Barbosa, J Immunodefic Disor 2014, 3:1
http://dx.doi.org/10.4172/2324-853X.1000107

Journal of Immunodeficiency & Disorders

Review Article A SCITECHNOL JOURNAL

Vitamin D and HIV Infection: A Systematic Review

Natália Barbosa[1], Laura Costa[1*], Mara Pinto[1], Patrícia Rosinha[1], Inês Rosinha[1] and Mariana Couto[1]

Introduction

The Human Immunodeficiency Virus (HIV) infects human T cells, causing a disease that progressively leads to a dramatic deterioration of the immune function. The Acquired Immunodeficiency Syndrome (AIDS) is present when CD4+ cell count is below 200 cells/mm3 or the patient has an opportunist infection, such as esophageal candidiasis or *Pneumocystis pneumonia.* Since life expectancy of HIV-infected individuals has increased, mostly as a result of advances in diagnosis and treatment, they are more willing to develop long-term chronic complications, some of which have been associated with vitamin D deficiency. Abnormalities in vitamin D status and metabolism might be an important concern in HIV patients, especially in those receiving Highly Active Antiretroviral Therapy (HAART). Beyond that, there seems to be evidence that antiretroviral therapy may be responsible for worsening of hypovitaminosis D [1-4].

In addition, vitamin D plays a crucial role in bone mineralization and calcium homeostasis, being essential not only to the skeletal but also to the immunologic response. It has been shown that hypovitaminosis D is more frequent among HIV-positive patients [2,3,5-7]. Therefore a potential role of vitamin D in HIV-infected patients has been greatly investigated.

Vitamin D supplementation has proved recently that it should be regarded as a way of slowing disease progression and preventing mortality in HIV-infected individuals. Furthermore, Vitamin D seems to play a promising and interesting role in a broad range of physiologic mechanisms, for instance, those involved in cardiovascular health [1,8].

In this systematic review we propose to summarize the available data on the role of vitamin D deficiency in HIV associated osteoporosis and in the modulation of the immune system in HIV-infected patients. We also aim to point out the most relevant consequences of hypovitaminosis D on the course of the infection as well as to address the potential benefits of vitamin D supplementation.

Methods

Four different databases were used to perform this search: PubMed, ISI Web of Knowledge, Scopus and Scirus. PubMed was chosen for its worldwide recognition in terms of biomedical articles. ISI Web of Knowledge and Scopus were included for their scientific international reference, as well as adequate specificity and article's high quality. Scirus was taken into account because of its wider criteria and broader coverage. We have decided to use four different databases in order to obtain the widest coverage of publications possible with trustable evidence in this topic.

We used "HIV AND vitamin D AND immune system" as our global search query in PubMed, ISI and Scopus. In Scirus we used the option "Advanced Search". By doing that we restricted our search to the articles that included "HIV AND vitamin D AND immune system" in the complete document and "HIV AND vitamin D" in the article title. We searched all databases in the April 15th, 2013. No limits were imposed at this stage in what concerns to language restriction or date of publication.

We included in our systematic review: randomized controlled trials (RCTs), observational studies, reviews (either classical or systematic) and laboratory studies. We excluded all animal research studies. In what concerns to articles' content, we included articles that assayed the immunological role of vitamin D in HIV-infected patients and excluded the ones that assessed exclusively the role of vitamin D in osteoporosis or refer to vitamin D only as a performer in tuberculosis and HIV associated tuberculosis.

In what concerns to data selection, we can divide our selection

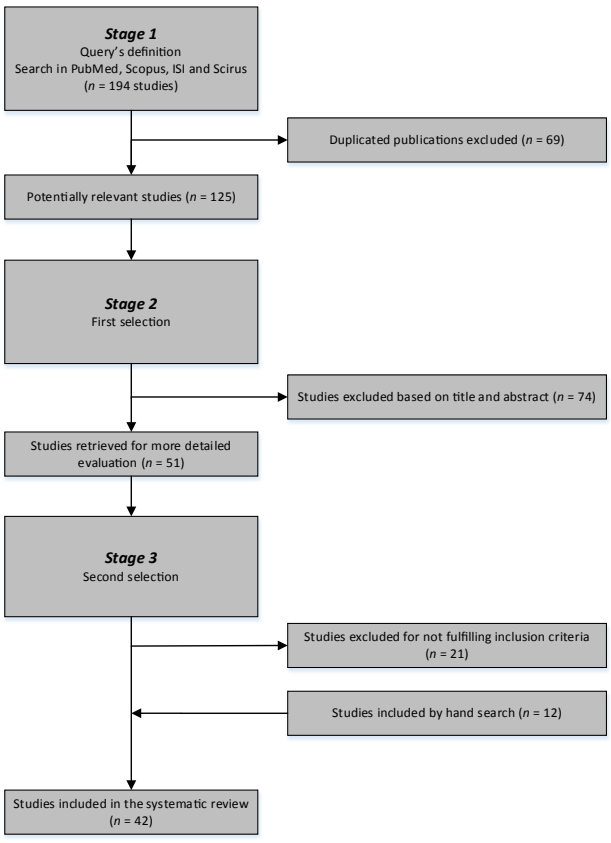

Figure 1: Flow chart of included studies.

***Corresponding author:** Laura Costa, Laboratory of Immunology, Basic and Clinical Immunology Unit, Faculty of Medicine, University of Porto, Al. Prof. Hernâni Monteiro, Porto, 4200-319, Portugal, E-mail: laura.a.costa@hotmail.com

Received: September 02, 2013 **Accepted:** February 10, 2014 **Published:** March 13, 2014

in three different and sequential stages, presented in the flowchart of Figure 1.

The first one was the database research, in which we inserted our queries and obtained a total of 194 articles (before repetitions' elimination).

In the second stage, we performed a general selection, based on the title and abstract of all articles randomly distributed by reviewers, who examined them in teams of two elements. In addition to this, 69 repeated articles were identified and eliminated in this phase. By the end of this stage, we had a total of 51 articles.

In the third stage we made a more rigorous, specific and demanding selection based on full text reading. The previously selected articles (51) were distributed by two teams of two members. Each group performed an independent analysis and only the articles included by both reviewers (with certified agreement) became part of the final article panel. 21 more articles were excluded in this stage. Hand searches for relevant papers were performed and 12 more articles were included and searched for significant information (marked with * in the Table 1- 3).

Ultimately, all authors agreed on 42 final articles for full-text assessment. These were examined to confirm they met the established criteria and then relevant data was extracted, analyzed and combined (Table 1- 3).

Vitamin D: Physiological Roles

Vitamin D deficiency is a worldwide health problem and also an under-diagnosed condition that might compromise not only musculoskeletal health, but also affect various acute and chronic diseases [9].

Vitamin D is an essential part of the human diet, taking part in bone mineralization and calcium homeostasis [5,6,10-13]. Furthermore, vitamin D plays a vital role in insulin secretion, lipid metabolism, autoimmune disorders, cell proliferation and cardiovascular diseases [5].

It is obtained by the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D3) during sunlight's skin exposure, by dietary intake and even through supplements. It can be ingested in two different forms: vitamin D2 (or ergosterol, its biological precursor) and vitamin D3, both of them hydroxylated after digestion in the liver and other tissues into 25-hydroxyvitamin D (25(OH) D3) and subsequently 1,25-dihydroxyvitamin D (1,25(OH)2D3) by CYP27B1 (1-α-hydroxylase) [6,10]. Furthermore, some peripheral blood mononuclear cells express receptors for vitamin D (VDRs) which enables them to produce 1,25(OH)2D3 by the expression of 1-α-hydroxylase. The ligand for VDR is 1,25(OH)2D3, although this active form of vitamin D is not the best option for diagnosis and monitoring of vitamin D status. 25(OH)D3 is a better indicator of overall vitamin D status because of its expanded biological half-life and higher serum levels. Therefore the standard biomarker is 25(OH) D3 and vitamin D deficiency is present if circulating 25(OH)D3 levels are below 20 ng/mL (50 nmol/L) [6,7,10,13].

Vitamin D also plays an important role in innate immunity and antigen-specific cellular immune response. 1,25(OH)2D3 interferes with cytokine production, growth and differentiation of a variety of immune cells, functioning as a vital immunomodulatory agent in some infectious diseases such as HIV infection [6,10,12,13]. On the other hand 25(OH)D3 has not shown any direct anti-mycobacterial or anti-HIV effects [14].

An adequate vitamin D status is important not only for bone tissue but also for the global health status of all people. There is potentially a great improve in terms of health and well-being if serum levels of 25(OH)D3 are above 30 ng/mL [9,15]. This is particularly relevant in HIV-positive individuals in whom seems to exist a significant association between vitamin D status and HIV disease's progression and survival [2,6].

HIV Infection, Vitamin D Deficiency and HAART

The WHO estimated an average of more than 30 million people infected with HIV in 2011 with Sub-Saharan Africa in the worst scenario [3]. The research in HIV/AIDS has led to great improvements in the prognosis of HIV-infected patients mainly after HAART [2,3]. Since its recognition, for over than 30 years, HIV infection went from a fatal diagnosis (mostly resulting in AIDS and death) to a chronic disease [2,3]. Investigation in this area has reduced the morbidity due to HIV/AIDS complications and has made the life expectancy of infected similar to that of uninfected individuals, however the studies' samples have been insufficient to establish broad standard protocols to monitor HIV-infected patients [2,3,16].

People with HIV are increasingly reaching older age and becoming more susceptible to age-associated complications, besides that they occur earlier and at higher rates than in general population. Cardiovascular diseases, diabetes, obesity, renal impairment, cognitive dysfunction, cancer, and bone disorders have all been reported [2,3,5,11]. Hypovitaminosis D is regarded as one of these complications and it has been found among HIV-infected patients at significant percentages (around 30%) [2,3,5,6].

Vitamin D has long been known to play an important role not only in skeletal health but also in the immune system. Several studies have attempted to clarify the relationship between vitamin D and HIV disease progression: low levels of vitamin D are believed to increase the risk of progression and long term complications of HIV infection (such as those above mentioned), while increased levels have been associated to inhibition of HIV replication and lower risk of all-cause mortality [1,5,17,18].

At the same time, hypovitaminosis D is more frequent in HIV-infected patients. One suggested explanation is that persistent immune activation, through elevated levels of TNF-α, blocks the stimulatory parathyroid hormone (PTH) effect on renal 1-α-hydroxylase lowering 1,25(OH)2D3 in HIV-infected patients [2,6,7,19]. This may explain why HIV-positive patients co-infected with intracellular M. avium have lower levels of vitamin D in comparison with individuals that are exclusively HIV-infected [7]. Vitamin D deficiency has also been associated with increased susceptibility to tuberculosis (both in HIV-positive or healthy subjects), a disease in which the role of either TNF-α or CD4+ cells is central [7]. Even though some studies found no correlation between vitamin D and CD4+ cell levels [1,3,5,11] there are several reports of advanced HIV infections associated with decreased levels of 1,25(OH)2D3, low CD4+ cell counts and increased mortality [6,7,16,19].

Vitamin D deficiency has also higher prevalence in the following circumstances: black ethnicity (19% in White and 62% in Black patients, since naturally dark skin tone people have natural sun protection requiring 3-5 times longer solar exposure to achieve the same amount of vitamin D as a white person) , low sunlight exposure or winter months, higher body mass index, older age, feminine gender (58,1% while 24,7% in masculine gender), physical inactivity, low dietary vitamin D intake, hypertension, hepatic/ renal failure, smoking, hereditary defects (vitamin D-dependent rickets type I), primary hyperparathyroidism and medications, such

Table 1: Studies included in the review– clinical trials, observational and experimental studies.

Publication	Publication year	Location	Study type	Study population	Control population	Findings/comments
Mehta, S. et al. [1]	2010	USA	Clinical trial	884 HIV-infected pregnant women	_	No significant relationship was observed between vitamin D status and T-cell counts during follow-up. Vitamin D status had a protective association with HIV disease progression, all-cause mortality, and development of anemia during follow-up in HIV-infected women.
Van Den Bout-Van Den Beukel, C. J. P. et al. [3]	2008	Netherlands	Prospective cohort study	252 HIV-infected patients	_	First study evaluating the prevalence of vitamin D deficiency among a large cohort of adult HIV-1-infected patients. First study evaluating the effect of antiretroviral therapy on vitamin D status. It was shown that PI- or NNRTI-treated patients may be at risk for vitamin D deficiency.
Conesa-Botella, A. et al. [5]	2010	Antwerp, Belgium	Retrospective cohort study	HIV-positive adults starting HAART with CD4+ T-cell counts > 100 cells/mm3, followed up for at least 12 months, without a treatment change in the first year of HAART	_	Vitamin D deficiency is frequent in HIV-positive individuals and NNRTI therapy further decreases 25(OH)D concentrations. Consequently, vitamin D status need to be checked regularly in all HIV-infected patients and vitamin D supplementation should be given when needed.
Anderson, J. L. et al. [8]*	2010	Utah	Prospective cohort study	Intermountain Healthcare system (n=41 497)	Vitamin D level > 30mg/dL (n=15 121)	The authors' findings suggest that vitamin D deficiency represents an important new cardiovascular risk factor and, they hypothesize, might play a causal role in the development of cardiovascular risk factors and cardiovascular diseases and adverse events, including death.
Khoo, Ai-Leng et al. [10]	2011	Netherlands	Prospective cohort study	22 vitamin D deficient HIV-1 seropositive patients	_	1,25(OH)2D3 directly affects Treg cell growth and promotes IL-10 production without apparent effects on activation status and suppressive phenotype whereas in vivo, high serum 1,25(OH)2D3 levels are associated with reduced Treg cell proliferation and number.
Sudfeld, C. R. et al. [11]	2012	Tanzania	Prospective cohort study; randomized trial	HIV-infected patients initiating ART	_	Deficient vitamin D levels may lead to increased mortality in individuals receiving ART and this relationship does not appear to be due to impaired CD4 T-cell reconstitution.
Rutstein, R. et al. [12]	2011	Philadelphia, USA	Retrospective cohort study	Children and young adults with perinatally acquired HIV (age 5–23 years)	Healthy children and young adults	This study aimed to assess vitamin D [serum 25(OH) D concentrations] in children and young adults with perinatally acquired HIV compared to geographically similar healthy children. Vitamin D deficiency was increased in subjects with perinatally acquired HIV and may be associated with disease severity.
Wiboonchutikul, S. et al. [13]	2012	Thailand	Cross-sectional study	HIV-1-infected patients	_	The results from this study have shown that vitamin D deficiency or insufficiency was highly prevalent among HIV-1-infected adults even in a tropical country such as Thailand. Also, there was no difference in vitamin D levels between patients who were naive or exposed to ART. Use of efavirenz was the only factor significantly associated with low vitamin D status.
Campbell, G. R. et al. [14]	2012	San Diego, California	Experimental study	HIV seronegative subjects	_	Physiologic concentrations of 1,25-dihydroxyvitamin D induce the production of CAMP and autophagic flux in HIV and M. tuberculosis co-infected human macrophages which inhibits mycobacterial growth and the replication of HIV, depending not only by the induction of autophagy, but also by the phagosomal maturation. Cathelicidin is essential for the 1,25-dihydroxyvitamin D induced autophagic flux and inhibition of HIV replication and mycobacterial growth.
Stein, E. M. et al. [16]	2010	New York, USA	Cross-sectional study	HIV infected women	Healthy women	In postmenopausal minority women, vitamin D deficiency was highly prevalent and associated with AA race and lack of supplement use, as well as lower current CD4 cell count. These results provide support for screening and repletion of vitamin D in HIV+ patients.

Mehta, S. et al. [17]	2009	Tanzania	Clinical trial	884 HIV-infected pregnant women	_	This study examines the association of maternal vitamin D status at 12–27 weeks' gestation with adverse pregnancy outcomes, MTCT of HIV, and child mortality. The association of maternal vitamin D status with HIV transmission and death among children has not been previously studied. These results are in accordance with some small studies of nonpregnant HIV-infected populations that have shown an association between low vitamin D levels and increased HIV disease progression and higher mortality.
Campbell, G. R. et al. [18]	2011	San Diego, California	Experimental study	HIV-seronegative donors	_	Physiologically relevant concentrations of 1,25-dihydroxycholecalciferol induce autophagy in human macrophages through a phosphatidylinositol 3-kinase-, ATG-5-, and Beclin-1-dependent mechanism that significantly inhibits HIV-1 replication in a dose dependent manner. 1,25-dihydroxycholecalciferol induces the secretion of human cathelicidin, at the concentrations produced in vitro, cathelicidin does not trigger autophagy.
Haug, C. J. et al. [19]	1998	Oslo, Norway	Prospective cohort study	54 HIV-infected patients	Healthy subjects	Inadequate 1a-hydroxylation of 25 hydroxyvitamin D seems to be the most likely cause of 1,25(OH)2D3 deficiency in HIV-infected patients, possibly induced by an inhibitory effect of TNF-α. The low 1,25(OH)2D3 and high TNF-α levels observed may impair the immune response in HIV-infected patients both independently and in combination and may represent an important feature of the pathogenesis of HIV-related immunodeficiency.
Ginde, A. A. et al. [20]*	2009	USA	Cross-sectional studies	Noninstitutionalized US civilian population NHANES III n=18 883 NHANES n= 13 369	_	It is demonstrated a marked decrease in serum 25(OH)D levels from the 1988-1994 to 2001-2004 NHANES data collections. Racial/ethnic differences have persisted and may have important implications for known health disparities. The authors consider the current recommendations for vitamin D supplementation inadequate to address the growing epidemic of vitamin D insufficiency.
Liu, P. T. et al. [21]*	2006	USA	Experimental study (report)	Human primary monocytes, macrophages and dendritic cells (several donors)	_	TLR activation of human macrophages up-regulate expression of the vitamin D receptor and the vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular M. tuberculosis. Sera from African-American individuals, with higher susceptibility to tuberculosis, have low 25-hydroxyvitamin D and are inefficient in supporting cathelicidin messenger RNA induction. These data support a link between TLRs and vitamin D-mediated innate immunity and suggest that differences in ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection.
Cozzolino, M. et al. [22]	2003	USA	Experimental study	Human cell lines	_	In intact cells in vitro, HIV-PIs markedly suppress the activities of 25- and 1α-hydroxylase, which are critical in 1,25(OH)2D3 synthesis, while exerting mild inhibition of 24-hydroxylase, responsible for 1,25(OH)2D3 catabolism. If PIs elicit a similar potency in inhibiting these critical steps for 1,25(OH)2D3 homeostasis in vivo, defective 1,25(OH)2D3 production could contribute to the bone demineralization in HIV patients.
Teichmann, J. et al. [24]	2003	Germany	Cross-sectional study	50 HIV-infected women	50 healthy women	Osteopenia in AIDS patients have been associated with antiretroviral therapy particulary with protease inhibitors and being more frequent in HIV-infected female subjects. There is a dissociation between lowered markers of bone formation rate and the increased bone reabsorption expressed as elevated urinary crosslinks and calcium excretion. Furthermore, the decreased levels of 1,25(OH)2D3 may contribute to a negative calcium balance and inhibition of bone formation.
Urashima, M. et al. [27]*	2010	Japan	Randomized control trial	Schoolchildren ages 6-15 years n=334 (followed until the end of the study)	n=167 (placebo group)	This study suggests that vitamin D3 supplementation during the winter may reduce the incidence of influenza A, especially in specific subgroups of schoolchildren.

Liu, P. T. et al. [28]*	2007	Ulm, Germany	Experimental study	Human monocytic cell line THP-1	Not treated with 1,25D3 cells/Not transfected with siRNA cells	1,25(OH)2D3 stimulation resulted in antimicrobial activity against intracellular M. tuberculosis an expression of cathelicidin mRNA and protein. Using siRNA specific for cathelicidin, 1,25D3-induced cathelicidn mRNA and protein expressions were efficiently knocked down, whereas a nonspecific siRNA against cathelecidin, instead leading to enhanced intracellular growth of mycobacteria. These data demonstrate that cathelicidin is required for the 1,25(OH)2D3-triggered antimicrobial activity against intracellular M. tuberculosis.
Torres, C. et al. [30]	2010	Spain	Experimental study	Healthy blood donors	_	The rs1544410_AA association with progression to AIDS and resistance to HIV-1 appears to be linked to an enhanced response to VD3.
Haug, C. J. et al. [31]	1998	Oslo, Norway	Experimental study	10 HIV-infected patients	5 healthy subjects	HIV infection may significantly modulate the macrophage response to 1,25D stimulation, and that 1,25D may have inhibitory effects on MAC replication in macrophages from HIV-infected patients.
Campbell, G. R. et al. [32]	2012	USA	Experimental study	HIV-seronegative subjects	_	The present study identifies how vitamin D deficiency may influence innate immunity against HIV infection. Stimulation of human macrophages with TLR8 agonists upregulates the expression of CYP27B1 and the VDR leading to the induction of CAMP and autophagic flux. These data support an important role for vitamin D in the control of HIV infection, and provide a biological explanation for the benefits of vitamin D.
Yamamoto, N. et al. [33]	2009	USA	Experimental study	15 asymptomatic HIV-1 infected patients	_	Treatment of purified Gc protein with immobilized b-galactosidase and sialidase generated GcMAF, which produces no side effects in humans. After less than 18 weekly administrations of 100 ng GcMAF for nonanemic patients, they exhibited low serum Nagalase activities equivalent to healthy controls, indicating eradication of HIV-infection.
Haug, C. J. et al. [34]	1996	Oslo, Norway	Experimental study	28 HIV-infected patients	10 HIV-seronegative blood donors	Addition of 1,25D significantly improved the growth and maturation in both patient and control groups. There was a significant negative correlation between response to 1,25D and CD4+ lymphocyte count in blood in HIV-infected patients. A greater response to 1,25D was seen in monocytes from patients with advanced immunodeficiency and symptomatic disease than in monocytes from asymptomatic patients.
Skolnik, P. R. et al. [35]	1991	Boston, USA	Experimental study	Human cell lines	_	This study demonstrate that 1,25(OH)2D3 enhances the replication of monocyte- and lymphocyte-tropic strains of HIV-1 up to 10,000-fold in monocyte cell lines, peripheral blood monocytes, and unfractionated peripheral blood mononuclear cells.
Pauza, C. D. et al. [36]	1993	San Diego, California	Experimental study	Healthy HIV-seronegative donors	_	Treatment of U937 cells with vitamin D3 compounds subsequent to infection caused a significant inhibition of HIV-1 replication. In contrast, enhanced virus replication was observed when cells were exposed to vitamin D3 compounds prior to infection. In addition to their effects on HIV-1 replication, these compounds induced differentiation of the U937 cell line.
Goletti, D. et al. [37]	1995	Milan, Italy	Experimental study	Human cell lines (chronically HIV-infected cells)	_	Vit.D3 treatment alone induced differentiation of U1, a promonocytic cell line chronically infected with HIV, toward an M/M phenotype but did not induce virus expression or cytokine secretion in these cells. Treatment of U1 cells with TNF-α in the presence of Vit.D3 resulted in an enhancement of HIV expression compared with TNF-α treatment alone. In contrast, the addition of Vit.D3 with IFN-γ, IL-6, or GM-CSF led to a strong suppression of HIV expression. These results suggest that in the absence of HIV-inductive cytokines, differentiation of an HIV-infected promonocytic cell to an M/M phenotype is insufficient to activate HIV expression.

Hollis, B. W. et al. [41]*	2011	Charleston, South Carolina	Randomized control trial	16 years or greater pregnant women (n=494)	400 IU vitamin D3/ day (n=166)	Vitamin D supplementation of 4000 IU/day for pregnant women was safe and most effective in achieving sufficiency in all women and their neonates regardless of race while the current estimated average requirement was comparatively ineffective at achieving adequate circulating 25(OH) D, especially in African Americans.
Afzal, S. et al. [42]*	2013	Copenhagen City Heart Study, Denmark	Prospective cohort study Metaanalysis	9 841 participants from national Danish Central Person Register (cohort study) 72 204 participants (metaanalysis)	Plasma 25(OH)D ≥ 20 ng/mL	The authors find an association of low plasma 25(OH)D with increased risk of type 2 diabetes in the general population. That finding was substantiated by the metaanalysis.

* Hand search

Table 2: Studies included in the review– synthesis studies.

Publication	Publication year	Number of authors	Number of included studies	Number of participants in included studies	Findings/comments
Giusti, A. et al. [2]	2011	3	Prospective studies:9 Cross-sectional studies:17 Randomized-controlled trial studies:3 Case series study:1 (30)	Prospective studies:5 407 Cross-sectional studies:6 111 Randomized-controlled trial studies:1 169 Case series study:12 (12 699)	Abnormalities in vitamin D status and metabolism are increasingly recognized as a major concern in HIV infection. Several cross-sectional and prospective studies have suggested a high prevalence of vitamin D deficiency in HIV-infected individuals.
Beard, J. A. et al. [6]	2011	3	Controlled studies (respiratory tract infection and influenza): 5 Observational studies (respiratory tract infection and influenza): 7 Observational studies (HIV): 4 (16)	Controlled studies (respiratory tract infection and influenza): 4 181 Observational studies (respiratory tract infection and influenza): 20 101 Observational studies (HIV): 1 605 (25 887)	Vitamin D induced LL-37, and to a lesser extent human beta defensin 2, may play a major role in the inhibition of viruses.
Ross, A. C. et al. [7]	2012	3	Prospective studies:2 Cross-sectional studies:6 Randomized-controlled trial studies:4 (12)	Prospective studies:872 Cross-sectional studies:695 Randomized-controlled trial studies:316 (1 883)	Vitamin D deficiency is widespread among HIV-infected adults and children. Chronic HIV infection causes an increased risk of osteoporosis, immune system dysfunction, and increased systemic inflammation – all pathophysiologic mechanisms where vitamin D is known to play an important role.
Hossein-nezhad, A. et al. [9]*	2013	2	(35)	(819 318)	The effect of vitamin D on fetal programming epigenetics and gene regulation could potentially explain why vitamin D has been reported to have such wide-ranging health and adults worldwide for improving musculoskeletal health and reducing the risk of chronic illness, including some cancers, autoimmune diseases, infectious diseases, type 2 diabetes mellitus, neurocognitive disorders, and mortality.
Annapoorna, N. et al. [23]	2004	5	(113)	_	*(Classic review)* Osteoporosis is a disease with high incidence in HIV-infected individuals. Progression in HIV infection and HAART with PI are the possible factors that precipitate osteoporosis in these patients.
Jolliffe, D. A. et al. [26]*	2013	3	Randomized-controlled trial studies:14 Cohort studies:13 Case-control studies:8 Cross-sectional studies:4 (39)	(47 360)	The authors demonstrate consistent associations between vitamin D deficiency and susceptibility to acute respiratory infections. By contrast, results of vitamin D supplementation trials did not demonstrate consistent protective effects against acute respiratory infections. The authors consider that null results may have arisen as a result of sub-optimal vitamin D deficiency among participants in some trials.
Raghavan, S. et al. [29]	2011	3	(174)	_	(Classic review) It is becoming clear that susceptibility to HIV/ AIDS as well as development of tuberculosis in HIV patients is most certainly multifactorial and is influenced by both environmental and genetic components (HLA or linked genes and/or non-HLA genes).

Maggie, Z. et al. [38]	2012	3	(35)	_	(Classic review) Nutritional supplements were found to have both positive and negative effects in HIV/AIDS children. Vitamin D supplementation was found to delay mother to child transmission of HIV and to reduce stunted growth associated with persistent diarrhea.
Wagner, C. L. et al. [39]*	2013	8	- NICHD trial - Thrasher Research Fund trial (2)	(504)	Supplementation with 4000 IU/day was associated with lower risk of hypovitaminosis D than Control and 2000 IU/day groups. While not statistically significant, there was a trend toward lower rates of comorbidities of pregnancy as supplementation dose increased. Maternal delivery 25(OH)D was inversely associated with any comorbidity of pregnancy, with fewer events as 25(OH)D increased.
Hollis, B. W. et al. [40]*	2013	2	(8)	(1 070)	Improving nutritional vitamin D status will improve birth outcomes; 4000 IU/day vitamin D3 during pregnancy will normalize vitamin D metabolism and improve birth outcomes including primary caesarean section and comorbidities of pregnancy with no risk of side effects.

* Hand search

Table 3: Studies included in the review– other studies.

Publication	Publication year	Study type	Findings/comments
Mascitelli, L. et al. [4]	2010	Letter to the editor	Dyslipidaemia relates to the duration of HAART, and contributes to an increased predicted risk of cardiovascular disease, although it represents only partly this risk. In vitro studies suggested that cholesterol-lowering therapy might represent a beneficial strategy for both preventing and treating HIV. However, in vivo studies have been discouraging because they found no beneficial effect and that hypocholesterolemia was significantly associated with impaired viro-immune response in participants with and without HAART. In the HAART era, the authors suggest that an optimal vitamin D status may lower the risk of both HIV infectivity and cardiovascular diseases. Vitamin D is associated with skeletal homeostasis as well as immune response. Vitamin D could slow HIV disease progression, and this association might be particularly important during HAART because antiretroviral therapy may further worsen hypovitaminosis D. Epidemiological studies have found an association between vitamin D deficiency and an overall increased risk of mortality.
Holick, M. F. et al. [15]*	2011	Clinical practice guideline	The authors recommend: - screening for vitamin D deficiency in individuals at risk for deficiency; - supplementation at suggested daily intake and tolerable upper limit levels, depending on the age and clinical circumstances; - vitamin D2 or D3 for treatment and prevention of vitamin D deficiency; - vitamin D supplementation for fall prevention, but not for cardiovascular disease/death/ improving quality of life.
van Den Bout-van Den Beukel CJ [25]	2009	Dissertation	Contents: Chapter 2 – Possible drug-metabolism interactions of medicinal herbs with antiretroviral agents. Chapter 3 – Antifungal activity of some Tanzanian plants used traditionally for the treatment of fungal infections. Chapter 4 – Evaluation of cytotoxic, genotoxic and CYP450 enzymatic competition effects of Tanzanian plant extracts traditionally used for treatment of fungal infections Chapter 5 – Toxic lopinavir concentrations in a HIV-1-infected patient taking herbal medicines. Chapter 6 – Vitamin D deficiency among HIV type 1-infected individuals in the Netherlands: effects of antiretroviral therapy. Chapter 7 – The effect of colecalciferol supplementation on vitamin D levels and insulin sensitivity is dose related in vitamin D deficient HIV-1-infected patients Chapter 8 – Vitamin D supplementation causes a dose dependant change in circulating CD4+CD25high regulatory T cell numbers in vitamin D deficient HIV-1-infected patients

* Hand search

as anticonvulsants or antiretroviral treatment (24,5% in patients without treatment and 30% in patients receiving HAART) [2,3,5-7,9,15,19-21]. Although some data support an association between vitamin D levels and HIV infection the nature of this relationship still cannot be clarified.

As already mentioned, HAART has dramatically improved the prognosis of HIV-infected patients despite its association with several complications such as vitamin D deficiency. 25(OH)D3 concentrations inferior to 20ng/ml are more prevalent among HIV-positive individuals treated with HAART than HAART-naive or HIV-negative patients [5]. Therefore, HAART impairs vitamin D metabolism by inhibiting key enzymes such as 25-hydroxylase and 1α-hydroxylase, especially when it includes non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) [2,5]. The impact of nucleoside reverse transcriptase inhibitors (NRTIs) has never been elucidated. Nevertheless, interactions between NRTIs and hipovitaminosis D are unlikely since NRTIs are not metabolized by cytochromes involved in vitamin D metabolism. Efavirenz (a NNRTI), on the other hand, has consistently been associated with low 25(OH)D3 concentrations as it can induce 24-hydrolyzis and inactivate vitamin D [2,5,11,13,16]. Similar but less consistent reports were found for NRTIs (like tenofovir) and for PIs. PIs, mainly

ritonavir, have been demonstrated to inhibit 25-hydroxylase and 1α-hydroxylase leading to lower activation of vitamin D. At the same time PIs are effective at exerting a mild suppression on vitamin D catabolism finally leading to a diminished vitamin D net production and increasing the risk of hypovitaminosis [16,22].

Vitamin D, HIV and Bone Health: A Dangerous Triad?

Vitamin D deficiency has been associated with a worse disease's progression in HIV-infected individuals of all ages. In fact, there is evidence of a positive relationship between HIV infection and a higher risk of decreased bone mineral density (BMD) and osteoporosis [7]. Significant changes in bone remodeling including weight loss, decreased lean body mass and impaired functional capacity affecting OPG/KANKL/RANK system may contribute to impaired skeletal strength and increased susceptibility to fractures [23].

Bone remodeling is somehow complex, involving a huge variety of hormones that constitute important regulators of calcium homeostasis (PTH, calcitriol, calcitonin, estrogens and androgens). These hormones interact with several local factors (for instance IL-1, IL-6, TGF, TNF, CSF), counting on OPG/RANKL/RANK system as a final osteoclastogenesis' enhancer [23].

Furthermore, in HIV-infected patients with undetectable 1,25(OH)2D3 there might be a diminished PTH production, with normal range of calcitonin even though it cannot be explained by vitamin D depletion [19]. PTH increases calcium absorption ensuring RANKL expression in osteoblasts, crucial to induce osteoclast maturation [7]. What is already known is that in HIV infection, apart from an important T lymphocyte turnover, there is a down-regulation of monocytes and macrophages' TNF receptors, leading to a down-regulation of PTH receptors and decreased cAMP response to PTH stimulation [19].

There is still a lot to clarify about the pathophysiologic role of vitamin D deficiency in osteopenia and osteoporosis, despite both having shown high incidence in HIV-infected patients as well as an association with the length of infection, high viral load, high lactate and alkaline phosphatase levels and low bicarbonate levels. Moreover, HAART greatly affects vitamin D metabolism increasing the risk of hypovitaminosis, as mentioned before [7,22,23].

Knowing that an adequate vitamin D status is essential for adequate bone mineral density, osteoprotective treatment should be started as soon as possible and vitamin D status should be measured by evaluating 25(OH)D3 and PTH levels [3,24].

Vitamin D and the Immune System Modulation

Vitamin D has numerous well-known metabolic functions regarding the regulation of calcium homeostasis and the skeletal system support [1,3,6,25].

In addition to this essential role regarding bone health, newer evidence suggests an important association between vitamin D and several chronic diseases, such as type 2 diabetes and cardiovascular diseases [2,12].

Perhaps the most significant findings are the ones that relate hypovitaminosis D to the susceptibility and response to viral infections (influenza and respiratory tract infections), particularly of enveloped virus, suggesting that vitamin D plays a major role in the regulation of immune system [2,6,12]. Jolliffe et al. [26] concluded a systematic review that revealed broadly consistent associations between vitamin D deficiency and susceptibility to acute respiratory infections, particularly in observational studies, with vitamin D supplementation trials demonstrating less consistent outcomes. In order to elucidate a possible association between seasonal oscillation of serum vitamin D concentrations, and the typical epidemic pattern of influenza Urashima et al. [27] designed a randomized, double-blind, placebo-controlled clinical trial to investigated the effect of vitamin D supplements on the incidence of seasonal influenza A. The results showed a significant preventive effect against influenza A, emphasizing the important role of vitamin D in the up-regulation of the immune system.

Several studies have also highlighted an association between vitamin D deficiency and tuberculosis which is partly explained by the existence of vitamin D dependent mechanisms in the anti-mycobacterium effector pathways responsible for mycobacterium tuberculosis elimination [14,28]. One example is the vitamin D-dependent production of cathelicidin that follows TLR2/1-activation of monocytes infected with intracellular Mycobacterium tuberculosis [28]. This is also relevant in HIV infection since tuberculosis is the frequent major opportunistic infection and the leading cause of mortality among HIV-infected patients [29].

Furthermore, several studies have identified an important association between HIV infection and vitamin D deficiency [1,3,11-13,19,25].

The effects of 1,25(OH)2D3 are mediated through its interaction to the vitamin D receptor (VDR), allowing its access to the nucleus where it binds vitamin D response elements (VDRE) and regulates gene transcription [6,7]. VDR expression is found not only in skeletal system tissues, but also in other locations such as monocytes, macrophages, dendritic cells, natural-killer cells, and T and B cells, which supports vitamin D immunomodulatory effects [7]. What also supports the immunomodulatory effects of vitamin D is the association between VDR polymorphisms and variable progression rates to AIDS and resistance to HIV infection as well as development of tuberculosis in HIV-infected individuals [29,30]. In fact, several *in vivo and in vitro* studies have demonstrated these immunomodulatory properties, both in innate and adaptive immunity [2,6,7,13,17,25].

Vitamin D effect on Innate Immunity

1,25(OH)2D3 can act as a potent stimulator of innate antimicrobial responses [14]. Monocytes and macrophages are some of the constituents of the innate immune system in which 1,25(OH)2D3 supplementation has been found to be particularly effective [31].

Several studies demonstrate that 1,25(OH)2D3 can improve phagocytosis and augment the respiratory burst in these cells. Moreover, it appears to enhance chemotaxis and improve maturation of monocytes [31].

1,25(OH)2D3 improves phagocytosis: In HIV-infected individuals the virus persists in long lived cells, including resting T cells, macrophages and dendritic cells [14,18]. As an obligatory intracellular parasite, its survival is dependent upon its ability to evade cellular processes that prevent its growth [32]. One such process is macroautophagy, which consists of a degradation pathway for organelles and microbial pathogens in macrophages [14,18,32]. Macroautophagy is an essential host defense mechanism against viral and mycobacterial infections. Several studies have demonstrated that its activation in macrophages reduces the viability of HIV and M. tuberculosis [14,18,32,33]. HIV evades autophagy by actively down-regulating autophagy regulatory factors [32].

Low serum levels of 1,25(OH)2D3 have been associated with an increased risk for HIV disease progression, suggesting that

physiological concentrations of vitamin D inhibit the replication of HIV through the induction of autophagy in human macrophages, based on a phosphatidylinositol 3-kinase, ATG-1 and beclin-1-dependent mechanism [14,18,32].

Recent research has focused on the role of Toll-like receptors (TLRs) in the macroautophagy process. In fact, cells detect intracellular pathogens through pattern recognition receptors (PRRs), which recognize signature molecules of microorganisms named pathogen-associated molecular patterns (PAMPs). TLRs are one important class of PRRs [32]. Recently it has been suggested that vitamin D plays an important role in the innate immune response via TLRs [1,7,32].

Liu et al. [21] demonstrated that TLR stimulation of human macrophages: induces the enzyme (1-α-hydroxylase) that catalyzes the conversion of vitamin D to its active metabolite (1,25(OH)2D3); up-regulates the expression of the VDR; and induces relevant downstream targets of VDR, such as the cathelicidin antimicrobial peptide (CAMP). Other studies highlighted the action of vitamin D as a key link between TLR activation and several antibacterial responses in HIV infected patients, pointing out the ability of Vitamin D in affecting disease progression and mortality among HIV-infected patients [1,32]. TLR8 is an important toll-like receptor with an interesting distribution: monocytes, macrophages, myeloid dendritic cells and regulatory T cells [32]. TLR8 recognizes single-stranded RNA (ssRNA) and, once activated, leads to the induction of an antiviral effector cascade, which is responsible for the induction of autophagy. Recent research has elucidated that TLR8 agonists inhibit HIV replication in macrophages through a vitamin D and CAMP-dependent process [32].

Some anti-microbial peptides associated with TLRs (for instance, CAMP LL-37 and human beta defensin 2) have demonstrated antiviral effects, and their expression is affected by vitamin D [6]. Expression of these antimicrobial peptides is also up-regulated in macrophages stimulated by 1,25(OH)2D3. Consequently, individuals with vitamin D deficiency may have impaired autophagy and oxidative burst, resulting in an increased incidence or even more severe opportunistic infections [2,6,14,32].

As previously mentioned, CAMP LL-37 enhances innate immunity through an increased autophagy in macrophages and is particularly important in the protection against pathogens such as *Mycobacterium tuberculosis* [7,32]. Furthermore, LL-37 has broad antimicrobial activity against bacteria, fungi and certain viruses. It also exerts chemotactic, immunomodulatory and angiogenic effects and decreases serum levels of pro-inflammatory cytokines [7]. These findings suggest that the induction of autophagy has the potential to be useful in the prevention and treatment of HIV-1 infection and related opportunistic infections [14,18].

1,25(OH)2D3 induces monocytes maturation: Macrophages play a critical role in protecting against intracellular pathogens. In fact, many of the opportunistic infections seen in HIV-infected patients are due to intracellular microorganisms, such as *Mycobacterium tuberculosis*, suggesting an impairment in the macrophage function. This raises an important question: could this impairment be due to a defect in maturation of monocytes in HIV-infected patients? [34].

1,25(OH)2D3 has been shown to induce maturation of normal monocytes to macrophages, as well as monocytes differentiation of bone marrow precursors [34,35]. Additionally, some in vitro studies have demonstrated that 1,25(OH)2D3 plays an important role in regulating macrophage function in HIV- infected individuals since it is able to modulate HIV infection in human macrophages, via the induction of cellular differentiation [36].

One important aspect of latently infected macrophages in HIV infection relates with their ability to function as a virus reservoir and to produce infectious virus [37]. Therefore it is possible that cellular differentiation plays a role in increasing HIV susceptibility and/or progression through the expansion of this viral reservoir [37]. Goletti et al. [37] verified that vitamin D3 monocytes stimulation induced cellular differentiation but did not induce HIV expression, demonstrating dissociation between cellular differentiation and viral expression. Furthermore, it was observed by this same study that vitamin D effect on viral expression was associated with the cytokine environment, since vitamin D3 enhanced HIV expression in the presence of TNF-a but inhibited viral expression in the presence of gamma interferon (IFN-γ), IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Adaptive Immunity

Some studies had described important effects of 1,25(OH)2D3 in adaptive immunity, particularly in T cell activation and phenotype modulation. 1,25(OH)2D3 also seems to play an important role in antigen-presenting cells' function and IL-10 production [2,7,10].

Treg cells have particular relevance as they are involved on inactivation and inhibition of T cell proliferation by shifting from a Th1 to a Th2 response. Recently, Treg cells have been subject of great interest not only in HIV infection, but also in transplants, autoimmune diseases and immune cancer. Treg cells may represent an interesting opportunity for the control of HIV infection, as they suppress T cell expansion limiting viral replication [2,25].

The progression of HIV infection is associated with a decrease in the number and function of Treg and CD4+ cells. In addition to this, recent studies have demonstrated an association between HIV infection and 1,25(OH)2D3 deficiency. The relationship between decreased levels of vitamin D and equally decreased Treg cells numbers has already been demonstrated, but the opposite was not verified yet [6,7,25]. Recent studies have showed that the increase in viral load is associated with Treg cells accumulation in secondary lymphoid tissues, explaining the decrease in plasmatic Treg cells during the process of HIV infection [25].

Moreover, Vitamin D affects the maturation and differentiation of dendritic cells, being also able to induce a tolerogenic phenotype [7,10].

It has also been proved in vitro that 1,25(OH)2D3 reduces B cell proliferation, plasmatic differentiation and immunoglobulin production. This can be important for the reduction of inflammation, tissue destruction, and immune response to opportunistic infections in individuals with adequate levels of vitamin D, attenuating its severity and mortality [11].

Vitamin D Supplementation and HIV Infection

Several studies had reported that vitamin D deficiency negatively interferes with the progression and mortality of HIV infection, and so adequate levels of vitamin D may be important for the global health status of HIV-infected children and adults [2,7,19,25].

Besides the overall benefit of vitamin D sufficiency status, there are some particular subsets of the HIV-infected population that may have specific advantages with vitamin D supplementation. It has been suggested that adequate levels of vitamin D are beneficial for pregnant women, even without HIV infection, due to its role in the development of the fetal immune function [17,38]. The Institute

of Medicine (IOM) recommends a vitamin D intake of 400–600 IU/day during pregnancy for all women whereas the Endocrine Society suggests an intake of 1,500–2,000 IU/day [39-41]. However, results of two studies support that, in comparison with the groups receiving supplements of 400 and 2000 IU/day, a daily vitamin D supplementation of 4000 IU was not only considered safe (neither hypercalcemia or hypercalciuria were observed) but it was also associated with a lower risk of hypovitaminosis D and comorbidities during pregnancy [39,41]. 884 HIV-infected pregnant women who received daily doses of a vitamin supplement (which had not included vitamin D) in Tanzania were followed in an observational analysis to assess the association between vitamin D status and pregnancy outcomes [17]. Low maternal vitamin D level at 12-27 weeks' gestation was not associated with outcomes as low birth weight, preterm birth or small for gestational age. Nevertheless, an insufficient maternal vitamin D level was significantly associated with an increased risk of mother-to-child transmission at 6 weeks of age and through breast-feeding and infant mortality during follow-up [17]. One of the limitations of this study, however, is related to the assay that was used to determine the vitamin D status which does not give an accurate measure [17].

Another situation was studied by Stein et al who observed that the lack of nutritional supplementation was associated with vitamin D deficiency in HIV-infected postmenopausal women [16]. In spite of this, it is important to refer that this study has some limitations such as small sample size, the cross-sectional design and a potential selection bias (subjects were women living in New York) [16].

Due to all the potential benefits of vitamin D supplementation, some researchers have attempted to explore the effects of external administration of cholecalciferol in vitamin D deficient HIV-infected adults [25]. One of these studies aimed to investigate the effects of cholecalciferol supplementation in vitamin D levels, BMD and insulin sensitivity (in general population, low levels of 25(OH)D3 are associated with increased risk of type 2 diabetes) [25,42]. Patients were treated with 2000 IU cholecalciferol/day for 14 weeks after which treatment was continued with 1000 IU/day until 48 weeks. After 24 weeks, an increase of 25(OH)D3 and 1,25(OH)2D3 levels was registered, as well as a decrease in PTH and insulin sensitivity. Nevertheless, after 48 weeks, the levels of 25(OH)D3 were the only with significant changes. Neither CD4+ cell number nor BMD were modified [25]. With a small sample size (20 vitamin D deficient HIV-1-infected patients), the results of this explorative study need to be confirmed in larger clinical trials [25].

Another study in the same population aimed to explore the effects of cholecalciferol supplementation on circulating CD4+ CD25 high Treg numbers, given their important role in immunity and tolerance [25]. Under the same supplementation regimen aforementioned, subjects showed a similar pattern of changes, with regard to 25(OH) D3, 1,25(OH)2D3 and PTH levels [25]. The absolute numbers of circulating CD4+ CD25 high Treg, as well as the percentage of CD4+ CD25 high Treg in the CD4+ cell subset, decreased with the administration of 2000 IU cholecalciferol/day [25]. However, with a lower dose of cholecalciferol (1000 IU/day), those values were again at baseline. Both studies indicate that, in HIV-infected patients the cholecalciferol supplementation appears to have a dose dependent effect because both Treg cells numbers and 1,25(OH)2D3 levels returned to baseline when the cholecalciferol's dosage was decreased (1000 IU/day) [25]. It is suggested that a supplementation of >2000 IU cholecalciferol per day would enable the achievement of the optimal levels of vitamin D in HIV-infected patients [25]. However, the development of insulin resistance may be an eventual side effect [25]. Besides the small sample size, another limitation of this study concerns the phenotypic analysis which does not allow an accurate understanding of the influence of vitamin D supplementation on the function of Treg or on their distribution [25].

While larger studies and randomized clinical trials should be developed to define its optimal doses, vitamin D supplementation seems to be a promising, simple and economical way of improving bone health and immune function in HIV-infected individuals [7,12,17,25].

Conclusion

Recently, mortality in HIV-infected individuals has dramatically decreased as a result of all the investment made in diagnosis and management of HIV infection [2]. This is, partly, a consequence of the implementation of successful interventions, from which HAART is a main reference.

Despite all the benefits of an anti-retroviral therapy (ART), some evidence suggests that HIV-infected subjects treated with HAART have higher risk of vitamin D deficiency and also cancer, cardiovascular disease, diabetes and other immunological diseases [5]. Not only vitamin D deficiency is highly prevalent in HIV-positive patients, but also NNRTI therapy further decreases 25(OH)D3 serum levels [3,5].

The importance of an adequate level of vitamin D and its beneficial effect on several chronic diseases, and not just bone health, are explored in several studies, most of which observational [2,25]. Due to the high frequency of hypovitaminosis D in HIV-infected individuals, possible implications of such status in HIV infection and in the disease progression are a subject of extensive research [1,2,19,30].

There are still aspects that need to be clarified in larger clinical randomized controlled trials such as the benefits of vitamin D supplementation for nonskeletal health and acute and chronic diseases. However, it seems that vitamin D supplementation could be a simple and low-cost way of improving health and postponing the initiation of ART in HIV-infected patients [1,3,9,25].

Conflict of Interests

All authors certify that there is no conflict of interest with any people or organizations, regarding the material discussed in the manuscript.

Acknowledgment

The authors are pleased to acknowledge Sílvia Ferreira (Laboratory of Immunology, Basic and Clinical Immunology Unit, Faculty of Medicine, University of Porto, Portugal) for the assistance provided in the writing of the manuscript and Luís Delgado, M.D., Ph.D. (Laboratory of Immunology, Basic and Clinical Immunology Unit, Faculty of Medicine, University of Porto, Portugal) for the critical review of the manuscript.

References

1. Mehta S, Giovannucci E, Mugusi FM, Spiegelman D, Aboud S, et al. (2010) Vitamin D status of HIV-infected women and its association with HIV disease progression, anemia, and mortality. PLoS One 5: e8770.
2. Giusti A, Penco G, Pioli G (2011) Vitamin D deficiency in HIV-infected patients: a systematic review. Nutrition and Dietary Supplements 3: 101-111.
3. Van Den Bout-Van Den Beukel CJ, Fievez L, Michels M, Sweep FC, Hermus AR, et al. (2008) Vitamin D deficiency among HIV type 1-infected individuals in the Netherlands: effects of antiretroviral therapy. AIDS Res Hum Retroviruses 24: 1375-1382.
4. Mascitelli L, Pezzetta F, Goldstein MR (2011) Cholesterol, vitamin D and cardiovascular prevention in HIV patients treated with antiretroviral therapy. Int J Cardiol 146: 441-442.
5. Conesa-Botella A, Florence E, Lynen L, Colebunders R, Menten J, et al.

(2010) Decrease of vitamin D concentration in patients with HIV infection on a non nucleoside reverse transcriptase inhibitor-containing regimen. AIDS Res Ther 7: 40.

6. Beard JA, Bearden A, Striker R (2011) Vitamin D and the anti-viral state. J Clin Virol 50: 194-200.
7. Ross AC, McComsey GA (2012) The Role of Vitamin D Deficiency in the Pathogenesis of Osteoporosis and in the Modulation of the Immune System in HIV-Infected Patients. Clinical Reviews in Bone and Mineral Metabolism 10: 277-287.
8. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, et al. (2010) Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol 106: 963-968.
9. Hossein-nezhad A, Holick MF (2013) Vitamin D for health: a global perspective. Mayo Clin Proc 88: 720-755.
10. Khoo AL, Joosten I, Michels M, Woestenenk R, Preijers F, et al. (2011) 1,25-Dihydroxyvitamin D3 inhibits proliferation but not the suppressive function of regulatory T cells in the absence of antigen-presenting cells. Immunology 134: 459-468.
11. Sudfeld CR, Wang M, Aboud S, Giovannucci EL, Mugusi FM, et al. (2012) Vitamin D and HIV progression among Tanzanian adults initiating antiretroviral therapy. PLoS One 7: e40036.
12. Rutstein R, Downes A, Zemel B, Schall J, Stallings V (2011) Vitamin D status in children and young adults with perinatally acquired HIV infection. Clin Nutr 30: 624-628.
13. Wiboonchutikul S, Sungkanuparph S, Kiertiburanakul S, Chailurkit LO, Charoenyingwattana A, et al. (2012) Vitamin D insufficiency and deficiency among HIV-1-infected patients in a tropical setting. J Int Assoc Physicians AIDS Care (Chic) 11: 305-310.
14. Campbell GR, Spector SA (2012) Vitamin D inhibits human immunodeficiency virus type 1 and Mycobacterium tuberculosis infection in macrophages through the induction of autophagy. PLoS Pathog 8: e1002689.
15. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, et al. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96: 1911-1930.
16. Stein EM, Yin MT, McMahon DJ, Shu A, Zhang CA, et al. (2011) Vitamin D deficiency in HIV-infected postmenopausal Hispanic and African-American women. Osteoporos Int 22: 477-487.
17. Mehta S, Hunter DJ, Mugusi FM, Spiegelman D, Manji KP, et al. (2009) Perinatal outcomes, including mother-to-child transmission of HIV, and child mortality and their association with maternal vitamin D status in Tanzania. J Infect Dis 200: 1022-1030.
18. Campbell GR, Spector SA (2011) Hormonally active vitamin D3 (1alpha,25-dihydroxycholecalciferol) triggers autophagy in human macrophages that inhibits HIV-1 infection. J Biol Chem 286: 18890-18902.
19. Haug CJ1, Aukrust P, Haug E, Mørkrid L, Müller F, et al. (1998) Severe deficiency of 1,25-dihydroxyvitamin D3 in human immunodeficiency virus infection: association with immunological hyperactivity and only minor changes in calcium homeostasis. J Clin Endocrinol Metab 83: 3832-3838.
20. Ginde AA, Liu MC, Camargo CA Jr (2009) Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 169: 626-632.
21. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, et al. (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 311: 1770-1773.
22. Cozzolino M, Vidal M, Arcidiacono MV, Tebas P, Yarasheski KE, et al. (2003) HIV-protease inhibitors impair vitamin D bioactivation to 1,25-dihydroxyvitamin D. AIDS 17: 513-520.
23. Annapoorna N, Rao GV, Reddy NS, Rambabu P, Rao KR (2004) An Increased Risk of Osteoporosis during Acquired Immunodeficiency Syndrome. Int J Med Sci 1: 152-164.
24. Teichmann J, Stephan E, Lange U, Discher T, Friese G, et al. (2003) Osteopenia in HIV-infected women prior to highly active antiretroviral therapy. J Infect 46: 221-227.
25. van Den Bout-van Den Beukel C (2009) Consequences of vitamin D and xenobiotic metabolism by cytochrome P450 in HIV infection [Dissertation]. Netherlands: RU Radboud University Nijmegen. 213 p.
26. Jolliffe DA, Griffiths CJ, Martineau AR (2013) Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies. J Steroid Biochem Mol Biol 136: 321-329.
27. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, et al. (2010) Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr 91: 1255-1260.
28. Liu PT, Stenger S, Tang DH, Modlin RL (2007) Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol 179: 2060-2063.
29. Raghavan S, Alagarasu K, Selvaraj P (2012) Immunogenetics of HIV and HIV associated tuberculosis. Tuberculosis (Edinb) 92: 18-30.
30. Torres C, Sánchez de la Torre M, García-Moruja C, Carrero AJ, Trujillo Mdel M, et al. (2010) Immunophenotype of vitamin D receptor polymorphism associated to risk of HIV-1 infection and rate of disease progression. Curr HIV Res 8: 487-492.
31. Haug CJ, Muller F, Aukrust P, Froland SS (1998) Different effect of 1,25-dihydroxyvitamin D3 on replication of Mycobacterium avium in monocyte-derived macrophages from human immunodeficiency virus-infected subjects and healthy controls. Immunol Lett 63: 107-112.
32. Campbell GR, Spector SA (2012) Toll-like receptor 8 ligands activate a vitamin D mediated autophagic response that inhibits human immunodeficiency virus type 1. PLoS Pathog 8: e1003017.
33. Yamamoto N, Ushijima N, Koga Y (2009) Immunotherapy of HIV-infected patients with Gc protein-derived macrophage activating factor (GcMAF). J Med Virol 81: 16-26.
34. Haug CJ, Müller F, Rollag H, Aukrust P, Degré M, et al. (1996) The effect of 1,25-vitamin D3 on maturation of monocytes from HIV-infected patients varies with degree of immunodeficiency. APMIS 104: 539-548.
35. Skolnik PR, Jahn B, Wang MZ, Rota TR, Hirsch MS, et al. (1991) Enhancement of human immunodeficiency virus 1 replication in monocytes by 1,25-dihydroxycholecalciferol. Proc Natl Acad Sci U S A 88: 6632-6636.
36. Pauza CD, Kornbluth R, Emau P, Richman DD, Deftos LJ (1993) Vitamin D3 compounds regulate human immunodeficiency virus type 1 replication in U937 monoblastoid cells and in monocyte-derived macrophages. J Leukoc Biol 53: 157-164.
37. Goletti D, Kinter AL, Biswas P, Bende SM, Poli G, et al. (1995) Effect of cellular differentiation on cytokine-induced expression of human immunodeficiency virus in chronically infected promonocytic cells: dissociation of cellular differentiation and viral expression. J Virol 69: 2540-2546.
38. Maggie Z, He G, Wang H (2012) Effects of nutritional supplementation on children with HIV/AIDS in China. Zhong Nan Da Xue Xue Bao Yi Xue Ban 37: 305-310.
39. Wagner CL, McNeil RB, Johnson DD, Hulsey TC, Ebeling M, et al. (2013) Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: a combined analysis. J Steroid Biochem Mol Biol 136: 313-320.
40. Hollis BW, Wagner CL (2013) Vitamin D and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes. Calcif Tissue Int 92: 128-139.
41. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL (2011) Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res 26: 2341-2357.
42. Afzal S, Bojesen SE, Nordestgaard BG (2013) Low 25-hydroxyvitamin D and risk of type 2 diabetes: a prospective cohort study and meta analysis. Clin Chem 59: 381-391.

Author Affiliations

Top

[1]*Laboratory of Immunology, Basic and Clinical Immunology Unit, Faculty of Medicine, University of Porto, Portugal*