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Vitamin D Deficiency in HIV: A Shadow on Long-Term Management?

Chloe Orkin[1], David A. Wohl[2], Andrew Williams[1] and Henri Deckx[3]

[1]Barts Health NHS Trust, London, UK; [2]University of North Carolina at Chapel Hill, North Carolina, USA; [3]Janssen Infectious Diseases BVBA, Beerse, Belgium

Abstract

Vitamin D deficiency in HIV infection has attracted much interest. The best known clinical outcomes of vitamin D deficiency are rickets (children) and osteomalacia (adults). Several non-skeletal disorders have also been linked to suboptimal vitamin D levels in the general population. The prevalence of vitamin D deficiency varies widely (6-100%) across diverse patient populations, with no evidence that it is higher in HIV-positive versus noninfected adults. Vitamin D deficiency may blunt immune restoration and exacerbate HIV complications (e.g. opportunistic infections, poor perinatal outcomes, wasting, HIV disease progression, AIDS events, and death). The nonnucleoside reverse transcriptase inhibitor efavirenz was associated with a relatively high risk of vitamin D deficiency; nevirapine, etravirine, and rilpivirine were noted to have less or no impact on vitamin D versus efavirenz in the limited data available. Protease inhibitors have either no or a low association with vitamin D deficiency. Nucleoside/nucleotide reverse transcriptase inhibitors (with the possible exception of zidovudine) also did not appear to be associated with vitamin D deficiency. Management of vitamin D deficiency in HIV-positive adults has not been rigorously evaluated; some guidelines recommend more vitamin D supplementation for HIV-positive adults on antiretrovirals versus the general population (e.g. 2-3 times higher vitamin D daily intake for the age group; loading dose up to 10,000 IU/day for 8-10 weeks and a maintenance dose of 800-2,000 IU/day). In conclusion, although vitamin D deficiency in HIV-positive adults can be prevalent, current evidence for its causes and impact is relatively weak. More data, particularly from large, controlled, long-term trials, regarding the benefits of correcting vitamin D levels in HIV-positive adults are needed. **(AIDS Rev. 2014;16:59-74)**

Corresponding author: Chloe Orkin, Chloe.Orkin@bartshealth.nhs.uk

Key words

Vitamin D. Vitamin D deficiency. HIV. Antiretroviral therapy.

Introduction

Vitamin D and its role in general human health have attracted considerable interest. Improved therapy for HIV infection has resulted in increased survival of HIV-1-infected individuals, and, subsequently, interest in the role of vitamin D has extended to this population.

Correspondence to:
Chloe Orkin
Department of Infection and Immunity
Barts Health NHS Trust
London, UK
E-mail: Chloe.Orkin@bartshealth.nhs.uk

Vitamins D_2 and D_3 are the human-relevant forms of this vitamin, and their sources are shown in Fig. 1[1]. The serum half-life of vitamin D_3 is 36-78 hours[2], and due to storage in adipose tissue, the total-body half-life is ≈ 2 months[3]. However, the active metabolite 1,25-dihydroxyvitamin D (1,25$[OH]_2$D) has a short half-life (3.5-21 hours)[4], and its serum levels are tightly controlled[5,6]. Levels of the intermediate, 25-hydroxyvitamin D (25OHD), are commonly used to assess vitamin D status[7] as it is the major circulating form of vitamin D[1], has a long serum half-life of ≈ 15 days[3], and levels are tightly regulated to between ≈ 75-220 nmol/l[8]. Decreases in serum 25OHD levels reflect clinically relevant vitamin D insufficiency/deficiency[6].

The major role of vitamin D is in the maintenance of bone health throughout life, including increasing

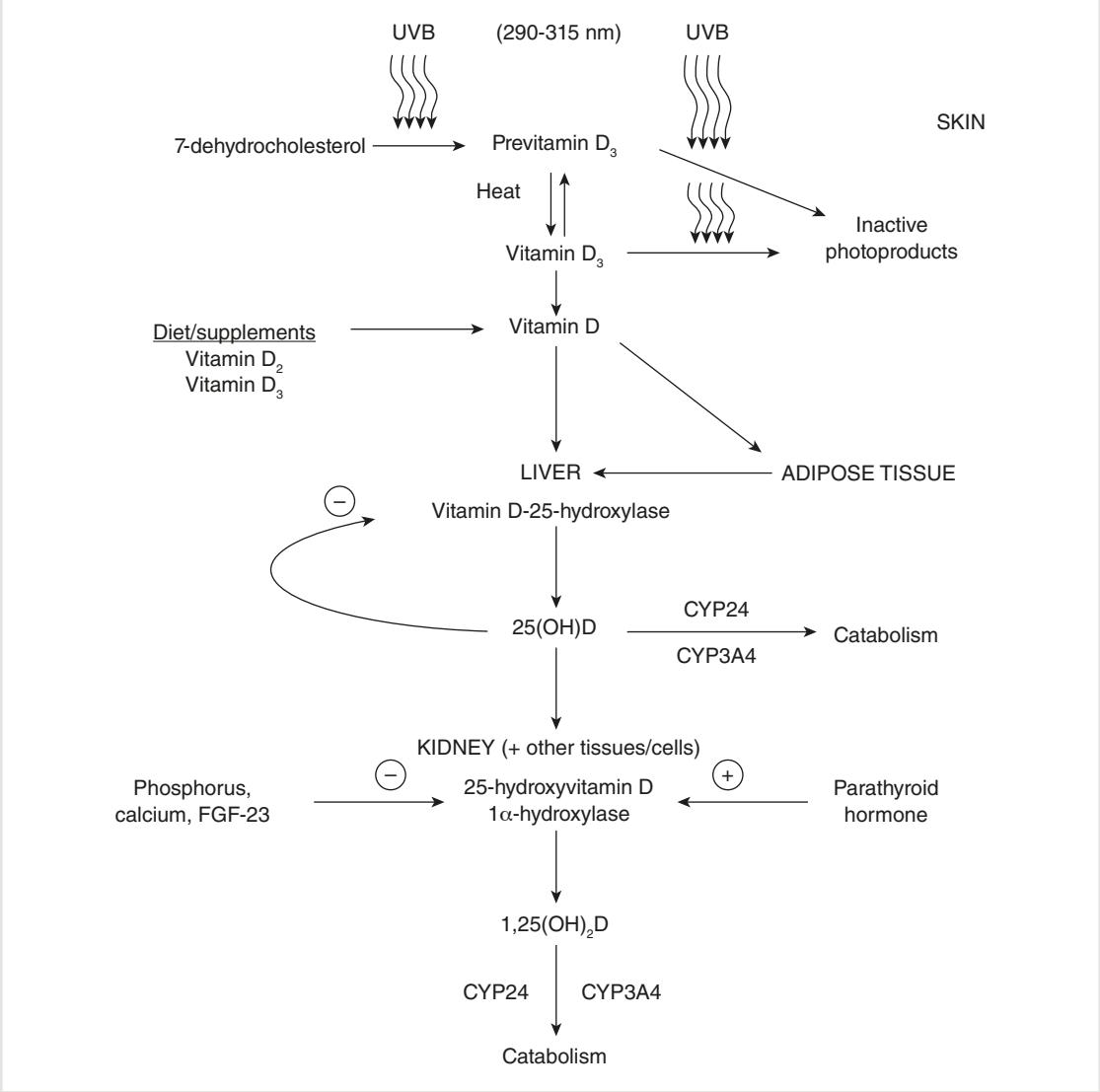

Figure 1. *Synthesis and metabolism of vitamin D.* CYP: cytochrome P450; FGF-23: fibroblast growth factor 23; $1,25(OH)_2D$: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D; UVB: ultraviolet B radiation *(reproduced with kind permission from Dr. M.A. Weinstock and Acta Derm Venereol[1]).*

calcium and phosphorus absorption[9], acting on osteoclasts and osteoblasts[10], and negative feedback control of parathyroid hormone levels[11]. Vitamin D is essential for bone mineralization, and the most well-characterized clinical effects of vitamin D deficiency are rickets (in children) and osteomalacia (in children and adults)[12].

Recently, vitamin D deficiency has been implicated in a wide range of physiologic and disease states in the general population. Systematic reviews and/or meta-analyses have reported on the potential role of vitamin D insufficiency/deficiency in, e.g. cardiovascular disease[13]; peripheral artery disease[14]; hypertension[15]; chronic kidney disease[16]; chronic pain[17]; neuropsychiatric disorders[18]; autoimmune diseases[19]; hyperglycemia[20]; certain cancers[21-24]; adverse pregnancy outcomes[25]; dermopathies[26]; and asthma[27]. However, the current evidence for vitamin D's role in such conditions is limited.

Serum levels of 25OHD are used to define vitamin D status, although cutoff values for classifying insufficiency/deficiency are inconsistent. A key reason for this inconsistency is that the optimal 25OHD levels

associated with functional (e.g. intestinal calcium absorption, parathyroid hormone levels) and clinical outcomes (e.g. bone fractures) vary with endpoint[6,28,29]. Nevertheless, general definitions for vitamin D status based on 25OHD serum levels have been established and broadly adopted: deficient < 20 ng/ml (50 nmol/l); insufficient 21-29 ng/ml (52-72 nmol/l); sufficient > 30 ng/ml (> 75 nmol/l)[6,28]. Information regarding threshold values of serum vitamin D levels associated with clinically significant changes is lacking. One study reported that in 398 children (≤ 15 years) with rickets, the median (range) 25OHD serum level was 11 (2-20) ng/ml (28 [5-50] nmol/l)[30]. The Institute of Medicine (IOM) acknowledges that serum 25OHD levels of < 12 ng/ml (< 30 nmol/l) are associated with an increased risk of rickets[29]. Low serum 25OHD levels and osteomalacia are apparently linked as a study in 675 adults (20-100 years) conservatively estimated that osteomalacia was not seen at serum 25OHD levels > 30 ng/ml (> 75 nmol/l)[31]; an IOM reanalysis of these data suggested a threshold of < 20 ng/ml (< 50 nmol/l) serum 25OHD for development of osteomalacia[29].

The prevalence of vitamin D deficiency in general healthy populations varies depending upon its definition, assay used[32], population characteristics, and other factors (e.g. season, latitude, use of supplements, etc), all of which impact on vitamin D status. Overall, prevalence of vitamin D deficiency is widely variable and can be very high in some studies[33,34]. A recent systematic review reported a high prevalence of vitamin D deficiency worldwide, and identified specific groups vulnerable to developing vitamin D deficiency (young children, pregnant women, the elderly, the institutionalized, and nonwestern immigrants)[35]. The worldwide prevalence of vitamin D insufficiency/deficiency has been estimated at one billion people[6]. General factors leading to vitamin D deficiency include reduced exposure to sunlight for a variety of reasons, aging, obesity, poor dietary intake or lack of supplement use, drugs that increase vitamin D catabolism, as well as liver and kidney dysfunction[6,28].

Strategy

This systematic review focuses on vitamin D deficiency in HIV-1-infected adults by providing an overview of the currently available evidence on the prevalence, consequences, contributory factors, effect of currently approved antiretrovirals (ARVs), and the management of vitamin D deficiency in HIV-1 infection. For simplicity, vitamin D refers to 25OHD levels throughout, unless otherwise stated.

A systematic PubMed search on HIV and vitamin D was conducted, as well as a limited search on abstracts for three major HIV meetings. These searches (for details see Supplementary data) identified a total of 121 articles that were of interest to the selected topics (Fig. 2). Of these 121 articles, the majority (84%) of the identified articles were published in 2010-2013 (2010: 16 [12 papers, four abstracts]; 2011: 25 [18 papers, seven abstracts]; 2012: 41 [33 papers, eight abstracts]; 2013: 20 [19 papers, one abstract]) suggesting a growing interest in HIV and vitamin D. As far as could be ascertained, the 121 articles reported 102 different studies. The four study types were: cross-sectional (n = 64, which included cross-sectional analyses of cohort studies); case series (n = 3); cohort/prospective cohort/retrospective cohort (n = 24); and randomized controlled trials (various descriptions, n = 12). Based on information outlined in the IOM review of dietary reference intakes for calcium and vitamin D[29], the quality of evidence for these four study types is low-moderate, moderate, high-moderate, and high, respectively.

Prevalence of vitamin D deficiency in HIV infection

The prevalence of vitamin D deficiency in HIV-positive adults was reported in 81 of the 121 articles. The vast majority of these papers reported on cross-sectional (47 articles) or cohort (27 articles) studies covering a wide range of populations, geographic locations, and primary objectives. Moreover, the definition of vitamin D deficiency used was not consistent across the studies. However, an evaluation of these data using vitamin D levels included in the range of 10-20 ng/ml (25-50 nmol/l, i.e. deficiency[6]) was possible.

The prevalence of vitamin D deficiency reported by geographic region in HIV-positive adults was: USA 19-100%[36-53]; Europe 14-81%[54-79]; Thailand 27-37%[80,81]; Tanzania 9.2%[82]; Iran 88%[83,84]; South Africa 45-86%[85-87]; India 73%[88]; Nepal 83%[89]; multiple locations 13-25%[90,91]. In HIV-positive women, the prevalence of vitamin D deficiency ranged from 6-100%[53,86,92-103]. In HIV-positive men, it ranged from 20-75%[51,76,104-109]. Collectively, these data indicate that vitamin D deficiency is frequent, though widely variable, in HIV-positive adults.

A question of general interest is whether the prevalence of vitamin D deficiency is higher in HIV-positive adults versus those not infected, which would justify special attention to vitamin D status in HIV infection. Of the 81 articles reporting on prevalence of vitamin D deficiency in HIV-positive adults, 22 also included comparator

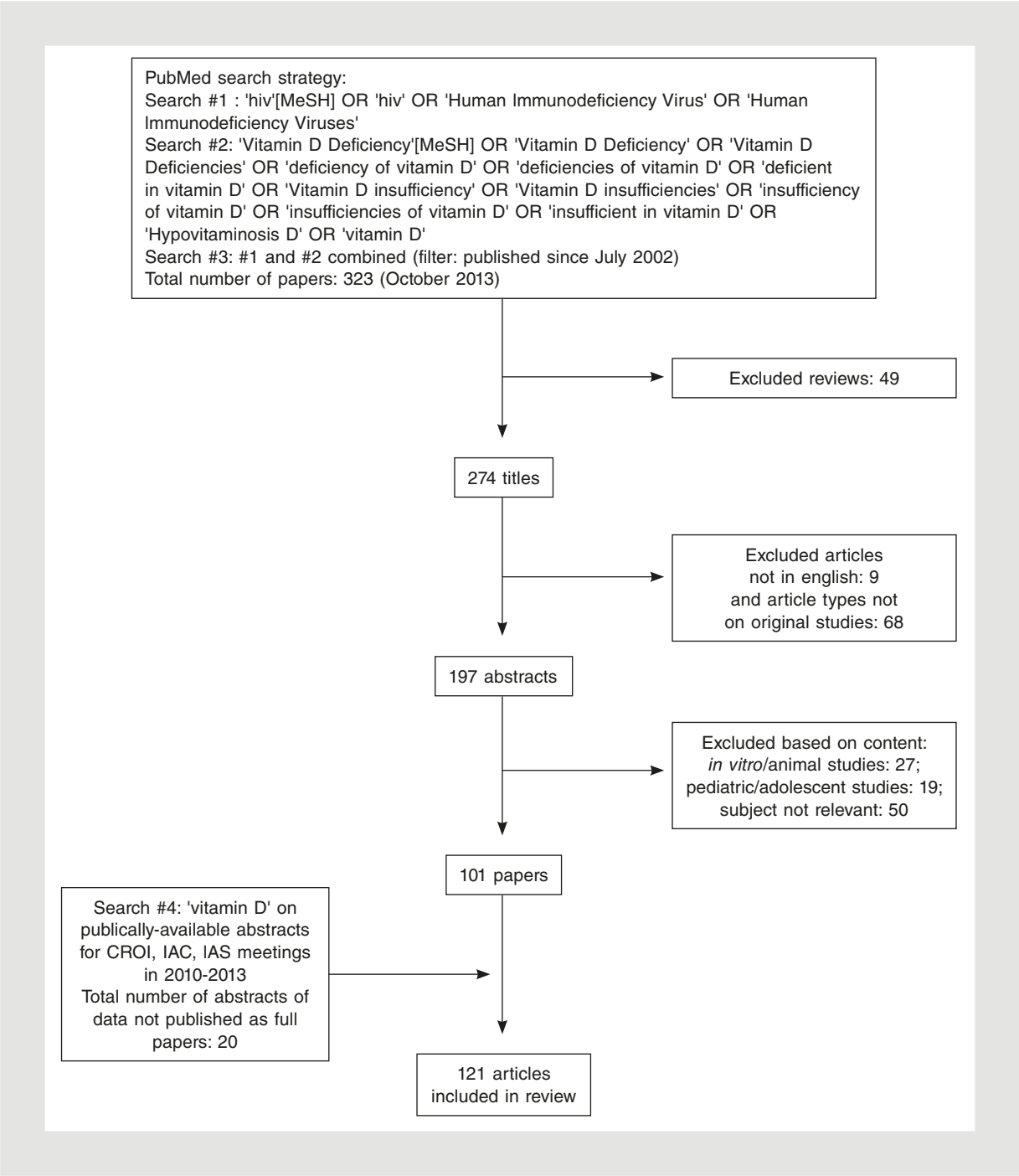

Figure 2. *Search strategy and article selection.*

information from HIV-negative adults (summarized in Supplementary data Table S1)[45,46,71,85,86,88,92,94,96-98,108-118]. As would be expected, ARVs were used in the majority of these 22 studies; in 15 studies, 42-100% of HIV-positive adults were on ARVs, whereas four studies were in ARV-naive patients, and in one study only 2% of patients received ARVs (Supplementary data Table S1). Although certain ARVs may result in vitamin D deficiency (see Effect of antiretrovirals on vitamin D levels in HIV-positive patients), ARV use is only one of many factors potentially involved in vitamin D deficiency that are likely to differ between the HIV-positive and HIV-negative adult populations compared in these studies.

Comparison of the reported prevalence of vitamin D deficiency, or the actual vitamin D serum levels in the evaluated papers, shows that vitamin D status in HIV-positive versus -negative adults was better in four, worse in eight, similar in nine, while not specified in one article (Supplementary data Table S1). Given the wide range of patient populations, geographic locations, different contributing factors (including ARV use), and that most of these studies were cross-sectional (15 of 22), there is no conclusive evidence that vitamin D deficiency in HIV-positive adults is more prevalent than in non-HIV-infected adults.

Potential consequences of vitamin D insufficiency/deficiency in HIV infection

Overall, our literature search indicated vitamin D insufficiency/deficiency as a contributory factor possibly implicated in 11 conditions (i.e. diseases and physiologic states) in HIV-positive adults (noted in 81 of 121 papers). However, it must be emphasized that the strength of evidence is weak for several reasons: study types were mainly cross-sectional (n = 45 papers) or cohort (n = 26 papers) studies; a small number of publications for any topic; small patient numbers in most studies. As previously mentioned, vitamin D has also been implicated in a wide range of conditions in the general population, including some of the topics noted here in HIV-positive adults[13-15,19,20,25].

Bone health

Of the 81 papers that reported vitamin D status in various disease states in HIV-positive adults, 39 included information on bone health. This is a complex topic confounded by differences in a wide variety of factors such as patient characteristics, study design, endpoints evaluated, etc. Therefore, unsurprisingly, the overall findings on the role of vitamin D in bone health of HIV-positive adults are inconclusive.

The most familiar clinical manifestation of primary vitamin D deficiency is osteomalacia as a direct link between vitamin D levels and this condition has been reported[29,31]. However, none of the 39 reports in HIV-positive adults evaluated osteomalacia. Bone health topics in these 39 papers included: parathyroid hormone[42,56,57,60,63,65,73-76,78,109,118-123]; bone markers[42,56,57,66,70,72,75,83,100,104,111,117,118,122-124]; and bone mineral density as an overall endpoint[76,86,104,109,115,118,122,125], or classified as osteopenia[49,66,72,105,106,108,110,111,117,126,127], or osteoporosis[49,66,91,105,106,111,117,126,128,129], or osteopenia/osteoporosis combined[56,100]. Furthermore, ARVs were used by the majority of patients in most studies, with three studies evaluating only ARV-naive, HIV-positive adults[86,110,117], and additional studies including ARV-naive groups[e.g.106,108,109,111]. A recent review has summarized the effects of ARV therapy on bone in HIV-positive patients[130].

Hyperparathyroidism is linked to reduced bone mineral density, and 18 out of 39 papers reported on this endpoint in HIV-positive adults. These papers supported a link between vitamin D deficiency and elevated parathyroid hormone levels in a wide range of patient populations treated with ARVs[42,56,57,60,63,65,73-76,78,109,118-121,123]. Nine of these papers focused on the effects of tenofovir disoproxil fumarate (TDF)[60,63,65,73,74,119,120,121,123]. The use of TDF may result in proximal renal tubulopathy, leading to renal calcium and phosphate depletion, thereby increasing serum parathyroid hormone levels (secondary hyperparathyroidism)[131]. Five of these studies reported an association between TDF and elevated parathyroid hormone levels in HIV-positive adults[60,63,65,119,120], with several reports indicating that vitamin D deficiency was a key factor in this effect[60,65,120]. A small retrospective case series comparing patients treated with TDF-containing HAART (n = 17) with those receiving non-TDF regimens (n = 13) reported proportionally more atraumatic foot fractures in the TDF group (57 vs. 43%, respectively)[129]. One cross-sectional study (n = 24)[121] reported that treating calcium and vitamin D deficiency in HIV-positive patients receiving TDF had favorable effects on bone density.

Changes in bone markers in HIV-positive adults have been measured in studies evaluating bone health (16 of 39 papers), although the link between vitamin D deficiency and bone markers is not clear. Eight small studies noted changes in bone markers and a high prevalence of vitamin D deficiency, although no formal analyses of the potential association between vitamin D levels and bone markers were reported in these studies (cross-sectional study in 115 HIV-positive men[104]; cross-sectional study in 42 HIV-positive men[124]; cohort study with 23 African Americans and 21 non-African Americans[56]; cross-sectional study in 68 HIV-positive adults, 81% were men[66]; interventional study in 121 HIV-positive adults, 74% were men[83]; cross-sectional study in 40 HIV-positive adults, 88% were men[118]; prospective cohort study in 35 HIV-positive adults, 63% were men[122]; cohort study in 56 HIV-positive adults, 77% were men[123]). When potential associations were analyzed, evidence for correlations between bone markers and vitamin D in HIV-positive adults was

inconsistent, with three out of eight studies showing a link[42,75,117], and four out of eight studies indicating no association[57,70,72,100]. Further, one study reported a negative correlation between $1,25(OH)_2D$ levels and bone markers[111]. In the two largest studies evaluating bone markers, one retrospective, cross-sectional cohort study demonstrated that in 463 HIV-positive adults in New York, severe vitamin D deficiency was associated with elevated alkaline phosphatase[42], whereas a cross-sectional survey of 1,077 HIV-positive adults in London reported that severe vitamin D deficiency was not associated with increased bone turnover[70].

Twenty three papers in our search reported on bone mineral density (including osteopenia and osteoporosis) in HIV-positive adults. A well-known factor linked to low bone mineral density is gender, with postmenopausal women, in particular, being susceptible to developing osteopenia and osteoporosis. This may partly explain why most studies (16 of 23) identified in our search evaluated either all male, or predominately (over two thirds) male HIV-positive populations.

Of the six studies in HIV-positive women only, two were in postmenopausal women[126,128]. In the first study, compared with historic HIV-negative controls, the prevalence of osteoporosis was significantly higher in 31 postmenopausal HIV-positive women (spine: 42 vs. 23%, $p = 0.03$; hip 1 vs. 10%, $p = 0.003$); however, vitamin D deficiency and ARV use were not associated with osteoporosis in these women[128]. In the second study in 35 postmenopausal HIV-positive women, 59% were osteopenic and 18% were osteoporotic; although the overall mean vitamin D level was low (25.8 ng/ml), no formal analysis linking vitamin D (or ARV use) to low bone mineral density was conducted[126].

Of the four remaining studies, one study in 50 ARV-naive, HIV-positive young women (mean age 37 years), serum $1,25(OH)_2D$ levels were significantly lower than in 50 age-matched healthy women, and 62 and 14% of the HIV-positive women had osteopenia and osteoporosis, respectively, of the lumbar spine, although there was no association between $1,25(OH)_2D$ levels and bone mineral density[117]. A study in 149 ARV-naive, HIV-positive young women (mean age 32 years) showed that there were no differences in bone mineral density or vitamin D status compared with 98 HIV-negative women[86]. In contrast, vitamin D deficiency was found to be associated with low bone mineral density in two other studies[100,115]. Secondly, in 75 HIV-positive women using ARVs (mean age 34.5 years), osteopenia in the lumbar spine, femoral neck, and total hip was significantly more prevalent in vitamin D-deficient patients (vitamin D levels < 10 ng/ml) than in those with vitamin D levels > 10 ng/ml (90 vs. 49%, $p < 0.01$; 69 vs. 42%, $p < 0.03$; 59 vs. 22%, $p < 0.001$, respectively)[100]. Finally, in a longitudinal subanalysis of 100 HIV-positive women (mean age 40 years) from the Women's Interagency HIV Study, bone mineral density at the lumbar spine and femoral neck at the first visit was not significantly different from that in HIV-negative women ($n = 68$)[115]. The annual decrease in bone mineral density was similar between HIV-positive and negative women, and in the HIV-positive women, vitamin D deficiency, but not ARV use, was associated with bone loss[115].

In three studies, the prevalence of vitamin D deficiency in HIV-positive men was high (33%, n = 476 [61 with DEXA evaluations][105]; 86%, n = 30[108]; 79%, n = 44[56]) and low bone mineral density was observed (osteopenia: 49%[105]; 53-62%[108]; osteopenia/osteoporosis: 26-59%[56]; osteoporosis: 21%[105]). Another study in 115 HIV-positive men, 60% of whom were vitamin D deficient, reported no differences in total bone mineral density between ARV-treated and ARV-naive patients (1.06 vs. 1.11 g/cm; $p = 0.08$)[104]. Declining vitamin D levels and low bone mineral density with time were reported in two studies[118,122]. However, none of these six studies analyzed the potential association between vitamin D and low bone mineral density. The involvement of vitamin D deficiency in low bone mineral density in HIV-positive individuals was analyzed in the 10 remaining studies, seven of which demonstrated that vitamin D deficiency was not associated with this bone health endpoint[49,66,72,106,109,127,129]. One study showed that low $1,25(OH)_2D$ levels were associated with low bone mineral density ($n = 92$, 65% men)[111], and one study noted a negative correlation between vitamin D levels and bone mineral density ($n = 43$ ARV-naive patients; 65% men)[110]. A prospective cohort study in 497 HIV-positive adults (75% men) reported a significant association between severe vitamin D deficiency and low bone mineral density[76]. Thus, the majority of evidence in HIV-positive men (seven studies) suggests that vitamin D deficiency is not a confounder for low bone mineral density. In the largest of these seven studies (n = 312; 88% men; 102 with bone mineral assessments), median vitamin D levels were 71, 71, and 58 nmol/l in patients with normal, osteopenic, and osteoporotic results, respectively[72].

In 15 of the above 16 studies in predominantly HIV-positive men, in which bone mineral density endpoints were measured, ARVs were used. In five of these studies, a statistical evaluation of the potential association of ARV use with low bone mineral density was not

conducted[56,72,76,105,127]. The ARV use was reported not to be associated with low bone mineral density in six studies[49,66,104,106,108,109], whereas an association between ARV use and low bone mineral density was reported in four studies[111,118,122,129].

In summary, bone health was a key endpoint for several studies in HIV-positive adults. Vitamin D deficiency was found to be linked to elevated parathyroid hormone levels, and TDF-induced secondary hyperparathyroidism may be exacerbated by low levels of vitamin D. Data on bone markers and vitamin D levels were inconclusive. Studies evaluating bone mineral density (including osteopenia and osteoporosis), in general, did not indicate an association between vitamin D deficiency and low bone mineral density, although no study assessed osteomalacia, a more relevant endpoint linked with vitamin D deficiency. Collectively, these results suggest that further study is required to advance our understanding of the role of vitamin D in bone health in HIV infection.

Other potential consequences

A potential role of vitamin D in HIV-positive adults in nine other health topics was also identified (in 44 out of 65 papers; Supplementary data Table S2). However, the evidence is limited based on the type of studies (Supplementary data Table S2). Vitamin D deficiency in HIV-positive adults was associated with various markers of cardiovascular disease[37,43,52,116,132-135] including significant coronary stenosis[43], increased carotid intima-media thickness[37,116] (although one study found no association between vitamin D deficiency and this endpoint[88]), coronary artery calcification[52], and low flow-mediated brachial artery dilation[133,134]. In HIV-positive patients with evidence of cardiovascular disease, vitamin D supplementation, whilst raising blood levels, did not improve flow-mediated brachial artery dilation over 12 weeks (n = 45)[133].

In five of six studies, increased inflammatory markers were reported in HIV-positive adults with low vitamin D levels[61,74,75,89,110]. Two studies noted that low vitamin D levels were associated with type 2 diabetes[136,137], and in another study low vitamin D levels were linked to higher insulin levels[138] in HIV-positive adults. One of these studies reported that vitamin D supplementation significantly reduced the hazard ratio (HR) for developing diabetes mellitus (HR: 0.17; 95% CI: 0.04-0.72)[137]. Low vitamin D status was associated with insulin resistance in three studies[97,139,140], and vitamin D supplementation led to lower blood glucose levels in one study[141]. In contrast, one small study (n = 20) reported that insulin sensitivity was negatively associated with serum vitamin D levels in response to supplementation[142]. In HIV-positive pregnant women, severe anemia was possibly linked to vitamin D deficiency[143,144]. Additionally, a subanalysis of the US Women's Interagency HIV study concluded a potential association between vitamin D deficiency and low ovarian function[145].

Four topics – immune function, infection, disease progression, and perinatal outcomes – were identified as having particular relevance to HIV infection. A review of the published evidence suggested that vitamin D deficiency blunted immune restoration and exacerbated HIV complications. Indeed, immune function was potentially linked with vitamin D deficiency, with six of nine papers reporting a positive association between vitamin D levels and $CD4^+$ cell counts[61,88,93,116,117,146]. One of these studies also demonstrated that increasing serum vitamin D levels by supplementation resulted in increased numbers of activated $CD4^+$ cells in HIV-positive men[146]. In contrast, three papers noted that vitamin D status did not affect $CD4^+$ cell recovery[50,67,82]. Vitamin D deficiency has also been potentially linked with opportunistic infections such as respiratory[85,147,148] (although two other studies did not find a link[87,149]), vaginal[46,147], and oral[95,148] infections in HIV-positive adults. Several poor perinatal outcomes have also been reported to be possibly linked with maternal vitamin D deficiency in HIV-positive pregnant women in one study[101,150]. In contrast, another study found no adverse pregnancy outcomes in vitamin D-deficient women[103]. Further, vitamin D deficiency has been potentially linked to other unfavorable outcomes including wasting[147,148], HIV disease progression[68,90,144], AIDS events[68,69], and death[68,69,82,90].

The potential link of immune function, infection, disease progression, and perinatal infection with vitamin D status was inconclusive and the published data were limited. Overall, due to limitations of the study designs and/or numbers of HIV-positive adults evaluated, more research is required to ascertain the impact of vitamin D deficiency on outcomes in HIV-positive patients.

Factors associated with vitamin D insufficiency/deficiency in HIV-positive adults

In the search results, many studies reported factors potentially leading to vitamin D insufficiency/deficiency in HIV-positive adults (Supplementary data Table S3). Again, the studies varied widely in terms of study population, location, number of subjects, primary objectives,

endpoints evaluated, definition of vitamin D insufficiency/deficiency, statistical analyses methods (including covariates accounted for or not), use of supplements, and ARV use. Thus, a detailed evaluation of differences and apparent contradictions in factors potentially involved in vitamin D insufficiency/deficiency across these studies is beyond the scope of this review. Furthermore, the evidence for any specific factor associated with vitamin D insufficiency/deficiency in HIV-positive adults is weak.

Despite the limitations described above, it is possible to make some general observations (Supplementary data Table S3). Previous factors associated with vitamin D insufficiency/deficiency in the general population (for which the evidence is strong) also appear to be relevant in HIV-positive adults, including certain patient characteristics, season, and nutritional intake. The majority of the "miscellaneous" factors detailed in Supplementary data Table S3 have also been implicated in vitamin D insufficiency/deficiency in the general population[6].

Limited evidence shows that certain HIV-specific factors may be associated with vitamin D insufficiency/deficiency in HIV-positive adults, such as $CD4^+$ cell count (five papers; Supplementary data Table S3), and viral load (three papers; Supplementary data Table S3). However, other studies contradict this evidence (Supplementary data Table S3), which may reflect differences in study populations. Indeed, prospective studies would be required to better understand the role of HIV-specific factors in vitamin D insufficiency/deficiency.

Effect of antiretrovirals on vitamin D levels in HIV-positive patients

Antiretrovirals are a diverse group of agents. Forty-one papers reported on the effects of different ARVs on vitamin D insufficiency/deficiency in HIV-positive adults. In 26 papers, ARV use was associated with vitamin D insufficiency/deficiency, whereas no association was noted in 20 papers (Supplementary data Table S3).

As ARVs are given in combination, it is unsurprising that studies have not evaluated effects of individual drugs on vitamin D levels in HIV-positive patients. However, general conclusions can be drawn from various statistical analyses of the contribution of ARV class and specific drugs in mainly cross-sectional (n = 32) or cohort (n = 10) studies, as well as two randomized controlled trials in a wide variety of HIV-positive patient groups.

Nineteen studies included general analyses of the effect of ARVs overall (i.e. not by ARV class or specific ARV) and showed no clear trend of ARV impact on vitamin D status. Of these 19 studies, 17 were cross-sectional, thereby providing limited information, and only three (including one cross-sectional study) were longitudinal studies. One of these longitudinal studies (n = 422)[59] reported no association between combination ARV therapy overall and vitamin D deficiency, as did nine other studies (n = 16[98], n = 89[96], n = 115[104], n = 200[38], n = 237[112], n = 263[75], n = 271[125], n = 312[72], n = 673[80]). Moreover, one small cross-sectional study (n = 74) reported significantly higher vitamin D serum levels in patients treated with HAART compared with treatment-naive patients[127]. However, the other two longitudinal studies (n = 89[55], n = 40[118]) and six other studies did report that combination ARV therapy resulted in vitamin D deficiency (n = 204[93], n = 35[109], n = 214[99], n = 1,077[70], n = 2,994[54], n = not stated[48]).

Collectively, these data are not consistent regarding the effect of ARVs in general (not separated by class/specific agent) on vitamin D levels in HIV-positive adults, probably due to the low power of cross-sectional studies, the wide range of ARV combinations used, and the use of specific classes/agents with differing effects on vitamin D status (see Nonnucleoside reverse transcriptase inhibitors). However, these conflicting findings could also reflect the differences in study populations, geographic location, and other factors potentially associated with vitamin D deficiency.

Nonnucleoside reverse transcriptase inhibitors

Findings from *in vitro* studies demonstrated that efavirenz reduced the expression of CYP2R1[151], involved in the production of 25OHD, and induced CYP24 expression[152], which is involved in the catabolism of 25OHD and $1,25(OH)_2D$ to their inactive metabolites (Fig. 1)[1]. Thus, there is a clinical interest regarding the role of efavirenz in vitamin D deficiency in HIV-positive adults receiving nonnucleoside reverse transcriptase inhibitor (NNRTI)-based ARV therapy.

Eleven studies reported on the class effect of NNRTIs on vitamin D status (Supplementary data Table S4). The association between NNRTIs and vitamin D deficiency in HIV-positive adults was reported in seven of these studies, none of which were randomized controlled trials; five were cross-sectional studies (n = 62[107], n = 90[74], n = 139[37], n = 172[111], n = 254[67]) and two were longitudinal (n = 211[62], n = 500[73]). Three cross-sectional

studies (n = 16 pregnant women[98], n = 89[96], n = 1,768[94]) and one cohort study (n = 70)[122] noted that NNRTI treatment was not predictive of vitamin D levels. Although most of this evidence is from cross-sectional studies, the overall findings are consistent across the different patient populations and locations.

Most studies evaluating NNRTIs identified in our search focused on the effect of efavirenz (17/27 papers; Supplementary data Table S4) on vitamin D levels. Only five of the 17 studies reported that efavirenz had no effect on vitamin D status: one longitudinal study (n = 422[59]) and four cross-sectional studies (n = 23[153], n = 89[96], n = 158[51], n = 312[72]). Strikingly, 12 studies, which covered a wide range of patient populations in many countries, demonstrated that efavirenz use resulted in vitamin D deficiency. Four longitudinal studies reported that vitamin D levels were significantly reduced with efavirenz use (n = 89[55], n = 221[58], n = 580[91]) or efavirenz use was significantly associated with vitamin D deficiency (n = 87[36]). Interestingly, in the longitudinal MONET trial, HIV-1-infected patients (n = 71) who switched from efavirenz (or zidovudine) to either darunavir/ritonavir monotherapy or darunavir/ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs) other than zidovudine had a significant improvement in vitamin D levels[58]. Eight large cross-sectional studies also reported a significant association between efavirenz and vitamin D deficiency (n = 178[81], n = 352[71], n = 463[42], n = 672[45], n = 673[80], n = 1,077[70], n = 2,044[79], n = 2,994[54]). With the majority of studies suggestive of an association, there is some evidence that efavirenz is linked to vitamin D deficiency in HIV-positive adults.

There has been debate about conflicting evidence on the effect of nevirapine on vitamin D levels in HIV-positive adults, mainly via commentaries that were excluded from our systematic search. Our findings noted that in one small longitudinal study (n = 89)[55], compared with pre-ARV use, nevirapine and efavirenz significantly decreased vitamin D levels after 12 months, whereas protease inhibitor (PI) use had no effect. In contrast, four larger cross-sectional studies concluded that nevirapine was not significantly associated with vitamin D deficiency (n = 221[58], n = 312[72], n = 1,077[70], n = 2,994[54]) (Supplementary data Table S4). Therefore, the true effect of nevirapine on vitamin D in HIV-positive adults cannot be concluded with sufficient evidence.

Only two publications detailed the potential effects of etravirine on vitamin D levels in HIV-positive adults. Both studies were cross-sectional and noted that etravirine appeared not to affect vitamin D levels (n = 2,994[54], n = 312[72]).

A 48-week subanalysis (n = 582) of a double-blind, randomized, controlled, phase III trial in ARV-naive, HIV-1-infected patients compared rilpivirine with efavirenz, both in combination with TDF/emtricitabine, with regards to their potential effect on serum vitamin D levels, and on the proportion of patients developing severe vitamin D deficiency after 48 weeks of ARV exposure[91]. At 48 weeks, vitamin D levels were not affected by rilpivirine but, consistent with above, were significantly decreased with efavirenz. Proportions of patients with severe vitamin D deficiency (< 25 nmol/l 25OHD) at baseline were similar between groups, but significantly more patients had severe vitamin D deficiency (< 10 ng/ml [25 nmol/l]) at week 48 with efavirenz compared with rilpivirine[91].

Overall, evidence from our search consistently suggests that HIV-positive adults on ARVs taking an efavirenz-based regimen are far more likely to be vitamin D deficient. Although data suggest that nevirapine, etravirine, and rilpivirine are not linked to vitamin D deficiency, evidence is more limited.

HIV protease inhibitors

Most evidence available from our search indicates that the PIs are not linked to vitamin D deficiency (Supplementary data Table S5), although it should be noted that no specific information was available for tipranavir, and only three cross-sectional studies (n = 23[153], n = 672[45], n = 2,994[54]) and one cohort study (n = 70)[122] mentioned the other PIs approved for use in HIV-positive adults. Nevertheless, use of PI-based regimens was reported to have no impact on vitamin D levels in seven cross-sectional studies (n = 16[98], n = 23[153], n = 89[96], n = 139[37], n = 312[72], n = 1,077[70], n = 2,994[54]), and three longitudinal studies (n = 70[122], n = 89[55], n = 422[59]). Specifically, darunavir, ritonavir, saquinavir, amprenavir, atazanavir, and lopinavir were noted to have no effect on vitamin D levels in a large French cross-sectional study (n = 2,994)[54]. Moreover, HIV-positive adults receiving PIs in their combination therapy were at lower odds of being vitamin D deficient in four cross-sectional studies (n = 450[77], n = 463[42], n = 1,768[94], n = 2,000[69]), as were those taking ritonavir in another study (n = 672)[45].

In a small cross-sectional study in men, those receiving a PI-based regimen (n = 37) had significantly higher levels of serum vitamin D (median: 64.9 nmol/ml) versus those on an NNRTI-based therapy (n = 19; 42.4 nmol/ml; p = 0.0017 by a median two-sample test [nonparametric method]), and the prevalence of vitamin D

deficiency was 30% (PI) versus 74% (NNRTI)[107]. And as mentioned above, vitamin D levels were increased in patients switching from efavirenz or zidovudine to darunavir/ritonavir in the MONET trial[58]. These latter two studies indicate a possible advantage of using PIs compared with certain NNRTI/nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTI) in minimizing the negative impact of ARV therapy on vitamin D levels in HIV-positive adults. A large cross-sectional study (n = 283) also reported that use of PI-based ARV therapy implied that patients were significantly more likely to be in the highest vitamin D quartile[135].

Of the 20 studies describing PI effects on vitamin D deficiency in Supplementary data Table S5, only two reported that PI-containing regimens resulted in low vitamin D levels[74,111]. In a cross-sectional study in Italy (n = 90), the prevalence of low vitamin D levels was significantly greater with PIs compared with NNRTIs[74]. In another small cross-sectional study, PI-containing regimens resulted in significantly lower vitamin D levels ($1,25[OH]_2D$; n = 90) compared with treatment-naive patients (n = 20)[111]. The reason for this "discrepancy" may reflect the evaluation of $1,25(OH)_2D$ as a surrogate marker for vitamin D status, and the inhibition of cytochrome P450 (CYP) by PIs; one paper proposed a mechanism for the effect of PIs on 25OHD serum levels[45]. The transformation of vitamin D to 25OHD and $1,25(OH)_2D$ involves the CYP enzymes 25- and 1α-hydroxylase, respectively (Fig. 1)[1]. Activities of these enzymes have been shown to be inhibited *in vitro* by the PIs ritonavir, indinavir, and nelfinavir[154]. A possible explanation of why PI administration does not result in vitamin D deficiency (as assessed by 25OHD levels) is the preferential inhibition of 25OHD conversion to $1,25(OH)_2D$, which then either increases or maintains 25OHD levels (although $1,25[OH]_2D$ levels would decrease as shown in the paper by Madeddu, et al[111]).

In conclusion, most studies evaluating 25OH vitamin D captured in our search suggest that treatment with PIs is not associated with vitamin D deficiency in HIV-positive adults.

Nucleoside/nucleotide reverse transcriptase inhibitors

Fourteen studies have described the effects of N[t]RTIs on vitamin D levels (Supplementary data Table S6). Two small cross-sectional studies (n = 139[37], n = 16 pregnant women[98]) and one cohort study (n = 70)[122] noted that NRTI use was not associated with vitamin D insufficiency. In a cross-sectional study (n = 172) in Italy, the significant decrease in $1,25(OH)_2D$ levels in patients on NNRTI/triple NRTIs (data not reported separately in paper)[111], compared with ARV-naive patients, may reflect the contribution of the NNRTI or PI backbone, since certain members of this ARV class are associated with vitamin D deficiency (as described above). The association of zidovudine use and low vitamin D levels was reported in two longitudinal studies (n = 221[58], n = 483[64]). In contrast, one cross-sectional study noted that zidovudine had no effect on vitamin D levels (n = 158)[51] and two large cross-sectional studies reported that zidovudine, as well as lamivudine, abacavir, emtricitabine, and didanosine had no effect on vitamin D status in HIV-positive adults (n = 2,994[54], n = 312[72]). Use of TDF was consistently found to have no effect on vitamin D levels in one longitudinal study (n = 422)[59] and five large cross-sectional studies (n = 185[39], n = 312[72], n = 672[45], n = 1,077[70], n = 2,994[54]). In addition, one cohort study (n = 56)[123] noted that 1,25(OH)2D levels were higher with TDF compared with other NRTIs in patients with sufficient vitamin D status, whereas for vitamin D-insufficient patients, levels of this metabolite were similar between the groups.

In summary, the data on the effect of N[t]RTIs on vitamin D status in HIV-positive adults are discordant. Data with zidovudine are conflicting as two studies reported an association between this NRTI and low vitamin D levels, whereas two other studies show no effect. These latter studies also reported no effect of the other N[t]RTIs, lamivudine, abacavir, emtricitabine, and didanosine, on vitamin D status. There was consistent evidence, however, on the lack of an effect of TDF on vitamin D levels.

Other classes

Very limited data are available on other classes of ARVs on vitamin D status in HIV-positive adults. Two large cross-sectional studies (n = 2,994[54], n = 312[72]) reported that raltegravir, an HIV integrase strand transfer inhibitor, was not associated with vitamin D deficiency. Further, in our search, only one cross-sectional study evaluated vitamin D status in patients receiving the HIV fusion inhibitor enfuvirtide, or the CCR5 receptor antagonist maraviroc; neither of these agents was associated with low vitamin D levels (n = 312)[72].

Management of vitamin D deficiency in HIV infection

Very few studies specifically assessed the effect of vitamin D supplementation in HIV-positive adults on

ARV treatment (17 of 121 papers: 10 randomized, controlled trials; five cross-sectional studies; two cohort studies). Moreover, most were aimed at assessing the effect of vitamin D repletion on the signs of its deficiency (mainly bone effects), with only one study providing a specific assessment of vitamin D doses to improve serum levels[59]. Using dose simulations from an evaluation of vitamin D population pharmacokinetics in HIV-positive adults on ARVs who were also taking vitamin D supplements (n = 135), one group of authors estimated that 100,000 IU vitamin D_3/month would attain serum vitamin D levels between 30-80 ng/ml[59].

Bone markers in HIV-positive adults receiving ARVs were favorably altered following vitamin D supplementation in several small studies, although the reported doses/units of vitamin D varied across studies, making the evaluation of suitable vitamin D doses difficult. A single dose of 300,000 IU vitamin D increased osteocalcin and collagen telopeptidase in 98 HIV-positive adults on efavirenz[83]. Vitamin D supplements (1.25 mg/month[155] [50 IU/month]; 50,000 IU/month[156]; 400 IU/day[157] [≈ 12,000 IU/month]; 500 IU/day[158] [≈ 15,000 IU/month]) taken with calcium and bisphosphonates also resulted in favorable bone marker changes in several small (n < 50) randomized controlled trials[155-158].

Unsurprisingly, treating HIV-positive adults with standard therapies for osteoporosis (i.e. vitamin D, calcium, and bisphosphonates) improved bone mineral density, albeit in small numbers of patients in randomized controlled trials (n = 17-82)[155-161]. One paper reported that women with reduced bone mineral density were approximately four-times more likely to receive bisphosphonates than men[49]. Two papers reported that raising serum vitamin D levels with supplements subsequently reduced parathyroid hormone levels as expected[40,64].

Although a limited number of studies indicate that vitamin D insufficiency/deficiency in HIV-positive adults on ARVs can be managed with the use of vitamin D supplements, much more research is required in large numbers of patients to provide adequate guidance on vitamin D dosage in HIV infection. Some guidance regarding vitamin D supplementation in HIV-positive patients is provided in the 2011 Endocrine Society Clinical Practice guideline for the evaluation, treatment, and prevention of vitamin D deficiency[28]. Although this guideline is aimed at the general population, the authors recommend that HIV-positive adults on ARVs should be given 2-3 times the recommended vitamin D intake for their age group[28] based on the risk of enhanced catabolism of 25OHD and $1,25(OH)_2D$ by some ARV. The EACS guidelines suggest that vitamin D-deficient HIV-positive adults receive an initial loading regimen (e.g. loading dose up to 10,000 IU/day for 8-10 weeks) followed by a maintenance dose of 800-2,000 IU vitamin D/day[162], while acknowledging that the value of vitamin D supplementation in HIV is not yet fully understood. However, these recommendations are not shared by other guideline panels, e.g. DHHS[163], IAS[164] and BHIVA[165].

Future perspectives

It is clear from the above synopsis that further targeted research is required to increase our understanding of the true role of vitamin D in HIV-1 infection and the consequences of its deficiency in this disease state. In non-HIV-1-infected individuals, there are additional data from mainly observational studies adding to the debate regarding the potential role for vitamin D in many diseases. For example, recent findings in HIV-negative patients, showing a marked decrease in serum 25OHD during systemic inflammatory response, may suggest that serum 25OHD is acting as a negative acute phase reactant, and dropping at times of acute or chronic illness, with implications for acute and chronic diseases[166]. However, it is less clear whether vitamin D deficiency may be a consequence, rather than a cause, of many chronic diseases[163].

The uncertainty of vitamin D's role in the health of persons living with HIV, as well as in the general population, and the benefits of managing its deficiency mean that, despite extensive research, HIV clinicians are faced with more questions than answers. Table 1 outlines several questions that we consider to be important in improving at least some of our understanding of the role of vitamin D in HIV infection and suggests what clinicians could do now (based on our synopsis).

Conclusions

In this systematic review, we found that there is much interest, particularly recently, in vitamin D deficiency in HIV-positive adults. Overall, the data regarding the prevalence, significance, causes, and management of suboptimal vitamin D levels in persons living with HIV are hugely inconsistent, making firm recommendations challenging to devise. Differences in study designs, methodologies, and populations are likely responsible for much of the variance in the results produced to date. However, the accumulated evidence supports several observations, which are summarized in Table 2.

Table 1. Summary of suggested recommendations for further investigations and management of low vitamin D levels in HIV-positive adults

Which questions could be considered in HIV-positive adults

- **Potential impact on bone health:** is there any association between vitamin D deficiency and musculoskeletal pain, and fractures?
- **Parathyroid hormone:** is measuring parathyroid hormone concentrations more useful than vitamin D levels to determine appropriate use of vitamin D supplementation? What are the predictive values of measuring vitamin D or parathyroid hormone concentration for bone problems? When (i.e. which season) is measuring vitamin D levels most relevant, and for which patients?
- **Vitamin D deficiency:** for vitamin D deficiency *per se,* is lipoatrophy a risk factor? What is the impact of renal and/or hepatic insufficiency on vitamin D deficiency? Are there mechanisms of action of ARVs and comedication to be further elucidated in vitamin D deficiency?
- **Secondary hyperparathyroidism:** is there an aggravating effect of efavirenz-induced vitamin D deficiency on the potential bone effect of TDF? Should a *priori* vitamin D supplementation be given to a patient receiving cART containing efavirenz and TDF?

What could the clinician do now for HIV-positive patients?

- Take a detailed history and baseline characteristics, encompassing factors associated with vitamin D deficiency, to help identify those patients who may become vitamin D insufficient/deficient.
- Analyze serum vitamin D in a newly diagnosed HIV-positive patient to establish their baseline status.
- Treat HIV-positive patients with combination ARV therapy as per recommended treatment guidelines, while being vigilant of agents associated with vitamin D deficiency versus the patient's characteristics associated with this deficiency.
- Routinely and longitudinally monitor serum vitamin D levels regularly in the individual HIV-positive patient.
- Actively manage vitamin D insufficiency/deficiency
  - In the absence of consensus, follow current available guidelines for vitamin D supplementation in HIV-positive adults (i.e. 2-3 x doses for noninfected people) and monitor blood levels of vitamin D, adjusting supplementation until vitamin D sufficiency is established – do this with the aim of improving/preventing bone health issues in the first instance.

ARV: antiretroviral; cART: combination antiretroviral therapy; TDF: tenofovir disoproxil fumarate.

Table 2. Summary of the main findings

Prevalence of vitamin D deficiency in HIV infection

- The prevalence of vitamin D deficiency in HIV-positive adults is widely variable, but does not appear to be significantly different from that of the general population.

Potential consequences of vitamin D insufficiency/deficiency in HIV infection

- **Bone health:** lower levels of vitamin D are not necessarily always associated with reduced bone mineral density in HIV-positive patients.
- **Other potential consequences:** in HIV-positive adults, vitamin D deficiency may blunt immune restoration and exacerbate HIV complications such as opportunistic infections, poor perinatal outcomes, wasting, HIV disease progression, AIDS events, and death.

Factors associated with vitamin D insufficiency/deficiency in HIV-positive adults

- Factors associated with vitamin D insufficiency/deficiency in the general population are also relevant to HIV-infected patients.
- Certain HIV-specific factors (e.g. $CD4^+$ cell count, viral load) may be associated with low vitamin D levels in HIV-positive adults, although the evidence is limited.

Effect of ARVs on vitamin D levels in HIV-positive patients

- Evidence from longitudinal studies of initiation or change in ARVs used for treating HIV suggests that such treatment can alter vitamin D levels. More specifically:
- **NNRTIs:** of the NNRTIs, efavirenz has the most consistent and profound effects on vitamin D levels; limited evidence indicates that nevirapine, etravirine, and rilpivirine have less or no impact.
- **HIV PIs:** current evidence suggests that PIs are not notably linked to vitamin D deficiency.
- **N[t]RTIs:** with the possible exception of zidovudine, the N[t]RTIs are not apparently associated with vitamin D deficiency.
- **Other classes:** very limited evidence to date is suggestive that other ARVs (raltegravir, enfuvirtide, maraviroc) are not linked to vitamin D deficiency.

Management of vitamin D deficiency in HIV infection

- Management of vitamin D deficiency in HIV infection has not been systematically evaluated; treatment (per the established guidelines) with vitamin D and calcium can increase bone density in HIV-positive adults.

ARV: antiretroviral; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor; N[t]RTI: nucleoside/nucleotide reverse transcriptase inhibitor.

This review also highlights significant gaps in understanding, including discordance in the causes and clinical outcomes of vitamin D deficiency in HIV infection, and a lack of consensus regarding the management of vitamin D deficiency in HIV-positive adults. Although some guidelines suggest that higher levels of vitamin D supplementation should be given to HIV-positive adults receiving ARV treatment compared with the general population, these recommendations are not well supported by research conducted to date and are not universal. Prospective, randomized, controlled trials in large numbers of volunteers are required to fully understand the benefits of vitamin D supplementation in HIV-positive adults.

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Supplementary Data

Supplementary data are available at AIDS Reviews journal online (http://www.aidsreviews.com).

These data are provided by the authors and published online to benefit the reader. The contents of all supplementary data are the sole responsibility of the authors.

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