may contribute to the observed increased incidence of fractures in this population [7,8]. Recent studies have shown that cART may have effects on vitamin D, parathyroid hormone (PTH), bone turnover, BMD and the risk of developing fractures. Consequently, measurement of 25-hydroxy vitamin D [calcidiol, 25(OH)D] and vitamin D replacement in those with low levels has been widely adopted in HIV clinical practice. However, evidence for the clinical benefit or cost effectiveness of such a strategy is lacking. Here we review the recent literature on vitamin D deficiency, the effects of cART on vitamin D status, the effects of vitamin D deficiency and cART on PTH levels, bone turnover, BMD and fractures, and on vitamin D supplementation in HIV-positive patients.

We used the PubMed database to systematically search the English language literature for relevant articles using the following terms: vitamin D, PTH and bone, each combined with HIV. Articles published up to 30 September 2011 were considered for inclusion in our review. We also reviewed conference abstracts from the 2011 International AIDS Society and Conference on Retroviruses and Opportunistic Infections meetings for novel, as yet unpublished, insights.

Vitamin D deficiency in HIV-positive patients

Vitamin D status should be assessed by measurement of 25(OH)D [9]. Low 25(OH)D levels identify patients with vitamin D insufficiency [(20–30 ng/ml (50–75 nmol/l)], deficiency [10–20 ng/ml (25–50 nmol/)] or severe deficiency [<10 ng/ml (<25 nmol/l)] [10]. The prevalence of vitamin D deficiency in HIV-positive patients ranges from 29 to 73% [4–6]. However, HIV infection *per se* is not associated with vitamin D deficiency (Table 1) [5,6,11,12]. Only one small study suggested that 25(OH)D levels may be lower in HIV-positive patients [13]. Subsequent studies have shown either similar or higher 25(OH)D levels [11,14], or similar or lower rates of vitamin D deficiency [5,6,11,12] in HIV-positive patients compared with either HIV-negative patients or general population controls. As for vitamin D deficiency in the general population [10,15], cross-sectional studies of vitamin D status in HIV-positive patients have identified the following risk factors for low 25(OH)D levels: black or Hispanic ethnicity [4,5,16–19], reduced ultraviolet exposure or measurements obtained in fall or winter season [4,5,16,18], increased BMI [5,16], hypertension and a low exercise level [5]. On the contrary, lower estimated glomerular filtration rate has been associated with reduced odds of low vitamin D status [5,17]. HIV-parameters associated with low 25(OH)D

Table 1. Vitamin D deficiency in HIV-positive versus HIV-negative patients.

Publication	Location	Study type	Study population	Control population	Prevalence of vitamin D deficiency (cutoff)		HIV-associated risk factors for VDD	Comments
					HIV +	HIV -		
Studies including HIV-positive and HIV-negative subjects								
Adeyemi *et al.* [6]	USA	Cross-sectional	1268 HIV-positive women (WIHS)	510 HIV-negative women (WIHS)	60% (<20 ng/ml)	72%	CD4 <200, undetectable HIV VL	EFV-sparing regimens assoc. with lowest odds of VDD
Ormesher *et al.* [11]	USA	Cross-sectional	199 HIV-positive African-American men	424 HIV-negative African-American men (NHANES)	77% (<30 ng/ml)	96%	None	
Dao *et al.* [5]	USA	Cross-sectional	672 HIV-positive adults (SUN)	US general population (NHANES)	70% (<30 ng/ml)	79%	EFV, RTV	NVP not assoc. with VDD
Stein *et al.* [12]	USA	Cross-sectional	89 HIV-positive women	95 HIV-negative women	~49% (<20 ng/ml)	~46%	Lower CD4 cell count in women on cART	

EFV, efavirenz; NVP, nevirapine; RTV, ritonavir; VDD, vitamin D deficiency; VL, viral load.

levels include intravenous drug use [16,18], longer time since HIV diagnosis [16], CD4 cell count less than 200 cells/μl [4,6], current use of cART [4,5], and an undetectable [6] or detectable [19] HIV RNA level. Although the clinical implications of vitamin D deficiency in HIV-positive patients remain to be defined, higher incidence rates of AIDS and death have been observed in patients with 25(OH)D levels less than 12 ng/ml at baseline [18].

Vitamin D deficiency and combination antiretroviral therapy

The potential effect of cART on vitamin D status has received considerable attention recently; the emerging view is that specific antiretrovirals may affect 25(OH)D levels (Table 2) [4,16–18,20–30]. Nonnucleoside-reverse transcriptase inhibitor (NNRTI)-based cART has most consistently been associated with low 25(OH)D levels [4,5,16,20,21], albeit not in all cross-sectional studies [6] (Table 2a). Within the class of NNRTIs, an association with low vitamin D status has been reported for efavirenz but not for nevirapine [4,5,26]. Protease inhibitor-based cART has either not been associated with low vitamin D status [4] or with reduced odds of vitamin D deficiency or insufficiency [5,6,18]. Among the NRTIs, zidovudine has been associated with lower 25(OH)D levels [27]. Tenofovir has not been associated with vitamin D deficiency or insufficiency [4,5,16], and no data are available for integrase inhibitors, CCR5 inhibitors or enfuvirtide.

In longitudinal studies, reduced 25(OH)D levels have been reported 12 months after starting efavirenz-containing cART [16,23,24] (Table 2b). Similar reductions in 25(OH)D levels were observed after 24 weeks of efavirenz or etravirine containing cART [29], whereas a clinical trial comparing efavirenz versus rilpivirine (both with 2NRTI) saw a significant 25(OH)D decrease (64.1–58.6 nmol/l) in the efavirenz group with unchanged levels (61.8–60.8 nmol/l) in the rilpivirine arm [30] (Table 2c). The results with nevirapine have been conflicting [31], with no changes in 25(OH)D observed in some studies [16,25,28], and reductions similar to those observed with efavirenz in others [22,24]. No significant change in 25(OH)D levels has been reported in patients commencing protease inhibitor-based cART [24,28]. By contrast, discontinuation of efavirenz or zidovudine while switching to darunavir/ritonavir monotherapy was associated with increased 25(OH)D levels [27].

In summary, data from cross-sectional and longitudinal studies are consistent with an effect of efavirenz on vitamin D homeostasis resulting in reduced 25(OH)D levels, with little or no evidence for an effect of protease inhibitors or NRTIs including tenofovir on 25(OH)D concentration. Efavirenz reduces expression of cytochrome P450 (CYP)2R1 [32], one of the enzymes involved in 25-hydroxylation of vitamin D_3 (and vitamin D_2) to 25(OH)D [33] (Fig. 1) [34]. In addition, efavirenz has been shown to induce CYP24 that converts both 25(OH)D and Calcitriol [1,25$(OH)_2$D] to their inactive metabolites [35], similarly to phenobarbital, a drug associated with vitamin D deficiency and osteomalacia [32,34]. The clinical significance of small reductions in 25(OH)D in patients taking efavirenz remains to be defined.

Vitamin D deficiency, combination antiretroviral therapy, 1,25$(OH)_2$D and parathyroid hormone levels

Although 25(OH)D is the most commonly used measure of vitamin D status in clinical practice, the effects of vitamin D are mediated through its active form, 1,25$(OH)_2$D (Fig. 1), a hormone with a relatively short half life (4 h) [9]. The relationship between 25(OH)D and 1,25$(OH)_2$D levels is not linear. Higher 1,25$(OH)_2$D levels, in parallel with higher 25(OH)D levels, were reported for cART-exposed compared with cART-naive patients [36]. No relationship, or a weak positive correlation ($r^2 = 0.19$) between 25(OH)D and 1,25$(OH)_2$D was observed in North American HIV-positive patients [14,21], whereas progressively lower 1,25$(OH)_2$D levels were observed in 74 Swiss HIV-positive patients with normal, insufficient and deficient 25(OH)D status [16]. In this study, prior AIDS, positive hepatitis C antibody status, higher current CD4 cell count and lower BMI were associated with lower 1,25$(OH)_2$D levels; 1,25$(OH)_2$D levels were unaffected by NNRTI exposure, whereas tenofovir use was associated with increased 1,25$(OH)_2$D levels [16].

As 1α-hydoxylation of 25(OH)D is regulated by PTH, increased 1,25$(OH)_2$D levels in patients taking tenofovir may reflect increased PTH levels. Indeed, tenofovir has been associated with secondary hyperparathyroidism [adjusted odds ratio (aOR) 3.2, 95% confidence interval (CI) 1.6, 6.3] [37], a phenomenon that appears largely restricted to patients with reduced 25(OH)D levels (<20–30 ng/ml) [17,38]. In a longitudinal study, significant increases in PTH were observed in the first 36 weeks of exposure to tenofovir/emtricitabine but not with abacavir/lamivudine, and tenofovir/emtricitabine exposure was an independent predictor of hyperparathyroidism [39]. Hyperparathyroidism in HIV-positive patients may, however, not be restricted to those taking tenofovir; in the Metabolic Effects of DIfferent CLasses of AntiretroviralS (MEDICLAS) study, a significant increase in PTH levels from baseline was observed at 24 months in patients starting cART (lopinavir/ritonavir with either

Table 2. Vitamin D deficiency in HIV-positive patients: relationship with combination antiretroviral therapy.

Publication	Location	Study population	Prevalence of vitamin D deficiency (cutoff)	HIV-associated risk factors for VDD	Comments
(a) Cross-sectional studies of HIV-positive patients					
Van den Bout *et al.* [20]	Netherlands	252 HIV-positive adults	29% (<35/<25 nmol/l)	NNRTIs	cART (NNRTI/PI) in 50% assoc. with elevated PTH
Rosenvinge *et al.* [17]	UK	227 HIV-positive adults	57% (<20 ng/ml)	None	Increased PTH in pts with VDD on TFV
Rodriguez *et al.* [21]	USA	57 HIV-positive adults	47% (<20 ng/ml)	NNRTIs	cART associated with elevated PTH
Welz *et al.* [4]	UK	1077 HIV-positive adults	34.8% (<10 ng/ml)	CD4 nadir <200, EFV	TFV and EFV assoc. with raised ALP
Pasquet *et al.* [22]	France	395 HIV-positive adults	41% (<30 nmol/l)	NNRTIs	No difference between EFV and NVP
Viard *et al.* [18]	Europe, Israel, Argentina	1985 HIV-positive adults (EuroSIDA)	67% (<20 ng/ml)	Reduced odds of VDD with PIs	25(OH)D >12 ng/ml assoc. with reduced incidence AIDS/death
Publication	Location	Study population	Prevalence of vitamin D deficiency (cut-off)	Changes in 25(OH)D	Comments
(b) Longitudinal studies of HIV-positive patients					
Brown and McComsey [23]	USA	87 HIV-positive adults starting cART	33% (precART, <37.5 nmol/l)	Decrease at 6–12M with EFV (−12.7 nmol/l)	EFV assoc. with VDD precART
Conesa-Botella *et al.* [24]	Belgium	87 HIV-positive adults starting cART	44% (pre-CART, <20 ng/ml)	Decrease at 12M with NNRTI (−5.0 ng/ml)	Similar reductions with EFV and NVP, no change with PIs
Lattuada *et al.* [25]	Italy	18 HIV-positive adults starting ZDV/3TC/NVP	12% (pre cART, <10 ng/ml)	Nonsign. increase at 12M (+14.9 nmol/l)	No patients developed hyperparathyroidism
Mueller *et al.* [16]; Fux *et al.* [26]	Switzerland	211 HIV-positive adults starting cART	42% (spring), 14% (fall) (precART, <30 nmol/l)	Decrease at 12M with NNRTI (−7 nmol/l)	TFV assoc. with higher $1,25(OH)_2D$ levels; NVP not assoc. with VDD
(c) Data arising from clinical trials of HIV-positive patients					
Fox *et al.* [27]	Europe, Russia, Israel	221 HIV-positive adults on cART	77% (study entry, <20 ng/ml)	Greatest increase in pts who discontinued EFV or ZDV (+8.1 and +7.8 nmol/l)	PI-monotherapy study; EFV assoc. with VDD at study entry
Van Vonderen *et al.* [28]	Europe	50 HIV-positive men starting cART	Not reported	No changes at 24M with ZDV/3TC/LPV/r or NVP/LPV/r	Significant increase in PTH in both study arms
Rockstroh *et al.* [29]	Europe	157 HV-positive patients starting cART	26% (study entry, <20 pg/ml)	Similar decrease at 24w with EFV vs. ETV (−21 vs. −20.3 nmol/l)	Combined use of ZDV and EFV assoc. with greater reductions in $1,25(OH)_2D$
Wohl *et al.* [30]	Global	586 HIV-positive adults starting cART	24.7% (study entry, <20 pg/ml)	Greater decrease at 48w with EFV vs. RPV (−6.2 vs. −0.6 nmol/l)	Greater proportion of patients developed severe VDD with EFV

3TC, lamivudine; ALP, alkaline phosphatase; cART, combination antiretroviral therapy; EFV, efavirenz; ETV, etravirine; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PTH, parathyroid hormone; RPV, rilpivirine; RTV, ritonavir; TFV, tenofovir; VDD, vitamin D deficiency; ZDV, zidovudine.

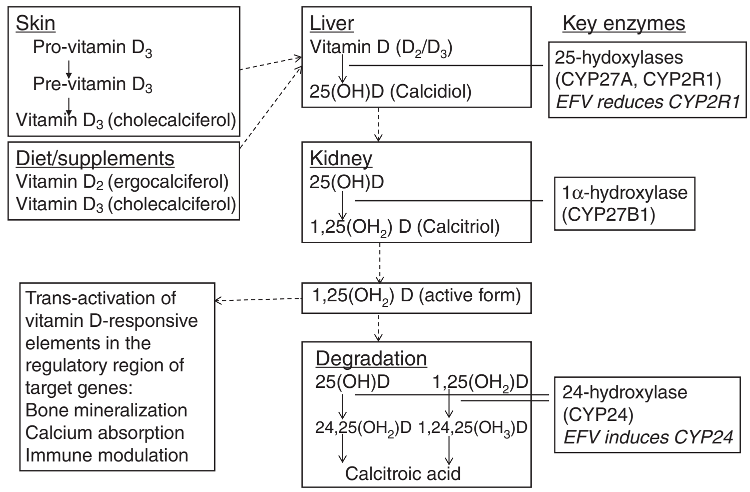

Fig. 1. Vitamin D is produced in sun-exposed skin or can be obtained from diet or dietary supplements. Two hydroxylation steps are required for vitamin D to become active, 25-hydroylation in the liver [through CYP27A and CYP2R1, resulting in the formation of calcidiol – 25(OH)D] and 1α-hydroxylation in the kidney [through CYP27B1, resulting in the formation of calcitriol – 1,25(OH)$_2$D]. 1α-hydroxylation is upregulated by parathyroid hormone and hypocalcaemia, and downregulated by hypercalcaemia, leptin and phosphatonin (FGF-23). 1,25(OH)$_2$D exerts its actions after binding to the vitamin D receptor, which then forms heterodimers with the retinoic acid receptor to bind and transactivate vitamin D-responsive elements in the regulatory region of target genes. Both 25(OH)D and 1,25(OH)$_2$D are catabolized through CYP24; 24-hydroxylation is upregulated by 1,25(OH)$_2$D and hypercalcaemia [34]. Efavirenz may affect vitamin D homeostasis by inhibiting CYP2R1 and inducing CYP24.

zidovudine/lamivudine or nevirapine), irrespective of the cART regimen and in the absence of changes in 25(OH)D levels [28]. Most studies have reported a negative correlation between 25(OH)D and PTH levels (r^2 ranging from −0.31 to −0.48) [14,20,21,37,39].

In summary, these data suggest a limited effect of vitamin D deficiency on 1,25(OH)$_2$D levels, and no evidence for an association between NNRTI exposure and reduced 1,25(OH)$_2$D levels. Elevated PTH levels are common in patients on cART and associated with tenofovir exposure; whereas in some patients this may reflect a (possibly enhanced) homeostatic response to low 25(OH)D levels, it may also be a direct effect of cART. The effects of tenofovir on proximal renal tubular function [40] do not appear to translate into reduced 1α-hydoxylase activity as assessed by reduced 1,25(OH)$_2$D levels.

Vitamin D deficiency, combination antiretroviral therapy and bone turnover

In cross-sectional studies, severe vitamin D deficiency was not associated with increased alkaline phosphatase (ALP), a nonspecific marker of bone formation [4], although others observed increased ALP in individuals with 25(OH)D less than 5 ng/ml [41]. Secondary hyperparathyroidism [37], but not lower 25(OH)D levels [42], has been associated with increased bone turnover in HIV-positive patients. Tenofovir has been associated with raised ALP in cross-sectional [4] and longitudinal studies [43,44], and efavirenz with raised ALP in patients with 25(OH)D levels less than 13 ng/ml [4]. Receipt of cART was associated with increased bone turnover in premenopausal women [42], Spanish [36], and Swiss cohorts [45], with no difference between exposure to NNRTIs or protease inhibitors, or to regimens with or without tenofovir [45]. Others have reported increased bone turnover with current protease inhibitor [46,47] or tenofovir [47] exposure, or no difference in bone turnover between patients on cART and those not on cART [48].

In the ASSERT study, increased bone turnover was observed following initiation of cART, with somewhat greater increases in patients randomized to tenofovir/emtricitabine/efavirenz versus abacavir/lamivudine/efavirenz [49]. In the MEDICLAS study, significantly increased bone turnover was observed from 3 to 24 months following initiation of lopinavir/ritonavir/nevirapine or lopinavir/ritonavir/zidovudine/lamivudine, with no difference between study arms [28]. In this study, markers of bone resorption reached a steady state within 3 months of cART initiation, whereas markers of bone formation took 12 months to reach their peak or steady state, thus representing a 'catabolic window' during the first year of cART, a period to which most of the cART-associated changes in BMD are confined [50].

In summary, available data suggest that cART *per se* is associated with increased bone turnover, and that bone turnover may be further increased in patients receiving tenofovir and in those with secondary hyperparathyroidism. It remains unclear if bone turnover is increased in vitamin D-deficient patients who do not have hyperparathyroidism.

Vitamin D deficiency, combination antiretroviral therapy and bone mineral density

Low BMD is common in HIV-positive patients; osteopenia was present in 52% and osteoporosis in 15% of patients in a meta-analysis that included studies published up to November 2005 [3]. Older age, smoking, lower BMI, white ethnicity, female sex, glucocorticoid exposure and increasing duration of HIV infection have been associated with low BMD in this population [51]. Although not associated with BMD in cross-sectional studies [36,52], vitamin D deficiency or low vitamin D levels have been associated with lower total hip BMD at baseline [53] or greater reductions in femoral neck BMD during follow-up in longitudinal studies [42], whereas higher PTH levels have been associated with greater reductions in BMD [28]. Exposure to cART [odds ratio (OR) 2.5 (1.8–3.7)] and protease inhibitors [OR 1.5 (1.1–2.0)] was associated with low BMD in a meta-analysis [3], and several antiretrovirals, including tenofovir [54,55], didanosine [54], and protease inhibitors [55] have been associated with greater reductions in BMD in cohort studies.

The effects of cART on BMD have also been investigated in several randomized controlled trials. Continuous versus intermittent cART in the Strategies for Management of Anti-Retroviral Therapy study was associated with greater reductions in BMD [56]. In Simplification with fixed-dose Tenofovir-Emtricitabine or Abacavir-Lamivudine in adults with suppressed HIV replication, a cART simplification study in patients with undetectable HIV RNA levels, reductions in BMD were observed in patients randomized to tenofovir/emtricitabine, with improvements in the abacavir/lamivudine arm; osteopenia and osteoporosis were encountered at a higher rate in the tenofovir/emtricitabine arm (8.54 vs. 4.37 events per 100 person-years in the abacavir/lamivudine arm) [44]. Rapid reductions of 2–6% in BMD during the first 24–48 weeks, with subsequent stabilization or improvement up to 192 weeks, have been observed in several studies comparing different cART regimens [28,49,57–61]. Greater reductions in spine and hip BMD at 48 and/or 96 weeks were observed in patients randomized to tenofovir/emtricitabine versus abacavir/lamivudine [49,57], atazanavir/ritonavir versus efavirenz [57], and lopinavir/ritonavir/zidovudine/lamivudine versus lopinavir/ritonavir/nevirapine [28]. Greater reductions in spine BMD were observed in patients randomized to ritonavir-boosted protease inhibitors (lopinavir/ritonavir or indinavir/ritonavir with two NRTIs) versus protease inhibitor-sparing regimens (efavirenz or nevirapine with two NRTIs) [58] and to tenofovir versus stavudine (both with lamivudine and efavirenz) [60]. Others, however, have found no difference in bone loss up to 144 weeks in patients randomized to lopinavir/ritonavir/efavirenz versus zidovudine/lamivudine/efavirenz [59], or to lopinavir/ritonavir versus efavirenz (both with zidovudine/lamivudine) [61]. Changes in BMD have been associated with increased bone turnover [28,49] and/or increased PTH levels [28], although between-arm differences in BMD change were not explained by these parameters [28]. In some of these studies, greater reductions in BMD occurred in those over 35 years old, nonblack ethnicity, lower CD4 cell count, higher HIV RNA level, higher glucose and lower BMI at baseline, and those experiencing a greater increase in total cholesterol [49,57–59,61].

In summary, results of observational studies suggest an increased prevalence of low BMD in HIV-positive patients on cART. Some of these studies have identified associations between low bone mass or bone loss and exposure to protease inhibitors or tenofovir. In clinical trials, early reductions of 2–6% in BMD following initiation of cART are a consistent finding, irrespective of the drugs included in the regimen, with stabilization of BMD after the initial 24–48 weeks. In these studies, tenofovir/emtricitabine has been associated with greater reductions in BMD than abacavir/lamivudine, and regimens containing ritonavir-boosted protease inhibitors may be associated with greater reductions in BMD compared with NNRTI-based cART. The magnitude of the initial reduction in BMD with cART is comparable to that observed during the first year of menopause or with glucocorticoid therapy, although the clinical significance, especially in young adults, remains unclear. The role of vitamin D deficiency in cART-associated bone loss remains to be defined.

Vitamin D deficiency, combination antiretroviral therapy and fractures

The reported incidence of fractures in HIV-positive patients ranges from 0.03–0.9 per 100 person-years in predominantly male study populations [8,56,62,63] to 1.8 per 100 person-years in women [64]. Consistent with an increased prevalence of low BMD in HIV-positive patients, an approximately 60% higher fracture rate in this population has been reported in some studies [7,8,65], although others found similar fracture rates among HIV-positive and HIV-negative indiduals after adjustment for potential confounders [64,66,67]. The majority of fractures in these studies were traumatic rather than due to fragility [8], and may thus have occurred irrespective of lower BMD. None of these studies reported data on vitamin D status. The use of cART has not been associated with an increased incidence of fractures [8,64], although somewhat higher fracture rates have been reported with continuous versus intermittent cART [56], and with tenofovir and/or ritonavir-boosted protease inhibitors [66,68], and somewhat lower rates with NNRTIs [64]. Other factors found to be associated with fractures in HIV-positive patients include older age, white ethnicity, low BMI, smoking, alcohol abuse, low CD4 cell count, AIDS, diabetes, hepatitis C coinfection, use of proton pump inhibitors or corticosteroids, and osteoporosis on dual *X-ray* absorptiometry (DXA) [8,62–64,66].

In summary, the limited available data suggest that the incidence of fractures in HIV-positive patients may be increased. There are insufficient data on fragility fractures and the potential contribution of vitamin D deficiency, hyperparathyroidism, increased bone turnover and low BMD to these fractures in HIV-positive patients.

Vitamin D supplementation in HIV-positive patients

Cohort studies have failed to show an association between higher vitamin D and calcium intake and reduced bone loss [54], or between vitamin D supplementation and protection against fractures [64]. Vitamin D supplementation (800–2800 IU/day) in HIV-positive patients with suboptimal 25(OH)D levels may reduce PTH levels [69]. A 48-week study of vitamin D supplementation (2000 IU for 14 weeks, 1000 IU thereafter) noted sustained improvements in 25(OH)D levels (from 26.4 at baseline to 79.8–101.95 nmol/l at weeks 12–48). However, improvements in $1,25(OH)_2D$ and PTH were transient and no effects on BMD, inflammatory markers, lipids, adiponectin or leptin levels were observed [70]. Significant early (12 weeks) reductions in PTH were also observed in a randomized controlled clinical trial of vitamin D (50 000 IU every 4 weeks for 12 weeks) supplementation in 118 HIV-positive adolescents who were stable on tenofovir-containing cART; these improvements in PTH were not observed in those on tenofovir-sparing regimens and were not associated with changes in markers of bone formation or bone resorption [71]. Two other clinical trials investigated the effect of 70 mg of alendronate or placebo (coadministered with 200 IU of vitamin D and 500 mg of calcium carbonate, or with 400 IU of vitamin D and 1000 mg of calcium carbonate daily) on bone. In the higher dosed study, patients in the alendronate arm experienced a 5.2% (95% CI 1.3, 6.4) increase in lumbar spine BMD at 48 weeks compared with a 1.3% (−2.4, 4.0) increase in the calcium/vitamin D arm. Hip BMD in both arms increased by approximately 2%, whereas bone resorption reduced with alendronate but not with calcium/vitamin D only [72]. In the lower dosed study, lumbar spine and total hip BMD at 48 weeks improved in both arms (3.38 and 3.95 vs. 1.10 and 1.31%, respectively, in the alendronate and placebo arms) [73].

Recommendations for vitamin D testing and supplementation

Guidelines for the general population suggest that adults aged 19–50 years require at least 600 IU/day of vitamin D to maximize bone health and muscle function [9]. The 2011 US Endocrine Society guidelines recommend that screening is restricted to persons at risk of vitamin D

Table 3. Risk factors for vitamin D deficiency, low bone mineral density and/or fracture.

(a) Risk factors for vitamin D deficiency in the general population (indications for 25(OH)D measurement, adapted from [9])	(b) Risk factors for low BMD and/or fracture in the general population (adapted from [74,75])
Rickets, osteomalacia, osteoporosis	Low weight or low BMI
Chronic kidney and liver disease	Older age and female gender
Malabsorption syndromes	History of low impact fracture
Hyperparathyroidism	Family history of hip fracture
Granulomatous diseases (including tuberculosis) and some lymphomas	Vitamin D deficiency
Pregnancy and lactation	Nonblack ethnicity
Obesity (BMI >30 kg/m^2)	Smoking
Older age, with history of falls or low impact fracture	Physical inactivity
Black ethnicity	Glucocorticoid exposure
Smoking	Hypogonadism
Glucocorticoid exposure	Excessive alcohol consumption (>3 units/day)
Hypogonadism	Recreational drug use
Excessive alcohol consumption	
Recreational drug use	
Antiseizure medications, glucocorticoids, antifungals, cholestyramine and antiretroviral medications	

BMD, bone mineral density; 25(OH)D, 25-hydroxy vitamin D.

deficiency (Table 3a) [9,74,75] and recommend vitamin D supplementation (1500–2000 IU/day) to achieve levels more than 30 ng/ml in those found to have 25(OH)D less than 20 ng/ml [9]. Higher doses, which may be required for cardiovascular prevention, are currently not recommended. Of note, 'AIDS medications' are listed among the indications for 25(OH)D measurement in this guideline [9]. The 2011 European AIDS Clinical Society guidelines recommend measurement of serum 25(OH)D levels in HIV-positive patients at HIV diagnosis who are at risk of vitamin D deficiency, and in those diagnosed with osteomalacia, osteopenia and osteoporosis. In addition, they recommend vitamin D supplementation (maintenance dose 800–2000 IU/day) if 25(OH)D levels are low (<10 ng/ml), aiming to increase 25(OH)D levels to more than 20 ng/ml and to maintain PTH within the normal range, calcium supplementation if there is insufficient dietary calcium intake (1–1.2 g daily), use of the FRAX score [76] to assess the risk of fractures, and to consider DXA scanning in those at increased risk of fractures [74].

With the majority of HIV-positive patients receiving cART aged below 50 years, the benefits of a universal vitamin D deficiency 'test and treat' strategy in terms of fracture prevention remain to be defined, especially if vitamin D is given without daily calcium supplements [77]. Vitamin D supplementation, however, may confer additional benefits in terms of reduced HIV transmission and reduced HIV disease progression [18,78,79], and randomized controlled studies of potential skeletal, immunological, cardiovascular and other benefits of vitamin D supplementation in HIV-positive patients are warranted. Until evidence to support widespread vitamin D supplementation becomes available, we suggest that decisions regarding vitamin D testing and supplementation may be best guided by fracture risk (Table 3b) rather than the risk of vitamin D deficiency. The FRAX score, although not validated for HIV-positive patients and those aged under 40, can help identify those at low risk of skeletal complications who are less likely, if at all, to benefit from vitamin D supplementation. In view of the modest effects of cART on vitamin D levels and the current lack of evidence that vitamin D supplementation reduces cART-associated reductions in BMD, it remains unclear whether receipt of cART in general, and efavirenz-containing cART in particular, should be considered an indication for vitamin D testing as suggested by the US Endocrine Society guidelines' reference to 'AIDS medications' [9].

Conclusion

Vitamin D deficiency and secondary hyperparathyroidism are common in patients with HIV infection. Efavirenz is associated with reduced 25(OH)D levels, whereas tenofovir is associated with elevated PTH levels in patients with vitamin D deficiency. Secondary hyperparathyroidism results in increased bone turnover and reductions in BMD. The most pronounced reductions in BMD are observed soon after initiating or changing cART, with subsequent stabilization of BMD in clinical trials and modest rates of bone loss in some cohort studies. The overall incidence of fragility fractures, especially in younger HIV-positive patients is low and this should be taken into consideration in deciding whether to measure 25(OH)D levels and recommend vitamin D supplementation.

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Conflicts of interest

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