

# Vitamin D deficiency in HIV-infected patients: a systematic review

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**Abstract:** Advances in the diagnosis and management of human immunodeficiency virus (HIV) have resulted in a dramatic decrease in mortality in HIV-infected individuals (HIV+). The subsequent increase in life expectancy of HIV+ has led to the need to consider the long-term complications of the disease and its treatment. Abnormalities in vitamin D status and metabolism are increasingly recognized as a major concern in HIV infection. In the last 5 years a number of cross-sectional and prospective studies have suggested a high prevalence of vitamin D deficiency in HIV+. Although few case-control studies have been published, it has been suggested that the prevalence of hypovitaminosis D in HIV+ is higher than in the general population, and at least in part, is related to the course of the disease and/or the antiretroviral drugs used to treat the disease. An adequate vitamin D status is important not only for bone tissue, but also for the global health status of HIV+ individuals, since a growing body of evidence has demonstrated the detrimental effects of vitamin D deficiency on multiple health outcomes. Therefore, definition of the size of the problem and identification of effective protocols for the prevention and management of vitamin D deficiency in HIV+ patients represent important steps in improving health status and reducing long-term chronic complications in individuals with HIV. Due to its immunomodulatory effects, vitamin D may also have implications in the progression of HIV infection. This systematic review was designed to determine the prevalence of vitamin D deficiency in HIV+ patients; to identify risk factors (related to the HIV infection or not) potentially associated with this condition; to describe the potential consequences of hypovitaminosis D on the course of the infection and the benefits of vitamin D repletion; and to make some suggestions about the future, considering the limitations of previous studies.

**Keywords:** human immunodeficiency virus, HIV, vitamin D, parathyroid hormone, bone, antiretroviral

## Introduction

Thirty years after it was first recognized, the natural history of the human immunodeficiency virus (HIV) infection has changed significantly in the Western World.<sup>1-5</sup> Progress in basic and clinical research in HIV and acquired immunodeficiency syndrome (AIDS) has led to the implementation of extraordinarily successful interventions such as Highly Active Antiretroviral Therapy (HAART), that have produced a reduction in mortality and morbidity due to HIV/AIDS and related complications.<sup>5</sup> Nowadays, life expectancies for people with HIV are improving, and becoming quite similar to those of uninfected individuals, and increasing numbers of HIV-infected patients (HIV+) are reaching old age.<sup>1</sup>

With “aging” of the HIV/AIDS epidemic, people with HIV are becoming increasingly susceptible to chronic diseases, recognized as long-term sequelae related

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to the infection or its management.<sup>1-5</sup> Long-term infected/treated HIV+ are at higher than expected risk for a number of complications typically associated with aging, including cardiovascular diseases, obesity, cancer, neurocognitive dysfunction, disorders of bone and mineral metabolism, and other end-organ diseases.<sup>1</sup>

In this context, several cross-sectional and prospective studies have shown a high prevalence of vitamin D abnormalities in HIV+ subjects.<sup>6-10</sup> The high frequency of vitamin D deficiency in this population has raised great interest, not only because of the potential implications for bone health, but also because of the detrimental effects of vitamin D deficiency on multiple health outcomes.

The active form of vitamin D, 1,25-dihydroxyvitamin D (1,25OH<sub>2</sub>D), acts not only in the intestines, kidneys, bones, and parathyroid glands to maintain calcium and phosphorus homeostasis, but also in other tissues, where it affects regulation of hormone secretion, immune function, and cellular proliferation and differentiation.<sup>11-14</sup> Thus, besides the fundamental role of vitamin D in calcium and phosphorus balance and skeletal health, the extra-skeletal effects of vitamin D and the consequences of vitamin D deficiency in humans have been recently highlighted.<sup>15-18</sup>

Evidence from large epidemiological studies and clinical trials has suggested an association between 25-hydroxyvitamin D (25OHD), the precursor of 1,25OH<sub>2</sub>D and the most suitable indicator of vitamin D status, and systolic blood pressure, risk of cardiovascular disease-related death, depression, cognitive impairment, lower extremity function and falls, periodontal diseases, colon and breast cancer, multiple sclerosis, infections, and death.<sup>15-18</sup> Although in most cases the bulk of evidence is based on epidemiological and observational studies, more useful for generating hypotheses rather than for proving causality, current data suggest that vitamin D may have beneficial effects on mortality and some common chronic illness.<sup>15-18</sup>

The growing awareness of vitamin D as a possible key factor in many chronic diseases beyond bone health, and early reports about hypovitaminosis D in HIV+ patients have created great interest in the potential implications of vitamin D deficiency for HIV infection and AIDS.<sup>19-21</sup> The present review was designed to describe current knowledge about vitamin D deficiency in HIV-infected subjects, to identify risk factors (related to the HIV infection or not) potentially associated with vitamin D status, to describe the potential consequences of hypovitaminosis D on the course of HIV infection and the benefits of vitamin D repletion, and to make some considerations about the future, considering the limitations of available studies.

## Methods

### Search strategy

We searched PubMed to July 6, 2011, using the following keywords: “vitamin D or vitamin D deficiency or 25-hydroxyvitamin D or cholecalciferol” and “HIV or antiretroviral”. We limited the search to studies carried out in humans, with no language restriction, and included articles ahead of publication. Moreover, we also searched for the keywords in headers and abstracts, and performed a manual search of reference lists in selected articles, and all published reviews, for additional relevant studies.

### Eligibility criteria

Titles and abstracts of the citations selected from the initial search were subsequently screened for eligibility. We specifically focused on studies reporting the prevalence of vitamin D deficiency in populations, cohorts or samples of HIV infected patients, with no age, race/ethnicity, gender, clinical, or other restrictions. Vitamin D status was defined according to the following cut-offs, suggested by the current literature: vitamin D deficiency, 25OHD <20 ng/mL; vitamin D deficiency or insufficiency, 25OHD <30 ng/mL.<sup>16,22</sup> To convert values from Système International units to conventional units, we divided by the conversion factor 2.496.<sup>22</sup>

We included retrospective chart reviews, cross-sectional and prospective studies with or without control groups, and randomized-controlled trials (RCTs) reporting baseline vitamin D status. Case series describing more than ten patients were also considered.

Studies were excluded if they included ten or less subjects, if they did not report vitamin D status according to the pre-specified cut-off values, or if they assessed vitamin D metabolites other than 25OHD (eg, 1,25-dihydroxyvitamin D). The last criterion was chosen because it is well established that the concentration of 25OHD is the best indicator of vitamin D status, and because most of the data on the relationship between vitamin D insufficiency/deficiency and adverse health outcomes are based on 25OHD concentration measurements.<sup>11-19</sup>

A single author (AG) reviewed all identified studies for eligibility, definitive inclusion/exclusion, and for data collection.

### Data extraction and handling

For each study identified and included in this review, we aimed to collect the following information: publication year; country where the study was performed; study type; number of participants (HIV-infected and controls, if present);

proportion of Caucasian subjects; proportion of women; age (expressed in years as mean or median); proportion of patients receiving antiretroviral therapy (ART) and duration of treatment (expressed in months as range or interquartile range); prevalence of vitamin D deficiency/insufficiency according to the pre-specified cut-offs; parathyroid hormone status (including the prevalence of secondary hyperparathyroidism); proportion of subjects using calcium and/or vitamin D supplements at the time of laboratory assessment; risk factors and/or variables (related to the HIV infection or not) potentially associated to vitamin D deficiency; and adverse clinical/health outcomes potentially related to hypovitaminosis D (including progression of HIV infection).

Where datasets overlapped or were duplicated, the most recent information was included, and duplicate reports from the same population were considered for retrieving additional data. When necessary, percentages were calculated from raw data. In recording data about factors associated with vitamin D status or adverse health outcomes, only variables showing significant differences after adjustment for potential confounders were considered (eg, multivariate analyses).

The primary authors were not contacted to retrieve additional information.

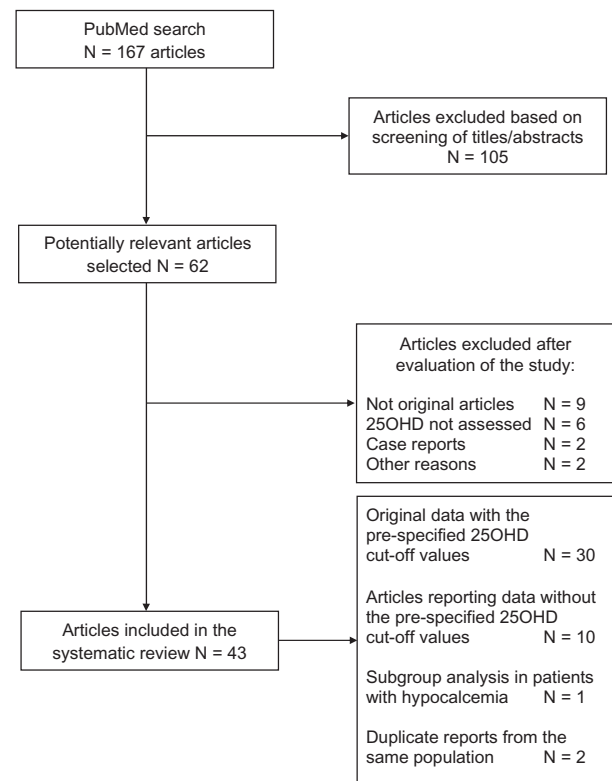
## Results

### Literature search

A flow diagram of our literature search is given in Figure 1. The search yielded 167 entries. After title and abstract assessment, 62 studies appeared to be potentially eligible for inclusion in the review. Of these, 19 articles were excluded for the following reasons: not original articles ( $n = 9$  editorials, commentaries, or reviews); 25OHD not assessed ( $n = 6$ ); case report/series with less than ten subjects ( $n = 2$ ); data on vitamin D status not described ( $n = 1$ ); and RCT undertaken in a selected sample of HIV+ patients with vitamin D deficiency ( $n = 1$ ). Of the remaining (43 papers), 30 articles reported original data with the pre-specified 25OHD cut-off values and were included in the review (Table 1).<sup>6,8–10,23–47,60</sup> One study describing the prevalence of vitamin D deficiency in a subgroup of 21 patients with hypocalcemia and ten articles reporting 25OHD status with different cut-off levels were considered only to retrieve information about predictors of vitamin D status,<sup>7,48–57</sup> and two duplicate publications were reviewed for additional data not presented in the original study.<sup>42,58,59</sup>

### Studies' characteristics

The characteristics of the papers considered are described in Table 1. The vast majority of studies were performed in Europe



**Figure 1** The literature search process.

**Notes:** Two articles that were duplicate publications from the same population were considered for retrieving additional data.<sup>42,58,59</sup> In eleven studies, it was not possible to retrieve data about vitamin D status according to the pre-specified 25OHD cut-off values (see Methods and Results).<sup>7,48–57</sup>

**Abbreviation:** 25OHD, serum 25-hydroxyvitamin D.

and the United States (28 articles), and most of them were cross-sectional analyses. Nine studies compared vitamin D status between HIV+ and “healthy” subjects,<sup>9,23,25,27,30,31,34,42,60</sup> but only three of them were matched case-control analyses.<sup>27,30,34</sup>

Overall, the studies were heterogeneous in terms of demographic and clinical characteristics of populations included. Even the data collected and the methods used to report the information were quite variable (eg, age and duration of ART therapy were described as mean  $\pm$  standard deviation, median with interquartile range, or range). Most of the articles described adult or young adult patients; two were undertaken in children or adolescents;<sup>25,44</sup> while one RCT was performed in pregnant women.<sup>41</sup> The proportion of subjects of Caucasian ethnicity varied from 0% to 100%, as well as the percentage of women. A great variability was also observed in the proportion of HIV+ receiving ART and duration of treatment (from 3 months to 168 months), indicating that these populations were quite different even allowing for the course/stage of HIV infection.

Considering the 41 studies reviewed, and excluding the duplicate publications (Figure 1), only 19 articles reported

Table 1 Studies estimating the prevalence of vitamin D deficiency in HIV-infected subjects, according to pre-specified 25-hydroxyvitamin D cut-off values.

Study, (country)	Study type	Healthy control (HIV-) group	Nr. HIV+ (% caucasian)	Mean age (years)	% Women	% ART (range, months)	25-hydroxyvitamin D (ng/mL)		Factors associated with vitamin D deficiency
							<20 (%)	<30 (%)	
Ross et al <sup>23</sup> (US)	Ongoing prospective	34 not matched	149 (52%)	49 <sup>a</sup>	15%	100% (6–124) <sup>b</sup>	46%	79%	CD4, sTNFR-I
Hammond et al <sup>24</sup> (Australia)	Cross-sectional	No	107 (84%)	42–55 <sup>a</sup>	0%	68% (0–144)	34%	74%	Ethnicity, season, ART
Kim et al <sup>6</sup> (US)	Cross-sectional	No	274 (26%)	47 <sup>a</sup>	23%	85% (6–25) <sup>b</sup>	NA	90%	Ethnicity, HIV viral load
Rutstein et al <sup>25</sup> (US)	Cross-sectional	372 not matched	81 (12%)	14	48%	85% (NA)	NA	89%	Ethnicity, season, BMI, immunosuppression
Viard et al <sup>26</sup> (EU, Israel, Argentina)	Prospective	No	1985 (87%)	38 <sup>a</sup>	24%	91% (NA)	NA	89%	Age, ethnicity, country, season, ART, non-homosexual exposure
Conrado et al <sup>8</sup> (Brazil)	Cross-sectional	No	214 (0%)	40	100%	100% (NA)	13%	41%	Total cholesterol, duration ART
Milazzo et al <sup>27</sup> (Italy)	Cross-sectional	76 age- and sex-matched	237 (97%)	44 <sup>a</sup>	32%	100% (72–168) <sup>b</sup>	NA	68%	Season, severity liver fibrosis in HCV
Terrier et al <sup>28</sup> (France)	Cross-sectional	No	189 (NA)	40	23%	17% (NA)	63%	86%	Season, severity liver fibrosis in HCV, HCV viral load, duration HIV
Pasquet et al <sup>10</sup> (France)	Cross-sectional	No	395 (86%)	45 <sup>a</sup>	32%	89% (NA)	NA	41%	ART
Fox et al <sup>29</sup> (Europe) <sup>*</sup>	RCT	No	221 (91%)	43	20%	100% (NA)	77%	NA	Season, ethnicity, ART
Ormesher et al <sup>30</sup> (US)	Cross-sectional	424 age- and sex-matched (NHANES, same race)	199 (0%)	NA	100%	NA	NA	77%	ART
Dao et al <sup>31</sup> (US) <sup>o</sup>	Ongoing prospective	General US adults population (NHANES)	672 (58%)	41 <sup>a</sup>	24%	79% (NA)	30%	70%	Ethnicity, BMI, hypertension, ART, physical exercise, renal function, sunlight exposure
Szep et al <sup>32</sup> (Italy)	Cross-sectional	No	1811 (NA)	44	38%	NA	64%	84%	NA
Choi et al <sup>33</sup> (US)	Ongoing prospective	No	139 (54%)	45	16%	76% (NA)	NA	52%	Ethnicity, BMI, multivitamins supplement, ART
Adeyemi et al <sup>9</sup> (US)	Ongoing prospective	510 not matched at-risk (same gender)	1268 (24%)	44 <sup>a</sup>	100%	72% (NA)	60%	NA	Ethnicity, BMI, renal function, age, place of living, HIV RNA, CD4, ART
Paul et al <sup>34</sup> (India)	Cross-sectional	35 age-, sex- and BMI-matched	70 (0%)	38	0%	50% (12–70)	56%	NA	Sunlight exposure, ART
Conesa-Botella et al <sup>35</sup> (Belgium) <sup>§</sup>	Prospective	No	87 (78%)	37–39 <sup>a</sup>	17%	0%	44%	70%	Ethnicity, season, ART, BMI
Childs et al <sup>36</sup> (US)	Cross-sectional	No	45 (80%)	49 <sup>a</sup>	100%	100% (NA)	NA	82%	Vitamin D supplements
Mueller et al <sup>37</sup> (Swiss) <sup>*</sup>	Prospective	No	211 (88%)	37 <sup>a</sup>	25%	0%	NA	77%	Season, ethnicity, duration HIV, intravenous drug use, ART
Welz et al <sup>38</sup> (UK)	Cross-sectional	No	1077 (39%)	41 <sup>a</sup>	41%	78% (NA)	74%	91%	Ethnicity, season, CD4, ART
Rosenvinge et al <sup>39</sup> (UK)	Cross-sectional	No	227 (NA)	NA	NA	85% (NA)	57%	85%	Ethnicity, blood glucose, renal function
Wasserman et al <sup>40</sup> (US)	Cross-sectional	No	62 (34%)	48 <sup>a</sup>	0%	92% (NA)	42%	76%	ART, tobacco use

Mehta et al <sup>41</sup> (Tanzania) <sup>†</sup>	RCT	No	884 (0%)	25	100%	0%	NA	39%	CD8, CD3, ESR, vitamin A and E, gestational age
Stein et al <sup>42</sup> (US)	Ongoing prospective	95 not-matched (same gender and MP status)	89 (0%)	56	100%	80% (NA)	36%	74%	Ethnicity, calcium and multivitamins supplement, CD4
Bang et al <sup>43</sup> (Denmark)	Cross-sectional	No	115 (91%)	44 <sup>‡</sup>	0%	62% (NA)	60%	NA	NA
Arpadi et al <sup>44</sup> (US)	RCT	No	64 (33%)	10	47%	0%	45%	NA	NA
Rodriguez et al <sup>45</sup> (US)	Cross-sectional	No	57 (60%)	46 <sup>‡</sup>	23%	81% (NA)	37%	74%	Vitamin D intake, physical exercise, ART
Woolley et al <sup>46</sup> (Australia)	Case series	No	12 (0%)	35	50%	58% (3–60)	NA	92%	NA
Curtis et al <sup>47</sup> (US)	Cross-sectional	No	44 (45%)	45	34%	100% (NA)	NA	79%	Ethnicity
Yin et al <sup>60</sup> (US)	Prospective	68 not-matched (same gender and MP status)	100 (18%)	40	100%	59% (NA)	69%	91%	Ethnicity, age

**Notes:** <sup>†</sup>Fox et al assessed prevalence and risk factors for vitamin D deficiency at baseline, and investigated the impact of changes in antiretroviral treatment on variations of vitamin D levels at 96 weeks. Data reported refer to baseline. The prevalence of vitamin D deficiency and insufficiency was age-, race- and sex-adjusted. <sup>‡</sup>Conesa-Botella et al evaluated the prevalence of vitamin D deficiency and insufficiency before and 12 months after the initiation of highly active antiretroviral therapy. Data reported refer to baseline. <sup>§</sup>Mueller et al assessed vitamin D status at baseline and 12 and 18 months after the initiation of ART treatment. Data reported refer to baseline. <sup>¶</sup>Mehta et al investigated the effect of baseline vitamin D status on HIV-related health outcomes and perinatal outcomes in HIV+ pregnant women, using data from a randomized, double-blind, placebo-controlled trial of vitamin A supplementation. Data reported refer to 56 patients included in the final analyses, except for the prevalence of vitamin D deficiency. <sup>||</sup>age and duration of antiretroviral therapy are expressed respectively as mean years and range in months, except when otherwise specified; <sup>∞</sup>age expressed as median; <sup>∞∞</sup>duration of antiretroviral therapy expressed as interquartile range.

**Abbreviations:** HIV+, HIV-infected subjects; HIV-, HIV-uninfected subjects; NA, not available; ART, antiretroviral therapy; sTNFR-I, soluble tumor necrosis factor- $\alpha$  receptor I; AA, African-American; RCT, randomized-controlled trial; MP, menopausal; NHANES, National Health and Nutrition Examination Survey.

information about calcium and/or vitamin D supplement use: in ten cases HIV+ were not using any supplement, while in nine studies the proportion of supplement users varied from 2% to 49%.

In 17 out of 40 studies, parathyroid hormone (PTH) concentration was also measured at baseline or during the follow-up.

## Vitamin D deficiency

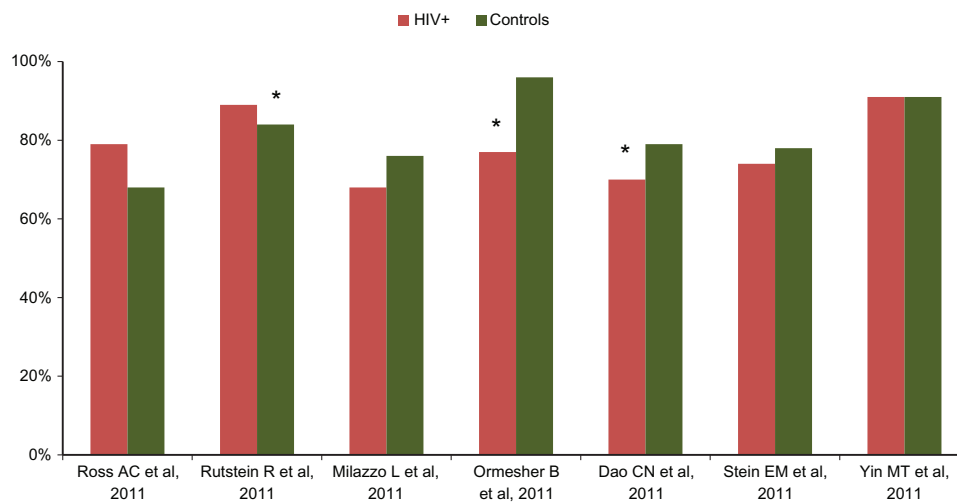
In the studies eligible for inclusion in this review (Figure 1), no consistent definitions of vitamin D deficiency and/or insufficiency were used, and several articles used multiple cut-off points for low vitamin D status according to 25OHD concentrations. In addition, there was considerable variability in the assays used to measure 25OHD (data not shown).

Eighteen studies reported levels of 25OHD <20 ng/mL (deficiency) ranging in incidence between 13% and 77% (Table 1). Using the threshold of 30 ng/mL, indicative of vitamin D deficiency or insufficiency, the frequency was between 39% and 92% (25 articles). In 19 trials (three of which are not depicted in the Table 1) the prevalence of 25OHD levels below 10 ng/mL was also estimated, ranging between 5% and 46%.<sup>6,9,23–28,38–40,42–45,49–51,60</sup>

The two articles that reported the lowest frequency of vitamin D deficiency or insufficiency were undertaken in Brazil and Tanzania.<sup>8,41</sup> Considering the countries where the other trials were performed, no clear trend in the prevalence of hypovitaminosis D was found, with studies performed in similar populations within the same country (eg, France, Italy) reporting quite different results.<sup>10,28,32,50</sup> We observed similar inconsistencies while exploring the overall frequencies of hypovitaminosis D taking into account the use of vitamin D supplements.

Few articles were designed to compare the prevalence of vitamin D deficiency between HIV+ and uninfected healthy controls (Table 1, Figures 2 and 3). In three of them, controls were age- and sex-matched to HIV+ (also BMI-matched in one study, same race in another).<sup>27,30,34</sup> Stein et al and Yin et al recruited controls of identical gender (women) and menopausal status (post- and pre-menopausal, respectively) as the HIV cases.<sup>42,60</sup> In the remaining four articles, authors used unmatched controls, as follows: healthy subjects from the community or the clinic (n = 2),<sup>23,25</sup> National Health and Nutrition Examination Survey (NHANES) 2003–2004 and 2005–2006 data for the general US population (n = 1),<sup>31</sup> uninfected at-risk subjects with the same gender (n = 1).<sup>9</sup>

Results from these reports were quite inconsistent (Figures 2 and 3). The three matched case-control analyses

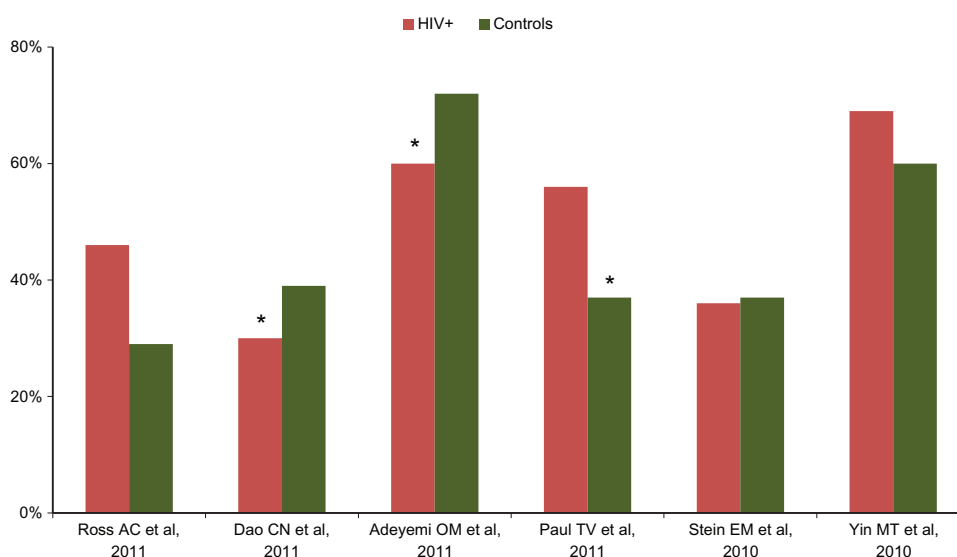


**Figure 2** Prevalence of serum 25-hydroxyvitamin D concentration below 30 ng/mL among HIV-infected patients (HIV+) and healthy controls in selected case-control studies. **Notes:** Control groups were: 34 unmatched, HIV-uninfected subjects from hospital staff or relatives of the cases (Ross et al<sup>23</sup>); 372 unmatched, HIV-uninfected children or young adults from the paediatric clinic or community (Rutstein et al<sup>25</sup>); 76 age- and sex-matched, randomly selected, HIV-uninfected healthy blood donors (Milazzo et al<sup>27</sup>); age- and sex-matched cohort (424 subjects of same ethnicity) from the 2005–2006 NHANES (Ormesher et al<sup>30</sup>); NHANES 2003–2004 and 2005–2006 data from the general US population (Dao et al<sup>31</sup>); 95 unmatched, HIV-uninfected subjects, recruited from the clinic, with the same gender and menopausal status as the cases (Stein et al<sup>42</sup>); 68 unmatched, HIV-uninfected subjects, with the same gender and menopausal status as the cases (Yin et al<sup>60</sup>); \*indicates  $P < 0.05$  in the between-groups comparison.

found completely different and contrasting results regarding the prevalence of vitamin D deficiency in HIV+ and healthy controls, with a nonsignificant difference between cases and controls in one study,<sup>27</sup> a significantly higher prevalence in healthy controls in another,<sup>30</sup> and a significantly higher prevalence in HIV-infected patients in the third.<sup>34</sup> The study with the higher prevalence in the control group was performed in African-American

subjects,<sup>30</sup> who are usually regarded as being at high risk of hypovitaminosis D.<sup>61</sup> As a result, both cases and controls had a very high rate of hypovitaminosis D. Paul et al<sup>34</sup> found a 20% greater prevalence of 25OHD <20 ng/mL in HIV-infected patients, but they enrolled a very small sample (70 cases and 35 controls).

All the other studies included unmatched healthy subjects as controls, and that bias may explain their inconsistent and



**Figure 3** Prevalence of serum 25-hydroxyvitamin D below 20 ng/mL among HIV-infected patients (HIV+) and healthy controls in selected case-control studies. **Notes:** Control groups were: 34 unmatched, HIV-uninfected subjects from hospital staff or relatives of the cases (Ross et al<sup>23</sup>); NHANES 2003–2004 and 2005–2006 data from the general US population (Dao et al<sup>31</sup>); 510 unmatched, HIV-uninfected at-risk subjects, with the same gender as the cases (Adeyemi et al<sup>9</sup>); 35 HIV-uninfected, age-, sex- and BMI-matched healthy subjects (Paul et al<sup>34</sup>); 95 unmatched, HIV-uninfected subjects, recruited from the clinic, with the same gender and menopausal status as the cases (Stein et al<sup>42</sup>); 68 unmatched, HIV-uninfected subjects, with the same gender and menopausal status as the cases (Yin et al<sup>60</sup>); \*indicates  $P < 0.05$  in the between-groups comparison.

contradictory findings: two of them reported a significantly greater prevalence of hypovitaminosis D in HIV-uninfected subjects;<sup>9,31</sup> in three cases no difference was found between the two groups;<sup>23,42,60</sup> while Rutstein et al<sup>25</sup> observed a higher frequency of vitamin D deficiency in HIV-infected patients.

## Variables associated with vitamin D deficiency

Thirty-three out of 41 articles investigated variables potentially associated with vitamin D deficiency or 25OHD concentration.<sup>6–9,23–31,33–47,50–54</sup> Both common risk factors for hypovitaminosis D (eg, ethnicity, season, age, BMI) and variables associated with the course of the HIV infection, such as absolute CD4 T-cell count, viral load, and ART, were tested.

Among the first group of variables, several well-known predictors of low 25OHD have been consistently identified (Table 1): Black ethnicity, higher BMI, winter months or reduced sunlight exposure (including the place of residence), older age, physical activity and vitamin D intake, or multi-vitamin supplement use.<sup>6,9,24–28,30,31,33–39,42,45,47</sup>

Interestingly, when authors conducted analyses to investigate factors related to the course of HIV infection associated with hypovitaminosis D, results were skewed and inconsistent (Table 1). In most cases however, the samples were small, and that probably reduced the ability to find significant associations.

Considering the main findings and studies undertaken in large populations, only some specific ART classes or agents were clearly found to be related to hypovitaminosis D.<sup>9,10,23,24,26,29–31,33–35,37,38,40,42,35</sup> Several authors demonstrated that non-nucleoside reverse transcriptase inhibitor (NNRTI) use was associated with 25OHD deficiency.<sup>10,35,37,40,45,51</sup> For efavirenz, in particular, an association with low 25OHD concentration has often been suggested.<sup>9,24,29,31,38</sup> Similar but less consistent findings were observed for some nucleoside reverse transcriptase inhibitor (NRTIs), such as emtricitabine, tenofovir, and zidovudine.<sup>7,29</sup> Results for protease inhibitors (PIs) suggested a protective effect against hypovitaminosis D.<sup>9,26,31</sup> A small prospective observational (96 weeks) study investigated the effect of ART regimen changes on vitamin D status, and demonstrated a beneficial effect (increase of 25OHD level) in switching from efavirenz (NNRTI) and/or zidovudine (NRTI) to darunavir/ritonavir (PIs).<sup>29</sup>

Although some authors presented evidence in support of a relationship between CD4 T-cell count and 25OHD levels (with lower CD4 T-cell count associated with higher

prevalence of vitamin D deficiency or lower 25OHD concentrations),<sup>9,23,38,42</sup> at least three large, well-designed trials failed to identify such association.<sup>27,31,41</sup>

Considering other HIV-related risk factors, patchy correlations were found between HIV viral load, duration of ART, duration of HIV, plasma neopterin, or soluble tumor necrosis factor-alpha receptor I and vitamin D deficiency.<sup>6,8,9,23,25,28,37,52,54,57</sup>

## Adverse health outcomes related to vitamin D deficiency in HIV-infected patients

Very few studies investigated the detrimental effects of vitamin D deficiency on health outcomes other than bone diseases in HIV+. They were primarily cross-sectional correlation analyses, and it was therefore not possible to establish a cause–effect relationship.<sup>23,24,27,28,32,33</sup> Two reports observed an independent correlation between vitamin D deficiency and higher carotid intima media thickness.<sup>23,33</sup> Other authors suggested an association between low 25OHD concentrations and diabetes type II or high serum insulin levels.<sup>24,32</sup> Finally, in two studies undertaken in HIV–HCV (hepatitis C virus) co-infected patients, hypovitaminosis D was related to the severity of liver fibrosis.<sup>27,28</sup>

In two well-designed, prospective, observational trials undertaken in large samples of HIV+, the potential detrimental effects of vitamin D deficiency on infection progression have been explored.<sup>26,41,58,59</sup> Mehta et al used the data from a large randomized, double-blind, placebo-controlled trial of vitamin A supplementation in HIV+ pregnant women, performed in Tanzania, to evaluate the role of vitamin D on the progression of HIV and on perinatal outcomes. In multivariate models, women with vitamin D <32 ng/mL had a significantly higher risk of progression to WHO HIV disease stage III or greater (incident rate ratio [IRR]: 1.25, 95% confidence interval [CI]: 1.05–1.50), and a 46% increased risk of developing anemia compared to those with adequate 25OHD levels.<sup>58</sup> Moreover, considering quintiles of 25OHD, patients in the highest quintile presented a 42% lower risk of all-cause mortality than those in the lowest. When the perinatal outcomes were investigated, the authors found that vitamin D deficiency/insufficiency was associated with a higher risk of mother-to-child transmission (relative risk [RR]: 1.46, 95% CI: 1.11–1.91) and that children born to women with low 25OHD presented with a higher risk of dying during the follow-up (RR: 1.61, 95% CI: 1.25–2.07).<sup>59</sup>

Viard et al examined the association between vitamin D status and disease progression in about 2000 HIV+ subjects,

enrolled in Europe, Argentina, and Israel.<sup>26</sup> Patients with 25OHD concentrations >12 ng/mL presented a significantly lower risk of clinical progression of the infection, AIDS events, and all-cause mortality compared to those with 25OHD levels <12 ng/mL. Adjusted IRRs for all-cause mortality were 0.68 (95% CI: 0.47–0.99) for subjects with 25OHD between 12 and 20 ng/mL, and 0.56 (95% CI: 0.37–0.83) for those with 25OHD >20 ng/mL. The corresponding figures for AIDS events were 0.58 (95% CI: 0.39–0.87) and 0.61 (95% CI: 0.40–0.93), respectively.

## Secondary hyperparathyroidism and parathyroid hormone status

The prevalence of secondary hyperparathyroidism (sHPTH) has been explored in nine out of 16 articles reporting data about PTH status.<sup>7,8,36,39–45,47,48,50,51</sup> None of these was a case-control study comparing the frequency of this condition between HIV+ and healthy controls. The reported frequency of sHPTH at baseline varied from 0% to 33%. As noted for 25OHD, no clear trend in the prevalence of sHPTH was found, when the characteristics of the populations included were considered.

Three case-control analyses compared absolute concentrations of PTH between HIV+ and healthy controls.<sup>34,42</sup> Paul et al found a significantly higher mean concentration  $\pm$  standard deviation (SD) of PTH in HIV+ receiving HAART ( $65 \pm 26$  pg/mL) compared to HIV+ ART naïve ( $43 \pm 23$  pg/mL) and sex-, age-, and BMI- matched healthy controls ( $42 \pm 26$ ,  $P < 0.001$ ).<sup>34</sup> However, Stein et al and Yin et al did not observe differences in mean PTH values between HIV+ and healthy controls (not matched).<sup>42,60</sup>

In some studies designed for the purpose, PTH concentration or prevalence of sHPTH was found to be consistently associated with 25OHD level and/or ART therapy (PIs and NNRTIs).<sup>7,34,36,39–42,45,51</sup> Three articles, in particular, found a correlation between tenofovir use and higher parathyroid hormone concentrations.<sup>7,36,39</sup> In addition, Masia et al evaluated changes in PTH after the initiation of two different ART regimens.<sup>7</sup> Both regimens produced significant increases in PTH concentration, and in the proportion of patients presenting with sHPTH during the follow-up period. After 36 months of treatment, subjects receiving tenofovir plus emtricitabine (71%) demonstrated a significantly higher prevalence of sHPTH compared to those receiving abacavir plus lamivudine (29%,  $P = 0.03$ ). In contrast with these findings, Lattuada et al did not observe any change in PTH values from baseline, 3 years after starting therapy with zidovudine–lamivudine–nevirapine.<sup>50</sup>

## Discussion

### Vitamin D deficiency

The successful development of ART drugs has significantly lengthened the life expectancy of people infected with HIV. Recent statistics from the Centers for Disease Control and Prevention have shown that people aged 50 years old or older account for 29% of persons living with AIDS, and 35% of all deaths of persons with AIDS.<sup>62</sup>

With the aging of the HIV infection, a number of new concerns related to the course of the disease have received attention in recent years. Several health problems characteristic of older people appear to occur at younger ages and at higher rates in people with HIV. This has been documented with cardiovascular disease, diabetes, and bone and mineral disorders.<sup>1–5,63</sup> Vitamin D deficiency is regarded as one of these health problems.

In reviewing the torrent of data about vitamin D deficiency in HIV, we have found numerous non-controlled studies describing a high prevalence of hypovitaminosis D in HIV+, but very few case-control analyses. Results from these trials were contradictory and failed to demonstrate a significantly greater prevalence of vitamin D deficiency in HIV-infected patients compared to controls (Figures 2 and 3).<sup>9,23,25,27,30,31,34,42,60</sup> The reasons for such disagreement may lie in the study designs, particularly in the sampling of controls. In six out of nine studies controls were not age-matched to cases,<sup>9,23,25,31,42,60</sup> and that is exceptionally important, since older age is an established risk factor for low vitamin D concentrations.<sup>64,65</sup> The three age- and sex-matched studies had other important limitations, which have been already emphasized.<sup>27,30,34</sup> Thus, we believe that it is not yet possible to establish whether or not HIV+ subjects are at higher risk of developing vitamin D deficiency, although some data support this hypothesis. Well-designed case-control analyses and large prospective trials are warranted to clarify this point.

To further elucidate the relationship between vitamin D and HIV, we then evaluated which variables were associated with vitamin D deficiency. As expected, those variables acknowledged as risk factors for hypovitaminosis D in the general population,<sup>61,64,66</sup> have also been identified in HIV-infected patients. Weaker evidence was available for HIV-related risk factors. Both NNRTIs and NRTIs have been suggested to play a role in the genesis and/or maintenance of vitamin D deficiency.<sup>9,10,24,29,31,35,37,38,40,45,51</sup> Such findings are supported by the pharmacology of these compounds, since it is well established that some of them may affect the metabolism of vitamin D (eg, via cytochrome P450 enzymes).<sup>19</sup> Similarly, the potential protective effect against



hypovitaminosis D of PIs is easily explained by the fact that they inhibit a key enzyme involved in vitamin D metabolism, leading to the accumulation of the precursor 25OHD.<sup>19</sup> For all other factors related to HIV infection, such as CD4 T-cell count, viral load, duration, and clinical stage of the disease, results were too weak to allow conclusions to be drawn. The paucity of studies undertaken in large samples and the heterogeneity of variables considered may explain the inconsistent findings.

## Vitamin D deficiency, comorbidity, and progression of HIV infection

Cross-sectional correlation analyses have shown an association between vitamin D deficiency and pre-morbid conditions or chronic diseases: diabetes type II, high carotid intima media thickness, and severity of liver fibrosis in HCV.<sup>23,24,27,28,32,33</sup> These findings are not surprising since similar findings have been reported also in HIV-uninfected individuals,<sup>67–70</sup> further supporting the role of hypovitaminosis D in the pathogenesis of several chronic diseases.<sup>15–18</sup>

The most important and striking findings are those that related low vitamin D concentrations to the progression of HIV infection.<sup>26,41,58,59</sup> Although only two well-designed trials have been published to date, their results support the hypothesis that the course of the HIV disease may be influenced by vitamin D status.<sup>21</sup>

Several lines of evidence have suggested that vitamin D plays a major role in regulating the immune system, perhaps including immune response to viral infections.<sup>21,71,72</sup> Both in vitro and in vivo studies have demonstrated the immunomodulatory effect of 1,25-dihydroxyvitamin D, the active metabolite of vitamin D. 1,25-dihydroxyvitamin D is capable of polarizing the adaptive immune system away from Th-1 and towards Th-2 responses, it affects toll-like receptors, and it upregulates and induces the active antimicrobial cathelicidin peptide LL-37 and, to a lesser extent, human beta defensin 2, which may play a role in the inhibition of viruses.<sup>72</sup> Furthermore, clinical data in humans have highlighted vitamin D's potential role in fighting viral respiratory infections. In this context, Mehta et al<sup>41,58,59</sup> and Viard et al<sup>26</sup> observed a protective effect of vitamin D sufficiency against HIV-related health outcomes, such as progression to more severe stages or AIDS, mortality, and transmission to children. These findings need to be extensively confirmed in future studies; and the potential benefit of vitamin D supplementation on HIV progression should be investigated in RCTs, including several different doses and regimens of cholecalciferol.

## Conclusion

In summary, bearing in mind the limitations emphasized by our review, studies are warranted to further clarify the relationship between vitamin D and HIV infection, in order to better understand the interactions between vitamin D status and the progression of the disease, and, eventually, to identify the best strategies to prevent and/or treat vitamin D deficiency in HIV-infected adults.

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